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ORIGINAL ARTICLE

Positive selection rather than relaxation of functional constraint drives the evolution of vision during chicken domestication

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As noted by Darwin, chickens have the greatest phenotypic diversity of all birds, but an interesting evolutionary difference between domestic chickens and their wild ancestor, the Red Junglefowl, is their comparatively weaker vision. Existing theories suggest that diminished visual prowess among domestic chickens reflect changes driven by the relaxation of functional constraints on vision, but the evidence identifying the underlying genetic mechanisms responsible for this change has not been definitively characterized. Here, a genome-wide analysis of the domestic chicken and Red Junglefowl genomes showed significant enrichment for positively selected genes involved in the development of vision. There were significant differences between domestic chickens and their wild ancestors regarding the level of mRNA expression for these genes in the retina. Numerous additional genes involved in the development of vision also showed significant differences in mRNA expression between domestic chickens and their wild ancestors, particularly for genes associated with phototransduction and photoreceptor development, such as *RHO* (rhodopsin), *GUCA1A*, *PDE6B* and *NR2E3*. Finally, we characterized the potential role of the *VIT* gene in vision, which experienced positive selection and downregulated expression in the retina of the village chicken. Overall, our results suggest that positive selection, rather than relaxation of purifying selection, contributed to the evolution of vision in domestic chickens. The progenitors of domestic chickens harboring weaker vision may have showed a reduced fear response and vigilance, making them easier to be unconsciously selected and/or domesticated.

***Keywords*:** chicken domestication; unconscious selection; genome evolution; evolution of vision
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Introduction

As noted by Darwin, chickens have the greatest phenotypic diversity among birds. Compared with their wild ancestor, the Red Junglefowl, domestic chickens harbor many typical domestication characteristics, such as larger body size, tame behavior, and higher egg productivity. Identifying the genetic changes underlying these phenotypic changes should provide new insights into the successful domestication of animals and further inform future breeding programs. A pioneering study by Rubin *et al*. [1] used re-sequencing of genomes of commercial chickens as well as populations of Red Junglefowl to identify several selective sweeps associated with reproduction and growth. However, their approach had

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limitations in comprehensively elucidating the genetic differences that account for the phenotypic differences between domestic chickens and Red Junglefowl. This was due to, for example, the use of commercial chickens that evolved from Red Junglefowl under strong selection by humans for specific traits associated with growth (e.g., meat production) and reproduction (e.g., egg production) as wells as the use of pooled re-sequenced genomes. Despite the great leap in genetic technologies witnessed in the recent past, the genetic mechanisms underlying many interesting evolutionary differences between domestic chickens and their wild ancestors, for example, reduced vision prowess in chickens, remain unclear.

Vision is one of the most crucial abilities affecting the survival of animal species, as it influences an array of core behavioral traits associated with mating, foraging, and predator avoidance [2]. However, domesticated animals including dogs, horses, and chickens, which are bred and protected by humans, seem to exhibit markedly weaker visual acuity compared to their wild counterparts [3-7]. Domestic chickens (except game fowl) share with these other domestic animals a reduced visual ability as compared to the Red Junglefowl, assumedly the cost of domestication due to the relaxation of selective constraints. The living condition changes that accompany domestication are a reflection of human interventions such as offering protection, provision of food and promotion of the animal breeding. These interventions reduce the pressure for sharp vision in the domestic chickens [3, 4]. However, unlike other phenotypic differences like growth and reproduction [1], no reports exist for the genetic mechanisms behind the change in visual acuity observed in domestic chickens.

To promote a better understanding of the underlying genes/variants responsible for phenotypic changes that occurred in the domestic chickens, specifically reduced visual capability, we generated genome sequences with high coverage (average ~18.9×) from Red Junglefowl and indigenous chickens bred in villages of Yunnan province, Southwest China, one of the regions where domestic chickens originated from [8]. Based on these genomes, we characterized potential mechanisms underlying the phenotypic evolution of domestic chickens by comparing genome sequences and integrating transcriptome data from different sub-regions of the brain and the retina.

Results

Positively selected genes in domestic chickens compared with the Red Junglefowl

Variants/genes underlying phenotypic changes in the domestic chicken likely evolved rapidly after domestication. Based on the genomic variation data obtained in this study, we identified candidate genes that potentially underwent rapid evolution in the domestic chickens, and thus might have contributed to the phenotypic differences between domestic chickens and the Red Junglefowl. We first employed an outlier approach to identify candidate selected genes based on the empirical data. This method is free from assumptions of demographic history and is considered to be robust to the confounding effect of population demographic history. Typically, regions or loci evolving rapidly that have experienced selection would show specific signatures of variation, including high population differentiation, significantly reduced nucleotide diversity levels and long-range haplotype homozygosity [9]. Based on these principles, we examined four different parameters to identify footprints of artificial selection associated with the evolution and domestication of chicken (Figure 1, Supplementary information, Figure S1): F_{ST} [10], nucleotide diversity (*Pi*), cross-population extended haplotype homozygosity (XP-EHH) [11] and the cross-population composite likelihood ratio (XP-CLR) [12]. The first percentile rank was used as a threshold to identify candidates throughout the analysis.

A number of protein-coding genes with significant higher F_{ST} (184 genes), XP-EHH (212 genes), XP-CLR (335 genes), and a lower value for nucleotide diversity (*Pi* , 284 genes) were identified, and considered to be potential candidate genes that experienced selection during domestication. Of these genes, only 36 were identified by all four methods (Figure 1C, Supplementary information, Table S12). It is not surprising that the overlap among the positively selected genes (PSGs) detected by the different statistical approaches was underwhelming. First, the distinct statistics applied to scan the genome for positive selection are based on different signatures of population variation [9]. Another reason might be attributable to a pitfall in the outlier approach, whereby an outlier value in one analysis, falling in the 99th percentile of the empirical distribution, may not be classified as an outlier in another study where it may fall within the 98th percentile of the study's empirical distribution [13]. This pattern is very common in studies on positive natural selection in humans. For example, only ~14.1% loci were identified in two or more studies with large-scale genome-wide scans of PSGs [13]. In the current study, possibly due to the above stated factors, no significant enrichment for any functional category associated with vision was found among the candidates identified by the F_{ST} test.

Gene ontology (GO) analysis for the genes showing signatures of positive selection pointed out a significant enrichment for categories associated with the develop-

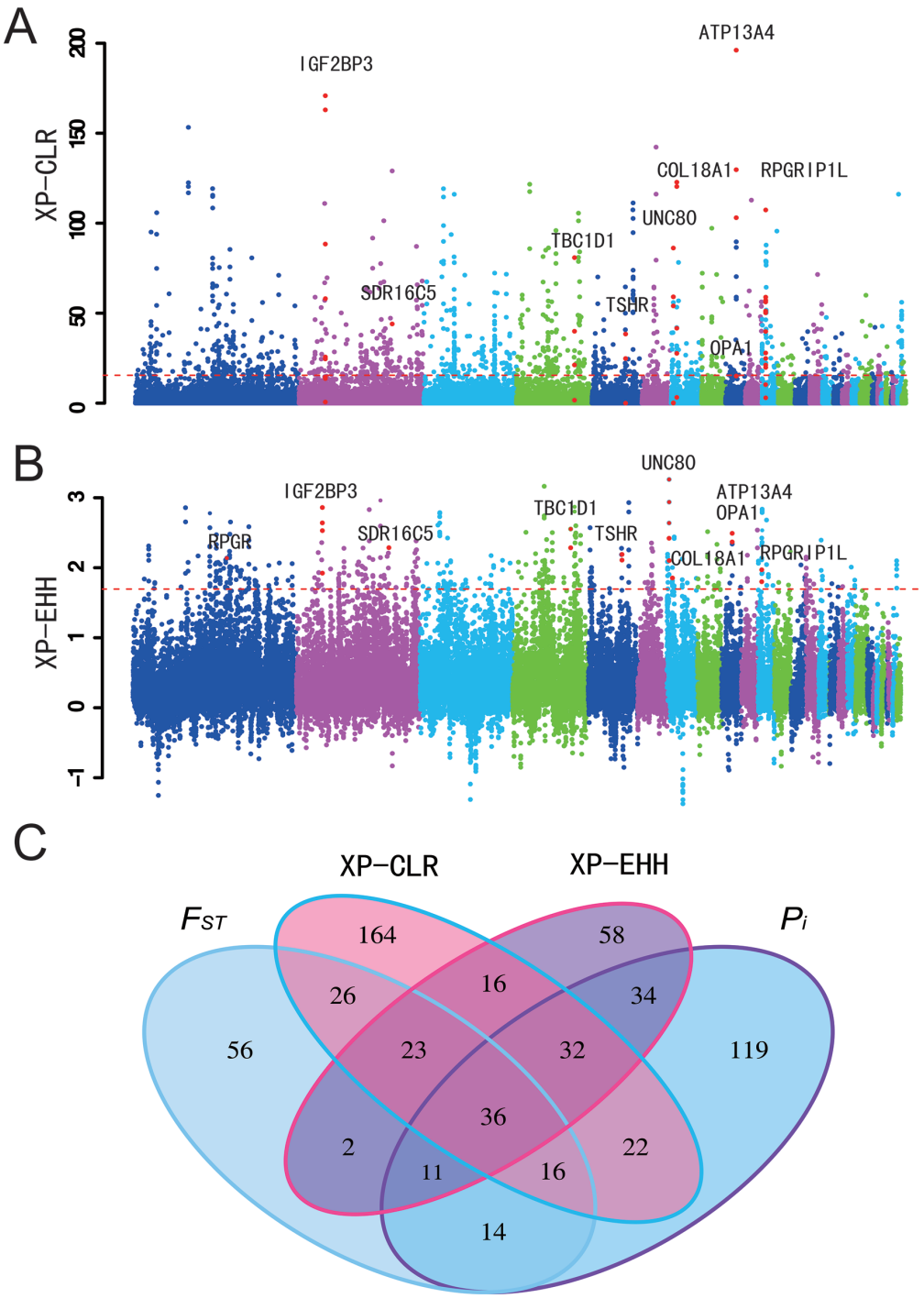

Figure 1 Analysis of the signatures of positive selection in the genome of domestic chickens. Genomic landscape of the XP-CLR values **(A)** and XP-EHH values **(B)** in the genome of domestic chickens. **(C)** Numbers of PSGs identified by the four methods listed in each of the Venn diagram components.

ment of the nervous system (Supplementary information, Tables S8-S11). This finding is not a surprise and is consistent with the rapid evolution of genes in the nervous systems of other domestic animals, which has collectively been attributable to behavioral shifts that accompany domestication [14-18]. In addition, functional enrichment analysis of genes in regions with the top 1% XP-EHH scores revealed that many candidate genes related to the

nervous system were over-represented in the following Human Phenotype Ontology (HPO) categories: abnormality of the nervous system (31 genes), abnormality of the central nervous system (30 genes), and cognitive impairment (25 genes) ($P < 0.05$) (Supplementary information, Table S8). After retrieving regions with the top 1% F_{ST} values, we found that 15 genes significantly over-represented in the HPO categories are related to brain disorders — abnormality of the hindbrain, abnormality of the metencephalon, and abnormality of the cerebellum (Supplementary information, Table S9). Our analysis also picked out these functional categories as regions with low nucleotide diversity (Supplementary information, Table S10). Taken together, these findings suggest that genes involved in both the function and development of the central nervous system showed strong directional selection, which may underlie some of the behavioral alterations occurring during chicken domestication.

For the top 10 SNPs with the highest XP-EHH values, only a single protein-coding gene, *ATP13A4*, was identified. The XP-CLR test also showed that this gene had the most significant XP-CLR values at 10-kb, 5-kb and 2-kb grid sizes (Figure 1; Supplementary information, Figure S2). *ATP13A4* plays vital roles in early neuronal development [19]. It is highly expressed in specific areas of the brain, including the lateral inferior frontal cortex and the temporoparietal cortex, and is associated with benign epilepsy with centrotemporal spikes [20]. It is also associated with speech apraxia among human children [21, 22]. These results collectively suggest that *ATP13A4* likely plays a key role in behavioral evolution during chicken domestication. Similarly, the gene *UNC80*, which has a function in the nervous system [23, 24], also experienced positive selection and had the highest identified XP-EHH score by the sliding window analysis (Figure 1B).

We also identified several other PSGs that are involved in body size development and growth rate, indicative of their role in evolution of the comparatively larger body size among domestic chickens compared to the Red Junglefowl. For example, using different analyses, we identified two genes, *TSHR* and *TBC1D1*, both of which were previously reported to regulate seasonal reproduction and growth among domestic chickens [1, 25]. *IGF2BP3* was identified by its high score in the 10-kb grid size XP-CLR test (Figure 1), and further supported by the 5-kb and 2-kb grid size analyses (Supplementary information, Figure S2). Three other methods that we used in the present study further detected selection signals for this gene (Figure 1, Supplementary information, Figure S1). This is not entirely surprising, as *IGF2BP3*, an important member of the insulin-like growth factor binding protein family, has pro-growth functions via regulating *IGFs* (*IGF1* and *IGF2*) to modulate the insulin signaling pathway [26-28]. Moreover, *IGF2BP3* is located within a QTL region associated with chicken body size (http://www.animalgenome.org/cgi-bin/QTLdb/GG/index) and has differential expression in the muscles of dwarf and normal-sized chickens [29].

To further confirm the findings in this study, we used the Sanger sequencing method to re-sequence and genotype 67 SNPs that cover seven candidate PSGs, *TSHR*, *ATP13A4*, *RPGRIP1L*, *COL18A1*, *VIT*, *OPA1* and *IGF2BP3*, in larger chicken populations. We found that the SNPs genotyped in the larger populations still showed higher F_{ST} values, which is strongly correlated with the genomic analysis ($P < 0.00001$) (Supplementary information, Figure S3 and Table S5). When we compared our candidate PSGs with those identified in the study of Rubin *et al*. [1], only a limited number of genes were shared (Supplementary information, Figure S9). Two important genes, *TSHR* and *TBC1D1*, previously reported by Rubin *et al*. to be involved in regulation of seasonal reproduction and growth in domestic chickens, were again identified to undergo positive selection in our study by the four methods applied.

Positive selection rather than relaxation of purifying selection of vision-related genes in domestic chickens

An additional group of genes possessing signatures of positive selection among the tested domestic chickens was found to be significantly enriched for categories associated with the development and maintenance of the eye as well as vision. Particularly, the PSGs detected by the XP-CLR and *Pi* tests included abnormality of the posterior segment of the eye (19 genes, HP:0004329), nystagmus (18 genes, HP:0000639), abnormality of the fundus (18 genes, HP:0001098), aplasia/hypoplasia affecting the eye (10 genes, HP:0008056), and visual loss (5 genes, HP:0000572) (full details in Table 1). Specific examples in this group are *ZNF469* and *RD3*, with selection signals supported by both XP-CLR and *Pi*, which have vital roles in vision. *ZNF469* encodes a zinc-finger protein and mutations in this gene are associated with brittle cornea syndrome and keratoconus, a common inherited ocular disorder resulting in progressive corneal thinning [30, 31]. *RD3* on the other hand encodes retinal degeneration 3 protein, and mutations in this gene cause Leber congenital amaurosis type 12, a disease that results in photoreceptor degeneration [32].

Positive selection on vision-related genes in the domestic chicken was unexpected since domestic chickens, as previously reported, have a significantly weakened vision compared to their ancestor, the Red Junglefowl [3-5]. Several other studies have proposed that the weakened

Table 1 Gene functional enrichment categories involved in the vision function found in positively selected genes detected by the methods *Pi*, XP-CLR and XP-EHH, and differentially expressed genes detected by Cuffdiff in retina

Methods	*P*-value*	Gene number	Term	Type	Description
Pi	0.0268	5	HP:0000572	hp	Visual loss
(top 1%)	0.0084	4	HP:0000519	hp	Congenital cataract
	0.0184	19	HP:0004329	hp	Abnormality of the posterior segment of the eye
	0.0394	18	HP:0001098	hp	Abnormality of the fundus
	0.0175	5	HP:0001103	hp	Abnormality of the macula
	0.0408	2	HP:0008059	hp	Aplasia/hypoplasia of the macula
XP-CLR	0.0263	4	HP:0000591	hp	Abnormality of the sclera
(top 1%)	0.0163	4	HP:0000592	hp	Blue sclerae
	0.0109	18	HP:0000639	hp	Nystagmus
	0.0118	10	HP:0008056	hp	Aplasia/hypoplasia affecting the eye
	0.0271	5	HP:0008062	hp	Aplasia/hypoplasia affecting the anterior segment of the eye
	0.046	4	HP:0008055	hp	Aplasia/hypoplasia affecting the uvea
	0.0428	4	HP:0008053	hp	Aplasia/hypoplasia of the iris
	0.0204	5	HP:0001103	hp	Abnormality of the macula
	0.0155	2	HP:0000493	hp	Abnormality of the fovea
	0.00277	3	HP:0008061	hp	Aplasia/hypoplasia affecting the retina
	0.00197	3	HP:0008059	hp	Aplasia/hypoplasia of the macula
	0.0105	2	HP:0008060	hp	Aplasia/hypoplasia of the fovea
	0.0105	2	HP:0007750	hp	Hypoplasia of the fovea
XP-EHH	0.0429	3	HP:0000608	hp	Macular degeneration
(top 1%)					
Cuffdiff analyses	0.0262	2	HP:0007663	hp	Decreased central vision
in retina	0.0395	4	HP:0000662	hp	Night blindness
	0.0164	2	HP:0007642	hp	Congenital stationary night blindness
	0.05	4	HP:0000512	hp	Abnormal electroretinogram
	0.05	2	KEGG:04744	ke	Phototransduction

**P*-values are corrected by Benjamini-Hochberg FDR.
No category involved in the vision function was found to be enriched among positively selected genes detected by the F_{ST} method.

visual ability observed in domestic chickens is attributed to relaxation of functional constraints during domestication [3, 4].

Functional enrichment analysis of the 36 genes that overlapped among the candidate gene lists identified by the four different methods showed that several genes are associated with vision-related functional categories — abnormality of the eye/vision (*OPA1*, *COL18A1*, *RPGRIP1L* and *NBAS*), and visual impairment (*OPA1*, *COL18A1* and *RPGRIP1L*) (Supplementary information, Table S13). *COL18A1* encodes the alpha subunit of type XVIII collagen and mutations in this gene are associated with Knobloch syndrome [33, 34], which features high myopia, vitreoretinal degeneration with retinal detachment, and macular abnormalities in humans. *Col18a1*$^{-/-}$ knockout mice display abnormalities in their iris and ciliary bodies, and retina vessel regression. These mice also show abnormal deposits between the basal infoldings of the retinal pigment epithelium, which could result in deterioration of retinal pigment epithelium function and attenuation of visual function as well as pathological electroretinograms (ERG) [35-38]. *OPA1*, encoding a dynamin-like mitochondrial GTPase, is reported to be involved in an autosomal dominant optic atrophy, which is known as Kjer's optic atrophy. It affects retinal ganglion cells and axons forming the optic nerve and leads to progressive visual loss [39, 40].

Demographic history, relaxation of purifying selection and hitchhiking could confound the detection of positive selection. The outlier approach to identify candidate genes used above is based on empirical data that is free from any assumption concerning demographic history, and is considered to be robust to the confounding effects of population demographic history, where genome-wide

forces affect the patterns of variation at all loci in a genome in a similar manner, whereas directional selection specifically acts on certain loci [9]. Notwithstanding the outlier approach already applied, we further performed coalescent simulation analysis based on simulated demographic histories (Supplementary information, Figure S4), and found that the candidate PSGs identified by the outlier approach still harbored statistically significant signals compared with simulated data (Figure 2A-2C). To exclude the possibility that hitchhiking possibly contributed to the signatures of selection on the vision-related genes, we retrieved the vision-related genes potentially

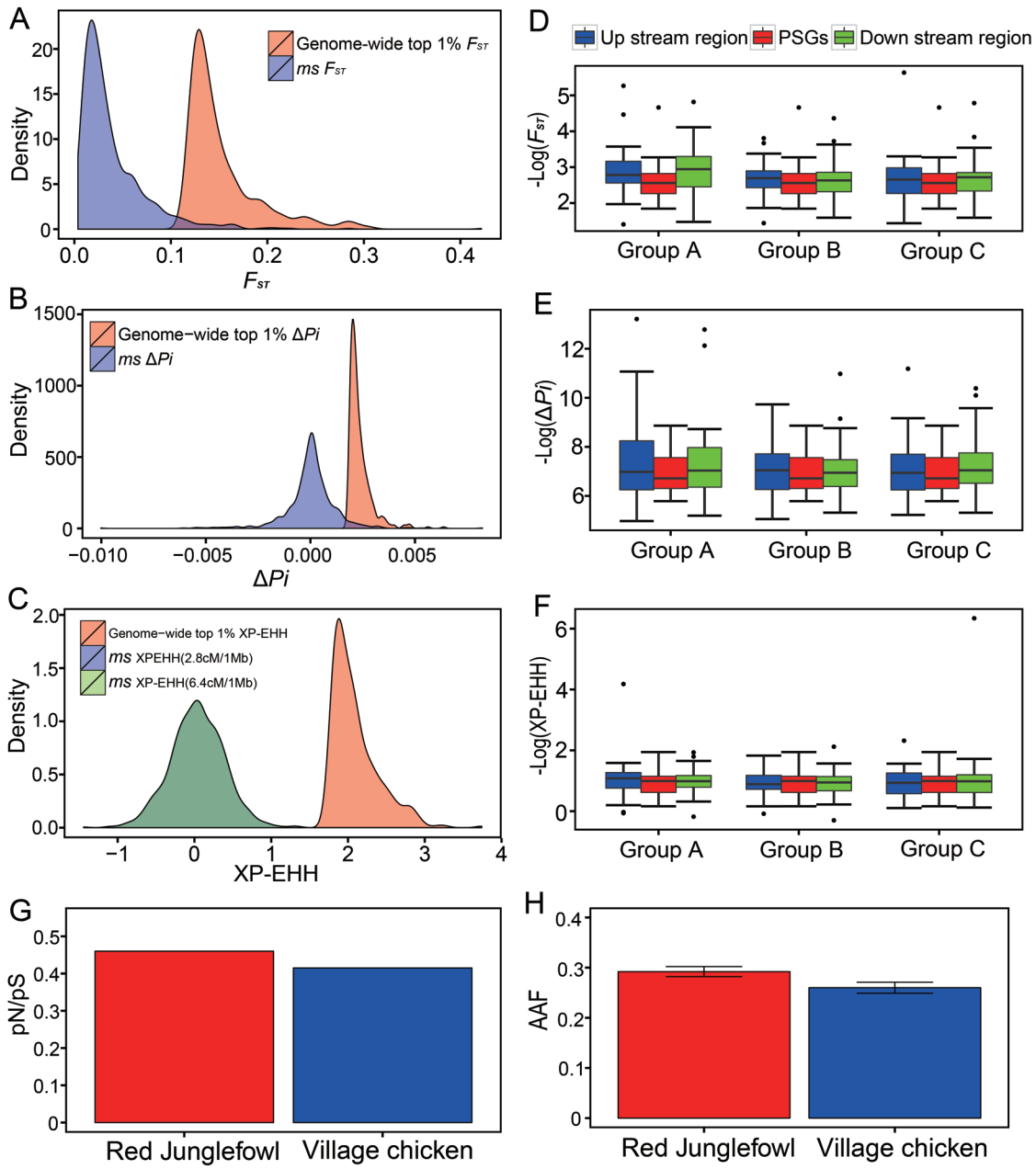

Figure 2 Positive selection on genes involved in vision. **(A-C)** Coalescent simulations (ms) of positive selection detected by F_{ST} **(A)**, *Pi* **(B)** and XP-EHH **(C)**. **(D-F)** F_{ST} **(D)**, *Pi* **(E)** and XP-EHH **(F)** values for the visual-related candidate genes compared with the values for their upstream/downstream sequences with the same length as the gene (Group A), adjacent genes (Group B) and upstream/downstream 50 kb sequences (Group C). **(G)** The ratio of the numbers of non-synonymous SNPs to the numbers of synonymous SNPs (pN/pS). **(H)** the alternative allele frequency (AAF) of the visual-related candidate genes in the village chickens and Red Junglefowl.

undergoing positive selection and compared the pattern of variation in regions upstream and downstream of the genes to that of variation within these vision-related genes. As expected, these vision-related genes harbored higher levels of population differentiation, and higher values of XP-EHH values, than adjacent genes and regions (Figure 2D-2F).

The ratio of non-synonymous to synonymous substitution rates (pN/pS) in the coding sequences was used to assess the relaxation of purifying selection, in which case pN/pS should increase [41, 42]. In this analysis, we retrieved SNPs in vision-related genes identified under potential positive selection by the four methods, and counted the numbers of SNPs unique to the domestic chicken or Red Junglefowl. We found lower pN/pS in domestic chicken than in the Red Junglefowl (Figure 2G). Compared with the Red Junglefowl, domestic chickens harbored a lower frequency of alternative alleles (Figure 2H). In addition, we employed different methods based on different population genetic theories to detect positive selection, which could possibly reduce the false discovery rate due to the relaxation of purifying selection and/or demographic history. Our analyses indicated a strong unlikelihood that relaxation of purifying selection occurred in the genes associated with vision.

Differential expression of PSGs in the retina between domestic chickens and Red Junglefowl

Since our results on positive selection in vision-related genes were somewhat surprising, given previous viewpoints [3, 4], we sought to better understand the evolution of the domestic chicken by sequencing (via RNA-seq) transcriptomes from five tissues (cerebral cortex, corpus striatum, optic lobe, cerebellar vermis, and retina) from the Red Junglefowl and domestic chickens. We calculated differences in expression levels for each gene between Red Junglefowl and domestic chickens (see Materials and Methods). This analysis showed that genes with signatures of positive selection presented significantly higher levels of expressional difference in retinal tissue between the domestic chicken and Red Junglefowl than other genes (Figure 3A-3D, F_{ST}, $P = 0.075$; *Pi*, $P = 2.99 \times 10^{-7}$; XP-CLR, $P = 0.015$; and XP-EHH, $P = 5.50 \times 10^{4}$, Mann-Whitney *U*-test). We sought to verify and replicate this result by profiling another 10 transcriptomes (6 transcriptomes of 3 retina from 3 Red Junglefowls and 4 transcriptomes of 2 retina from 2 village chickens) with two replications per sample using a different sequencing platform (see Materials and Methods). The results remained synonymous to the earlier analysis when the data from two platforms were analyzed separately (Supplementary information, Figure S5A, F_{ST}, $P = 0.104$; *Pi*, $P = 0.018$; XP-CLR, $P = 0.178$; and XP-EHH, $P = 0.005$, Mann-Whitney *U* test), or jointly (Supplementary information, Figure S5B, F_{ST}, $P = 0.040$; *Pi*, $P = 2.23 \times 10^{-4}$; XP-CLR, $P = 0.049$; and XP-EHH, $P = 8.52 \times 10^{-4}$, Mann-Whitney *U* test). However, the four brain regions did not show significantly differential expression patterns except for the corpus striatum by the *Pi* method (Figure 3B, $P = 0.036$, Mann-Whitney *U* test). It is possible that some PSGs are upregulated while others are downregulated in the brains of the village chickens, resulting in the non-significant variations noted when all PSGs were analyzed together. In addition, a greater number of PSGs exhibited expression level changes between the Red Junglefowl and village chicken in the eye than any of the four brain regions (Supplementary information, Figure S6). This pattern supports the hypothesis that positive selection drove changes in the regulation of gene expression that attenuated vision in the domestic chickens.

We then used Cuffdiff [43] to retrieve a series of genes that exhibited significant differential expression between the Red Junglefowl and domestic chicken in the cerebral cortex (137 genes), corpus striatum (24 genes), cerebellar vermis (9 genes), optic lobe (19 genes), and the retina (57 genes). Functional enrichment analysis of the 57 differentially expressed genes in the retina between the Red Junglefowl and domestic chickens showed that four genes (*RPGR*, *GUCA1A*, *TRPM1* and *PDE6B*) were involved in several HPO categories including decreased central vision, congenital stationary night blindness, and abnormal ERG (Table 1). We verified the differential expression of these four genes, as well as two additional genes that are important for vision, *RHO* [44] and *NR2E3* [45-47], via quantitative real-time PCR (qPCR) for retina mRNA (Figure 3E). Differences in gene expression measured by qPCR and RNA-seq were significantly correlated (Figure 3F). The significant changes in the mRNA expression in the retina between Red Junglefowl and the domestic chickens potentially have functional consequences in vision due to their respective functions. For example, *NR2E3* (photoreceptor cell-specific nuclear receptor, group E, member 3) is a vital transcriptional regulator essential for photoreceptor development and differentiation due to its capability as an activator of rod cell development and a repressor of cone development [45-47]. In domestic chickens, downregulation of *NR2E3* expression is associated with weaker visual ability and lower optical sensitivity [3]. Similarly, *RHO* (rhodopsin), *GUCA1A* (guanylate cyclase activator 1A) and *PDE6B* (phosphodiesterase 6B) are all vital genes in the phototransduction pathway [44, 48, 49]. Among domestic chickens, expression of *GUCA1A*, *PDE6B* and *RHO* were downregulated in the retina, suggesting a depres-

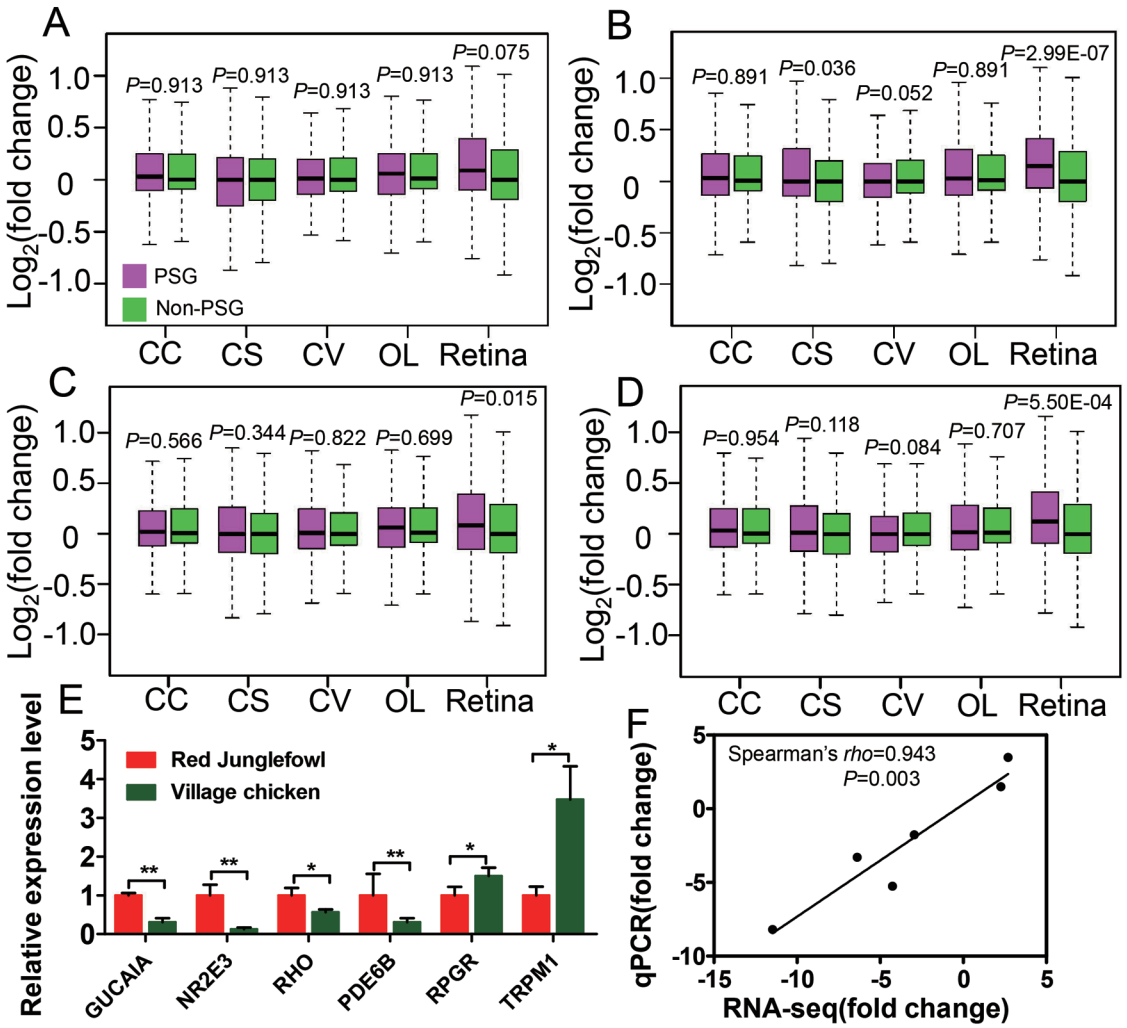

Figure 3 Gene expression for PSGs in five tissues (cerebral cortex (CC), corpus striatum (CS), cerebellar vermis (CV), optic lobe (OL), and retina) comparing domestic chickens and Red Junglefowl. **(A-D)** PSGs as identified by F_{ST} **(A)**, *Pi* **(B)**, XP-CLR **(C)** and XP-EHH **(D)**. **(E)** Difference in expression for six genes between the village chicken and Red Junglefowl in the retina verified by qPCR. **(F)** Correlation of the gene expression measured by qPCR versus RNA-seq. Fold change, implying $(FPKM + 1)_{VC}/(FPKM + 1)_{RJF}$ for each gene. Statistical significance is indicated by *, where $P < 0.05$, and **, where $P < 0.01$.

sion in the phototransduction pathway in the domestic chicken. In addition, *RPRG* and *TRPM1* exhibited upregulation in domestic chickens. Both genes play important roles in vision [50, 51], for instance, *RPGR* encodes a retinitis pigmentosa GTPase regulator and overexpression of a *RPGR* transcript leads to severe photoreceptor degeneration in mice [52].

Functional analysis of VIT, a PSG presumably involved in vision

PSGs presented significantly higher levels of differential gene expression in retinal tissue between the domestic chicken and Red Junglefowl and differentially expressed genes in retinal tissue were also involved in visual ability. However, only two genes, *RPGR* and *VIT*, were identified to undergo positive selection in domestic chicken (Figure 1B; Supplementary information, Figure S1B; Figures 3E, 4A-4C). *RPGR* was supported with signal of positive selection by both *Pi* and XP-EHH tests (the first percentile rank as threshold) (Figure 1B; Supplementary information, Figure S1B) and had an increased level of expression in village chickens compared to Red Junglefowl (Figure 3E). Mutations in *RPGR* are associated with X-linked retinitis pigmentosa (XLRP) and result in severe and progressive loss of vision in dogs and humans [50]. The second gene, *VIT*, showed a higher level of population differentiation (F_{ST}) and lower level of nucleotide diversity (*Pi*) in village chickens (Figure 4A),

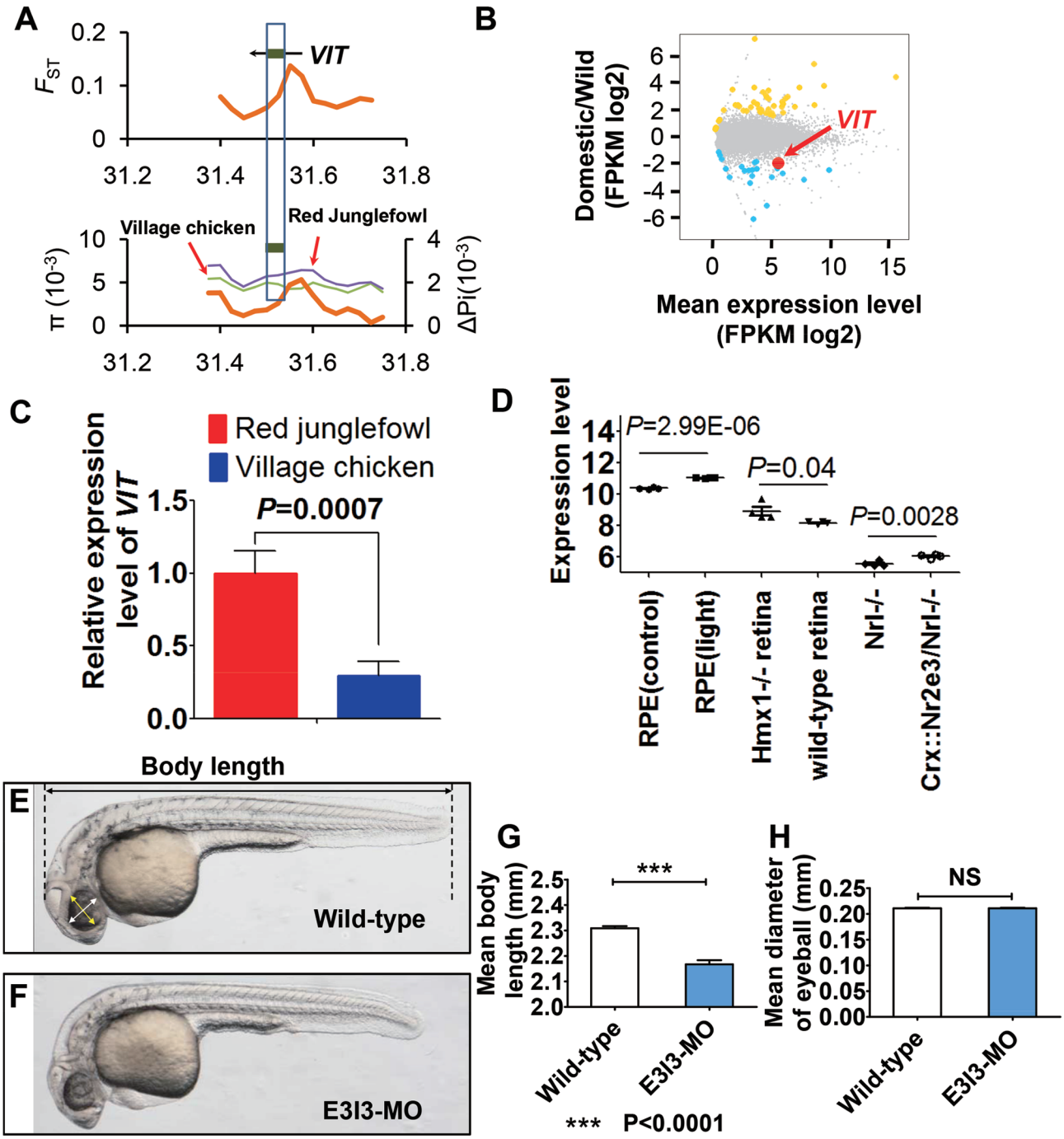

Figure 4 Signal of positive selection and knockdown array of *VIT* in zebrafish. **(A)** F_{ST} and *Pi* values showed selection signal for *VIT* gene. **(B)** RNA-seq analysis presented differential expression of *VIT*. **(C)** qPCR confirmation of the downregulation of *VIT* in retinal tissue between the domestic chicken and Red Junglefowl. **(D)** Expression analysis of *VIT* in mice. Expression profiling in retinal pigment epithelium (RPE) of mice exposed to 10 000 lux of cool white fluorescent light for 18 h was based on expression data of retina from *Hmx1* loss-of-function mice (GSE37773) and wild-type mice (GSE47002), and expression data from photoreceptor cells of *Nrl*$^{-/-}$ mice and *Crx::Nr2e3/Nrl*$^{-/-}$ mice (GSE5338). **(E-F)** Lateral view of a zebrafish with measurements of body length **(E)** and eyeball diameter **(F)**. Scale bar, 0.5 mm. **(G-H)** Body lengths **(G)** and eyeball diameters **(H)** of embryos injected with *VIT-e3i3*-MO (E3I3-MO) or wild-type control at 32 h post-fertilization (hpf) (*VIT* morphants and control embryos, *n* = 10 each; mean ± SEM). Body length is significantly decreased in *VIT* morphants; **P* < 0.0001; NS, not significant.

and was found to show significant differential expression in the retinal tissue in domestic chicken compared to Red Junglefowl (Figure 4B). Results from qPCR further confirmed the downregulation of *VIT* in the village chicken compared with Red Junglefowl (Figure 4C). Until now, the function of *VIT* remains unclear. However, it demonstrated specific expression in the eye in the mice (Supplementary information, Figure S7), leading us to reason that *VIT* is likely involved in vision and that downregulation of *VIT* expression might play a role in the evolution of vision in domestic chicken.

To obtain a better understanding of the function of *VIT,* we first examined the *VIT* expression data available for the mouse. Expression of *VIT* was significantly upregulated in the retinal pigment epithelium of mice after exposure to 10 000 lux of cool white fluorescent light for

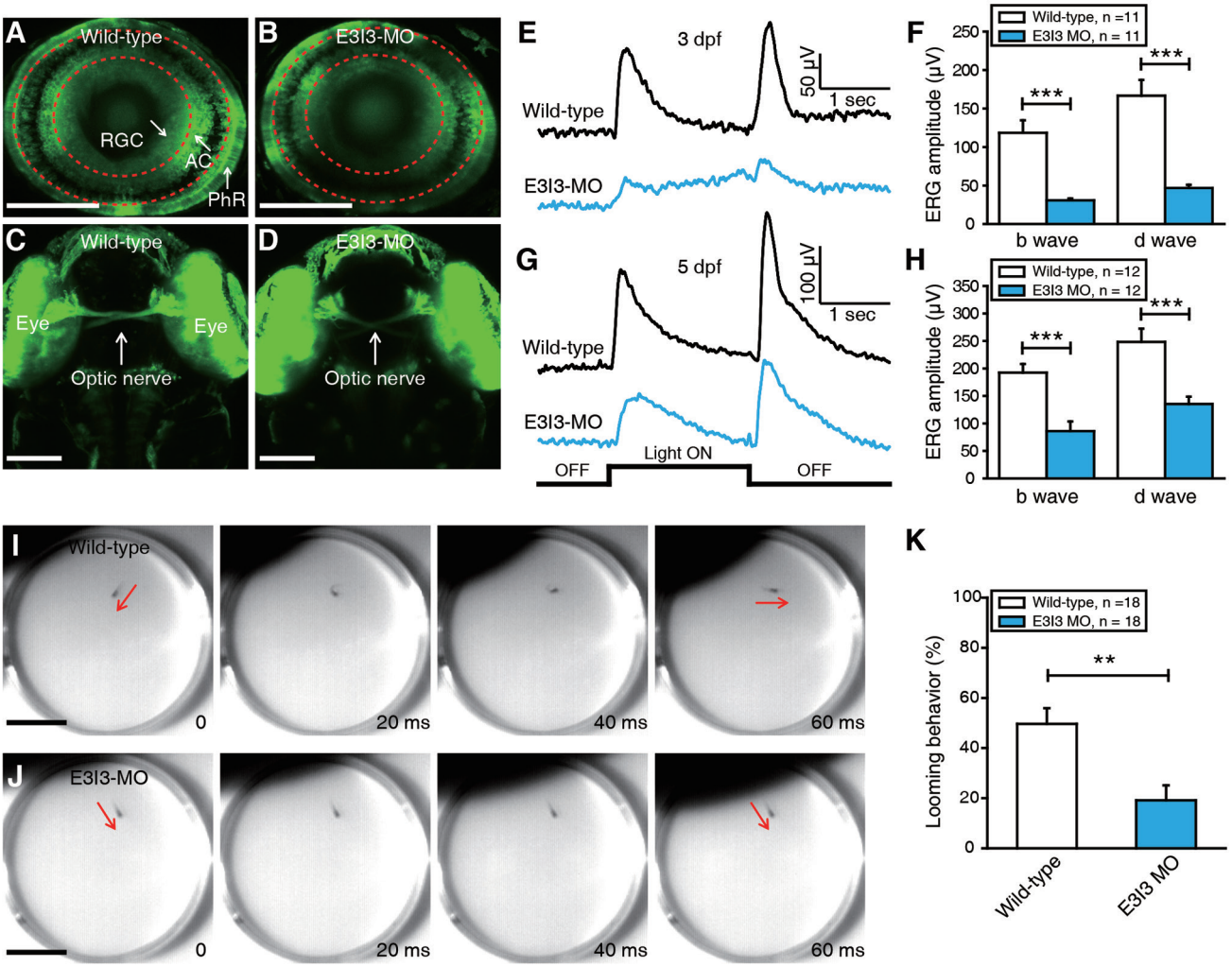

Figure 5 Electrophysiological recordings and behavioral tests showed that *VIT* is necessary for normal physiological function of zebrafish retina. **(A**, **B)** Confocal images showing GCaMP1.6 expression in photoreceptors (PhR), retinal ganglion cells (RGC) and amacrine cells (AC) of a 3-dpf Tg (Ath5-gal4:UAS-GCaMP1.6) larva **(A)** and a *VIT* morphant **(B)**. The two red dash circles indicate the position of inner and outer plexiform layers. Scale bar, 100 μm. **(C**, **D)** Confocal images showing the projection of optic nerves from two eyes of a 3-dpf wild-type larva **(C)** and a *VIT* morphant **(D)**. Scale bar, 100 μm. **(E**, **G)** ERG recording averaged from ten responses to a 2-s light ON stimulus in 3-dpf **(E)** or 5-dpf **(G)** wild-type larvae and *VIT* morphant. **(F**, **H)** Summary of ERG recording data at 3 **(F)** or 5 dpf **(H)**. **(I**, **J)** Examples showing a looming stimulus-induced escape behavior in a 5-dpf wild-type larva **(I)**, but not in a 5-dpf *VIT* morphant **(J)**. The red arrows indicate the body axis of the larvae before and after looming-induced C-startle escape. Scale bar, 1 cm. **(K)** Summary of data showing the probability of looming-induced escape behaviors in 5-dpf wild-type larvae and *VIT* morphant. The number in the inset of **F**, **H** and **K** represents the number of larvae examined. $^{**}P < 0.01$, $^{***}P < 0.001$; two-tailed unpaired Student's *t*-test for the data in **F**, **H** and **K**. Data are represented as mean ± SEM.

18 h (Figure 4D). Expression of *VIT* also changed after the knockout of several genes that are crucial for the development of vision. For example, *VIT* was upregulated in the retina of *Hmx1*-knockout mice (Figure 4D). *Hmx1* (H6 family homeobox 1) is a transcription factor crucial for the development of the eye. Other transcriptional regulators like *NRL*, *CRX* and *NR2E3*, are also important for photoreceptor differentiation [46]. From a past study, endogenous *NR2E3* transcript or protein was not detectable in the retina of $Nrl^{-/-}$ mice [46]. However, when exogenous *NR2E3* was expressed in post-mitotic photoreceptor precursors using the *Crx* promoter in $Nrl^{-/-}$ mice, expression of *VIT* was significantly upregulated (Figure 4D). Consistently, the expression levels of both *NR2E3* and *VIT* were lower in village chicken than in Red Junglefowl. These expression data suggest a potential function of *VIT* in vision.

To further study the function of *VIT*, we performed a knockdown array of *VIT* in zebrafish (*Daniorerio*) embryos by targeting its expression with a specific antisense morpholino (MO) oligonucleotide preventing the proper splicing of exon 3 (E3I3-MO) (Figure 4E-4H). While the body length of *VIT*-knockdown zebrafish is significantly decreased compared with controls (Figure 4G), no significant change in eye size was observed (Figure 4H), suggesting that the phenotypic effects of *VIT* knockdown are in tissues other than the eye in the zebrafish. However, since expression of *VIT* is highly eye-specific in mice (Supplementary information, Figure S7), downregulation of *VIT* might have greater influence on the eye than other tissues in species such as chicken. We then examined the effect of *VIT* knockdown on the general morphology of the zebrafish retina by using Tg (Ath5-gal4:UAS-GCaMP1.6) larvae, where most photoreceptors, retinal ganglion cells and some amacrine cells are labeled with GCaMP1.6 (Figure 5A). Compared with control larvae, the general structure of the retinal layers and the projection of the optic nerves were not changed in the *VIT* morphant (Figure 5A-5D), consistent with the above observation that there is no significant change in eye size between control and *VIT* morphant (Figure 4H).

To determine whether the knockdown of *VIT* gene leads to defective retinal function, we performed electrophysiological recordings and behavioral tests. Application of a 2-s whole-field flash near the eyes of zebrafish elicited a clear ERG response from the eye, where b and d waves occurred at the onset and the offset of the flash, respectively (Figure 5E). Knockdown of *VIT* dramatically decreased the amplitude of b and d waves in both 3-dpf and 5-dpf larvae (Figure 5E-5H). Since b and d waves are generated mainly by ON and OFF bipolar cells, respectively [53], this result indicates that *VIT* might be necessary for the normal function of bipolar cells. Furthermore, we examined the effect of *VIT* knockdown on visual-induced escape behaviors. A looming stimulus, an expanding black disc, was applied to mimic the approaching of a predator in the natural environment. Wild-type larva exhibited a fast C-shape escape response to an approaching looming stimulus (Figure 5I), but this visual behavior was largely impaired in the *VIT* morphant (Figure 5J and 5K).

Apoptosis plays an important role in embryogenesis and tissue homeostasis [54]. The early steps in eye development involve extensive cell death associated with morphogenesis, and the suppression of apoptosis in cells of the lens lineage by fibroblast growth factors is an important component of lens morphogenesis [55]. We therefore examined the role of *VIT* in apoptosis in developing eyes by staining zebrafish embryos with acridine orange (AO). We detected few apoptotic cells in wild-type control zebrafish. In contrast, significantly increased levels of staining were observed throughout the eyes of zebrafish injected with 4 ng of *VIT*-e3i3-MO (the antisense MO oligonucleotide), suggesting increased levels of apoptosis (Figure 6). In addition, we detected increased levels of apoptosis in other tissues including brain and heart (Figure 6, Supplementary information, Figure S8).

All these analyses collectively indicate that the *VIT* gene is necessary for normal physiological function of zebrafish retina, and the evolutionary changes in *VIT* might play a vital role in the evolution of vision in the domestic chicken.

Discussion

By an extensive analysis of the genome sequences of Red Junglefowl and village chickens, we found that a series of vision-related genes have undergone positive selection rather than relaxation of purifying selection in domestic chickens. In particular, *VIT* likely has a function in vision and the evolution of *VIT* might play a role in the evolution of vision in domestic chicken. A caveat of our approach is that the individuals studied possibly do not represent the entirety of genetic variation seen among chickens.

Functional enrichment analysis showed that a group of genes identified by several approaches based on the genomic and transcriptomic data were involved in the vision-related categories. We compared our result with a previous report by Rubin *et al.* [1]. Only limited number of genes overlapped (Supplementary information, Figure S9), among which were two important domestication-related genes, *TSHR* and *TBC1D1*. The limited overlap between our report and study by Rubin *et al.* [1]

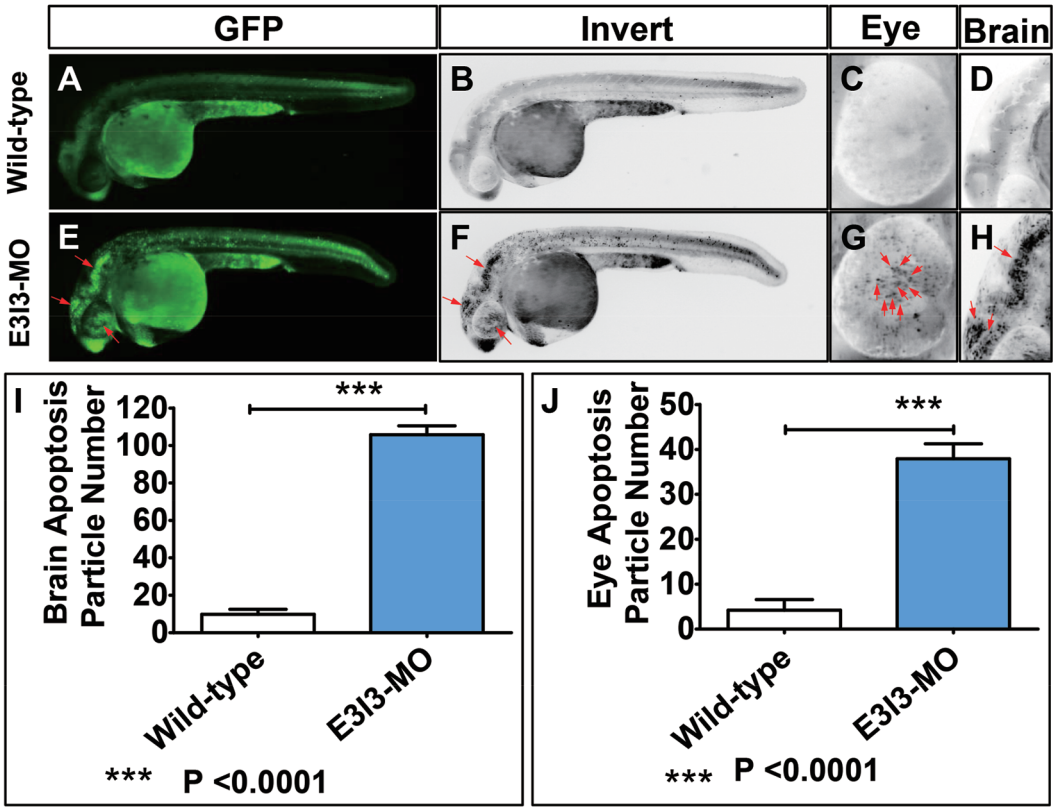

Figure 6 Morpholino knockdown of *VIT* induces potent apoptosis in the eye and brain. Wild-type control embryos and embryos injected with *VIT*-e3i3-MO (E3I3-MO) were stained with acridine orange (AO) at 32 hpf. Apoptotic cells are visible as bright green spots or black spots, and less bright homogenous green or black staining, an unspecific background staining. **(A-D)** Uninjected wild-type control zebrafish exhibited few or no apoptotic cells in whole organism. In contrast, significantly increased staining was observed throughout the brain and eye in zebrafish injected with 4 ng *VIT*-e3i3-MO **(E-H**, red arrows). Lateral view, anterior, left **(A-H)**. **(I)** Quantification of apoptosis particle number in brain shows a 10-fold increase in *VIT* morphants (n = 10) at 32 hpf. **(J)** Quantification of apoptosis particle number in eye shows a 9-fold increase in *VIT* morphants (n = 10) at 32 hpf.

might be due to differences in sequencing and statistical approaches or the use of different chicken breeds. The complicated history of domestic chicken could also contribute to the observed differences [56]. However, functional enrichment analyses of PSGs reported by Rubin and colleagues showed that many of the genes identified in all domestic lines (AD), commercial broiler lines (CB) as well as in layer lines were functionally involved in vision-related categories (Supplementary information, Table S14-S16), which is synonymous with our results. Since the precise nature of the variations that were selected in our study remain unclear, additional functional, biotechnological and physiological experiments will be needed to identify the mechanisms that explain the attenuated vision in domestic chickens.

Using the parsimony principle, the comparatively weaker eyesight in domestic chickens has been explained as a consequence of relaxation of the functional constraints, as domestic chickens are far less dependent on vision for their behaviors like foraging, avoiding predators and mate choice. They live in a predictable farm environment compared to the Red Junglefowl, which does not require acute vision for survival. However, our present study identified many candidate genes involved in the development of vision with signatures of positive selection, including lower nucleotide diversity and long range of haplotype homozygosity, rather than signatures of relaxation of purifying selection. Moreover, the PSGs show significant changes in their expression in the retina between village chickens and Red Junglefowl. Weakened visual ability in domestic chickens as a by-product of artificial selection on other traits, such as large body size, could be another possibility. Larger body size, for instance, could induce larger eyes that may lose optical

sensitivity [3]. Nevertheless, it is implausible that the large number of genes involved in vision with signatures of positive selection identified in our study (Table 1) could be due to hitchhiking with other genes involved in other selected traits, such as body size. First, vision-related genes are distributed on multiple chromosomes, and thus each gene would have to hitchhike. Second, the levels of population differentiation and XP-EHH values within each of the vision-related genes were higher than those for the adjacent regions/genes, showing that hitchhiking could not generate the signatures of selection seen in these vision-related genes (Figure 2).

It is evident that hitchhiking, relaxation of selection or demographic history cannot offer a concrete explanation to our findings. However, nearly 150 years ago, Darwin mentioned a kind of selection that may be unconscious [57]. Given the results of this study, we propose that during domestication, this unconscious selection may have driven the weakening of vision among domestic chickens. Birds gather visual information through a scanning behavior (also known as vigilance) to make decisions relevant for survival (e.g., detecting predators, making mating choices and finding food) [58]. Presumably, the progenitors of domestic chickens that harbored weaker vision may also have possessed a reduced fear response hence vigilance, allowing them to be more easily caught, reared, and domestic by humans. Chickens with higher constant vigilance would not be easily kept in a cage, particularly in the evening, and thus might not have been selected for domestication. In addition, growth and egg production improves with blindness in chickens. Blind chickens tend to thrive better under more crowded conditions than their sighted counterparts [59]. It is therefore plausible to reason that selection on behavior — which is well documented for many domestic species [17] — unknowingly promoted the selection for chickens with weakened vision.

Dogs also harbor weaker visual acuity compared to their wild ancestors, however, in contrast to chickens, there was no evidence for positive selection in vision-related genes in previous studies [14-16]. Vision is important in birds for survival [58], but other sensory abilities including hearing and smell, might play more important roles in mammals. In dogs, many hypotheses have been proposed to explain the tameness necessary for successful domestication [17]. In chickens, besides behavioral evolution, the evolution of vision might have also been important for successful domestication. Clearly, more targeted studies should clarify this hypothesis, but at the moment this explanation offers a compelling model that may shift some of our perspectives on the genetic history of human-driven domestication of key animals, and raise the appreciation of unconscious selection in the characterization of the evolution of domestic animals [60].

Materials and Methods

This study was approved by the Ethics and Experimental Animal Committee of Kunming Institute of Zoology, Chinese Academy of Science, China.

Genomic and RNA-seq data collection

Genome sequences of domestic chickens from the area of origin might be more suitable for revealing the phenotypic changes after early domestication from the Red Junglefowls (RJF), than those from commercial layer and broiler chickens bred during the 20th century in Europe. To identify potential underlying gene/variants responsible for phenotypic changes in domestic chickens, we used genome re-sequencing data with high-depth from 5 RJFs and 8 village chicken (VCs) bred as a food source in the villages of Yunnan Province, Southwest China, an area believed to be one of the origins for domestic chickens [8] (Supplementary information, Table S1). We also obtained RNA-seq data for the retina and four regions of the brain (cerebral cortex, corpus striatum, optic lobe, and cerebellar vermis) from RJF and VC. RNA-seq libraries with insert size around 300 bp were prepared using the Illumina standard RNA-seq library preparation pipeline and sequenced on the Illumina Hiseq 2000 platform (Supplementary information, Table S2). In total, transcriptomes of three retinas, two cerebral cortex, two cerebellar vermis, one corpus striatum and two optic lobes for VCs and two retinas, one cerebral cortex, one cerebellar vermis, one corpus striatum and one optic lobe for RJFs were used to perform comparative analysis. In addition, another ten transcriptomes were re-sequenced to verify the results, including six transcriptomes of three retinas from three RJF, and four transcriptomes of two retinas from two VCs with two experimental repeats per sample on the Hiseq 4000 platform (Supplementary information, Table S2). Sequencing data from this study have been submitted to the NCBI Sequence Read Archive (SRA; http://www.ncbi.nlm.nih.gov/sra) under accession number SRP040477.

Genomic sequence alignment and genotyping

Sequence reads were filtered by removing adaptors and low-quality bases using cutadaptor and Btrim [61] (http://graphics.med.yale.edu/trim/). Only qualified paired-end reads were aligned onto the chicken reference genome (Galgal4) using BWA-MEM with default settings, except "-t 8 -M" options (https://github.com/lh3/bwa). A series of post-processes were then carried out with the alignment bam format file, including sorting, duplicate marking, local realignment and base quality recalibration. All of them were carried out using the relevant tools from the Picards 1.56 (http://picard.sourceforge.net) and Genome Analysis Toolkit 2.6 [62] (GATK). SNPs and indels were called and filtered using UnifiedGenotyper and VariantFiltration command in GATK. Loci with more than 2 alleles were removed. All SNPs were assigned to specific genomic regions and genes using ANNOVAR [63] based on the Ensembl chicken annotations.

A total of 17 115 375 SNPs were identified, around half (51.6%) of which were mapped to intergenic regions in the genome (Sup-

plementary information, Table S3). Among the SNPs that locate to protein-coding regions, 70 990 were non-synonymous and 174 748 were synonymous, with 445 genes (including 446 transcripts) having SNPs that cause the gain or loss of a stop codon (Supplementary information, Table S4).

Genome-wide selective sweep scans

To identify genomic regions harboring footprints of positive selection in native chickens, we employed multiple tests to investigate selection in both populations and in a single population. Here, we used the F_{ST}, *Pi*, XP-EHH and XP-CLR statistical methods. F_{ST} values for each SNP were calculated between RJF and VC as previously described [10]. Nucleotide diversities ($\Delta\pi$ or ΔPi) = $\pi_{RJF} - \pi_{VC}$ were calculated using a sliding window analysis with a window size of 50 kb and a step size of 25 kb. XP-EHH value for each variant was calculated according to [11]. XP-CLR test [12] was performed with scripts available at http://genetics.med.harvard.edu/reich/Reich_Lab/Software.html using the following parameters: sliding window size 0.1 cM, grid size 10 k, maximum number of SNPs within a window 300, correlation value for 2 SNPs weighted with a cutoff of 0.99. Here, VC was taken to be the object population, and RJF was chosen as the reference population. Haplotypes for each chromosome were deduced by shapeit.v2.r727 [64] (http://www.shapeit.fr/). General genetic map for chicken used here was 2.8 cM/Mb for chr1-9 and 6.4 cM/Mb for chr10-28 and chr32 [65].

SNP validation in larger population

We choose 67 SNPs that were mapped to the *TSHR*, *ATP13A4*, *RPGRIP1L*, *COL18A1*, *VIT*, *OPA1*, *IGF2BP3* and *MAP3K5* genes (see Supplementary information, Table S5) to validate in larger population, including ~25 RJFs and ~20 VCs by Sanger sequencing. Primer pairs used for these genes are listed in Supplementary information, Table S6.

Demographic history and coalescent simulations

Demographic histories for RJF and VC were inferred using MSMC [66] based on haplotypes from multiple individuals in each population. We performed our analysis using 2 individuals (4 haplotypes), 3 individuals (6 haplotypes), 4 individuals (8 haplotypes) and 5 individuals (10 haplotypes) for each group (VC and RJF) independently. To assess the significance of the selective sweep signals identified by the above-mentioned methods, we stimulated two groups of genome sequences (one for VC and one for RJF) under a neutral evolutionary model taking into account the inferred demographic history. Coalescent simulations were performed using the ms program [67]. In total, 26 sequences of 50 kb were simulated 1 000 times and applied to the F_{ST} and *Pi* test. In addition, 26 sequences of 1 Mb were simulated 1 000 times and the mean XP-EHH value of the middle 50 kb (475-525 kb) in each simulated sequence was calculated as simulated data. Population sizes for the common ancestors (> 8 kya and ~2 kya) of RJF and VC were obtained from our MSMC analysis. Since MSMC has a low power to estimate population size at relatively recent times, the effective population sizes for present day RJF and VC populations were taken from elsewhere [68] (1.6×10^5 and 4×10^5, respectively). Generation time (g) and mutation rate per year (u) for chicken used here is 1 year and 1.91×10^{-9}, respectively [69].

Scripts used for simulation were as follows:

For F_{ST} and *Pi:*

ms 26 1000 -T -I 2 10 16 -t 191 -en 0.003 1 0.16 -en 0.003 2 0.22 -en 0.001 1 0.8 -eg 0.001 1 0 -en 0.001 2 0.32 -eg 0.001 2 0 -ej 0.004 1 2 | tail -n +4 | grep -v // >fst-pi-treefile

seq-gen -mHKY -l 50000 -s .017 <fst-pi-treefile> fst-pi-seqfile.ms

For XP-EHH:

ms 26 1000 -I 2 10 16 -t 3820 -en 0.003 1 0.16 -en 0.003 2 0.22 -en 0.001 1 0.8 -eg 0.001 1 0 -en 0.001 2 0.32 -eg 0.001 2 0 -ej 0.004 1 2 -p 6 >XP-EHH.ms

Test for the effect of relaxation of constraints and hitchhiking

Relaxation of purifying selection should increase pN/pS (the ratio of the number of non-synonymous substitutions per non-synonymous site (N) to the number of synonymous substitutions per synonymous site (S)) as selection against non-synonymous substitutions is lowered [41, 42]. Here, we retrieved SNPs in vision-related genes identified under potential positive selection by the four methods, according to functional category enrichment, and calculated the ratio of the number of pN SNPs to the number of synonymous SNPs (N/S) in the VC and RJF populations. To exclude the possibility of hitchhiking, we compared the F_{ST}, *Pi* and XP-EHH values for the visual-related candidate genes with their related upstream/downstream sequences of the same length as the gene, sequences at distance of 50 kb and in adjacent genes.

Comparison of gene expression

The RNA-seq data were trimmed to filter out adaptor sequences and low-quality bases using cutadaptor and Btrim (http://graphics.med.yale.edu/trim/) and were mapped onto the chicken reference using Tophat [43, 70]. Cufflinks and cuffcompare [43] were then used to assemble transcripts and compare the assembled transcripts with the annotated reference transcripts, generating a newmerged GTF annotation file. New transcripts assembled here were defined as: having at least 2 exons and length ≥ 200 bp with class code j, c, o, e, and new loci with all class codes being u, or i, or x. Cufflinks was run using the GTF file with parameter "-G" to retrieve expression profile for each gene. Cuffdiff [43] was used to detect the significance of the gene expression differences from four brain regions (cerebral cortex, corpus striatum, optic lobe, and cerebellar vermis) and retina between the RJF and VC. *P*-value was corrected by FDR (default by cuffdiff program).

To assess whether the expression changes in retina, cerebral cortex, corpus striatum, optic lobe, and cerebellar vermis between RJF and VC may have been driven by positive selection at local regulatory sites during domestication, a series of statistic tests were performed. The expression level (FPKM) for each gene in each tissue was retrieved and transformed according to $\log_2$(FPKM + 1) [68]. The difference of expression level for each gene between VC and RJF was calculated using $\log_2((FPKM + 1)_{VC}/(FPKM + 1)_{RJF})$. We then compared the expression levels of PSGs identified by F_{ST}, *Pi*, XP-EHH and XP-CLR with those of other genes (all genes in whole genome excluding PSGs) by Mann-Whitney *U* test and Kolmogorov-Smirnov test in each tissue. *P*-values were corrected by FDR. Since the two different batches of data employed different sequencing platforms and different runs, we performed the comparative analysis on data generated on the Hiseq 2000 and the Hiseq 4000 platforms independently, and also analyzed the combined

data generated on both platforms.

Selective sweep region annotation and gene functional enrichment analysis

Candidates' selective sweeps detected by the above-mentioned methods were annotated using the Variant Effect Predictor available at http://asia.ensembl.org/info/docs/tools/index.html. Functional enrichments of the protein-coding genes including GO categories, KEGG pathway and HPO were analyzed using g: Profiler [71].

VIT expression data in mouse

Expression data for *VIT* in different tissues of the mouse was retrieved from Biogps (http://biogps.org/). Expression profiling by array in retinal pigment epithelium (RPE) of mouse exposed to 10 000 lux of cool white fluorescent light for 18 h was from a previous study [72] (GSE37773). The expression data from retina after *Hmx1* loss and in wild-type mice were from another study [73] (GSE47002). Expression data from photoreceptor cells of $Nrl^{-/-}$ mice and $Crx::Nr2e3/Nrl^{-/-}$ mice were also from a previous study [46] (GSE5338).

RNA extraction and real-time quantitative PCR assay

Total RNA was isolated from chicken retina tissues using TRNzol-A+ (Tiangen Biotech, Beijing, China) and purified using RNeasy Micro kit (Qiagen, Germany). Concentration and integrity of the RNA was measured using electrophoresis and NanoDrop spectrophotometer 2000. Total RNA (2 μg) was used to synthesize single-strand cDNA using the PrimeScript RT-PCR Kit (TaKaRa, Japan) in a final volume of 25 μL reaction mixture according to the manufacturer's instructions. The relative mRNA expression levels of *RPGR* (retinitis pigmentosa GTPase regulator), *GUCAIA* (guanylate cyclase activator 1A), *TRPM1* (transient receptor potential cation channel, subfamily M, member 1), *PDE6B* (phosphodiesterase 6B), *NR2E3* (nuclear receptor subfamily 2, group E, member 3), *VIT* (vitrin) and *RHO* (rhodopsin) genes were measured using real-time quantitative PCR (qPCR) and the relative standard curve method, with normalization to the house-keeping gene *GAPDH*. qPCR was performed on the platform of the iQ2 system (BioRad Laboratories, Hercules, CA, USA) with SYBR Premix Ex Taq II kit (TaKaRa, DRR081A). Student's *t*-test was used to analyze the differences and measure the statistical significance. Primer pairs used for these genes are listed in Supplementary information, Table S7.

Zebrafish care and maintenance

Adult wild-type AB strain zebrafish were maintained at 28.5 °C on a 14 h light/10 h dark cycle [74]. Five to six pairs of zebrafish were set up for each natural mating each time. On average, 200-300 embryos were generated. Embryos were maintained at 28.5 °C in fish water (0.2% Instant Ocean Salt in deionized water). The embryos were washed and staged according to published guidelines [75]. The zebrafish facility at Shanghai Research Center for Model Organisms is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.

Zebrafish microinjections

Gene Tools, LLC (http://www.gene-tools.com/) designed the MO oligonucleotide. Antisense MO (GeneTools) was microinjected into fertilized one-cell stage embryos according to standard protocols [76]. The sequence of the exon 3-intron 3 splice *VIT* MO (*VIT*-e3i3-MO) was 5′-CCTGAATAGTCTACAGTACCTGAGA-3′. For the *VIT* knockdown experiment, 4 ng of *VIT*-e3i3-MO was used per injection. Total RNA was extracted from 80 to 100 embryos per group in Trizol (Invitrogen) according to the manufacturer's instructions. RNA was reverse transcribed using the PrimeScript RT reagent Kit with gDNA Eraser (Takara). Primers spanning *VIT* exon 2 (forward primer: 5′-GTTCGCCTCCATATCCAGCATCTGC-3′) and exon 9 (reverse primer: 5′-TTCCCCTGGACGCTCTGAGACTGTC-3′) were used for RT-PCR analysis for confirmation of the efficacy of the E3I3-MO.

AO staining for apoptosis

Wild-type control embryos and embryos injected with 4 ng *VIT*-e3i3-MO were immersed in 5 μg/ml AO (acridinium chloride hemi-[zinc chloride], Sigma-Aldrich) in fish water for 60 min at 32-hpf and 80-hpf. Next, zebrafish were rinsed thoroughly in fish water three times (5 min/wash) and anaesthetized with 0.016% MS-222 (Tricaine methanesulfonate, Sigma-Aldrich, St. Louis, MO). Zebrafish were then oriented on their lateral side and mounted with methylcellulose in a depression slide for observation by fluorescence microscopy.

In vivo ERG recording

Zebrafish larvae were first paralyzed with α-bungarotoxin (100 μg/ml, Sigma), and then embedded in 1% low melting-point agarose (Sigma) with one eye upward in a custom-made chamber as described previously [77]. The cornea and lens of the upward eye were removed to expose retinal surface by using a glass micropipette with a tip opening of 1 μm. After dissection, the larvae were transferred to a recording setup, and perfused with extracellular solution, which consists of (in mM) 134 NaCl, 2.9 KCl, 4 $CaCl_2$, 10 HEPES and 10 glucose (290 mOsmol/l, pH 7.8). ERG responses were recorded with an EPC-10 amplifier (Heka, Germany) through inserting the pipette of ~3-μm tip opening into the interface of photoreceptors and bipolar cells. The ERG signals were amplified at 1 000 total gain and low-pass filtered at 100 Hz. Whole-field light stimuli were given by a white LED controlled by the Master 8 stimulator (A.M.P.I., Israel).

Visual escape behavioral test

Larval behavior was monitored by an infrared-sensitive high-speed camera at the acquisition rate of 250 Hz (Redlake Motionscope M3, US). In one experiment, the behaviors of 12 larvae were simultaneously recorded. Each larva was put in an individual 3.5-cm Petri dish under the light background for 30 min to adapt. During each test, 10 trials were carried out for calculating the probability of escape behavior with a 5-min interval. A successful escape was scored when a C-shape movement finished within 20 ms after movement onset [78]. Visual stimuli were generated by a self-written Matlab program and delivered through a mini-projector. The dark shadow would gradually cover the fish's body when an expanding black disc was projected on the Petri dish at the expanding speed of ~5.4 cm/s.

Image acquisition

Embryos and larvae were analyzed with Nikon SMZ 1500 fluorescence microscope and subsequently photographed with digital cameras. A subset of images was adjusted for levels,

brightness, contrast, hue and saturation with Adobe Photoshop 7.0 software (Adobe, San Jose, CA, USA) to optimally visualize the expression patterns. Quantitative image analyses processed using image-based morphometric analysis (NIS-Elements D3.1, Japan) and ImageJ software (National Institutes of Health, Bethesda, MD, USA; http://rsbweb.nih.gov/ij/). Inverted fluorescent images were used for processing. Positive signals were defined by particle number using ImageJ. In total, 10 animals for each treatment were analyzed and the total signals per animal were averaged. All data were presented as mean ± SEM. Statistical analysis and graphical representation of the data were performed using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA). Statistical significance was performed using a Student's *t*-test as appropriate. Statistical significance is indicated by *, where $P < 0.05$, and ***, where $P < 0.0001$.

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Author Contributions

YPZ and DDW led the project and designed the study. MSW, RWZ, LYS and JLD performed experiments. MSW, DDW, LYS, YL, MSP, RWZ, JLD, HQL and LZ performed the analyses. MSW, HQL and LZ sampled chickens and tissues. MSW, DDW, DMI and YGY drafted the manuscript. All authors read and improved the manuscript.

Competing Financial Interests

The authors declare no competing financial interests.

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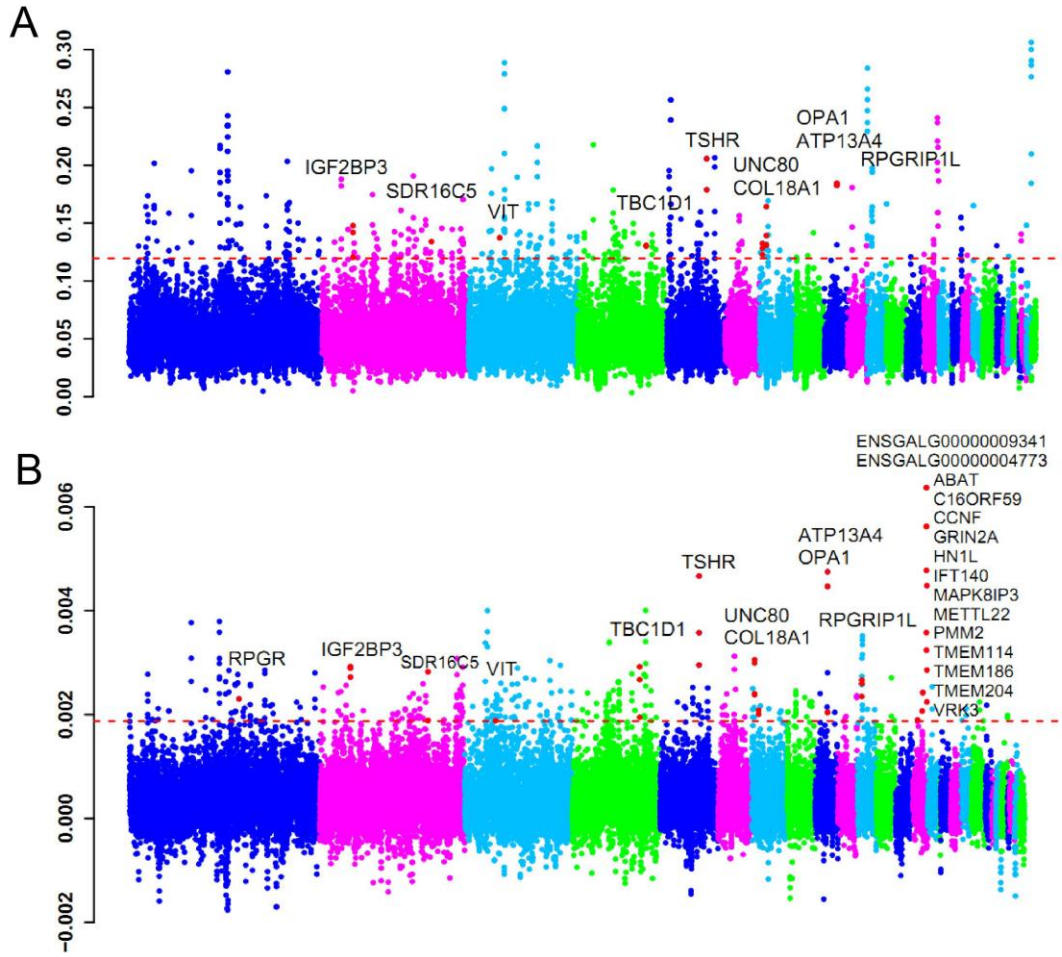
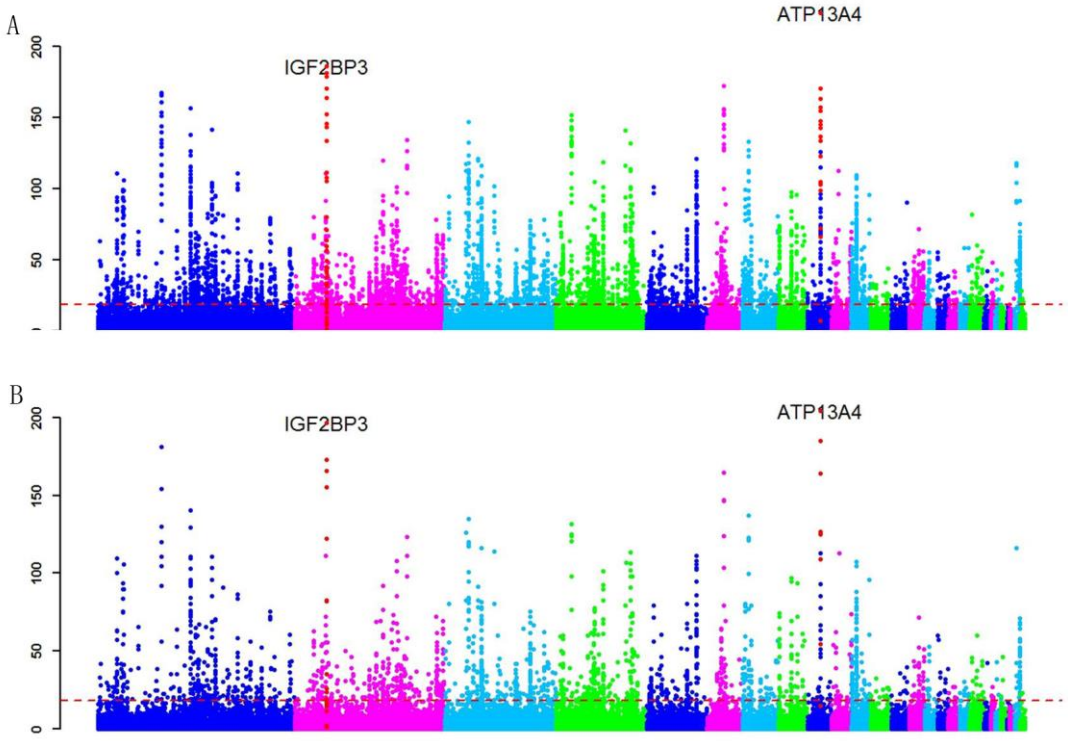
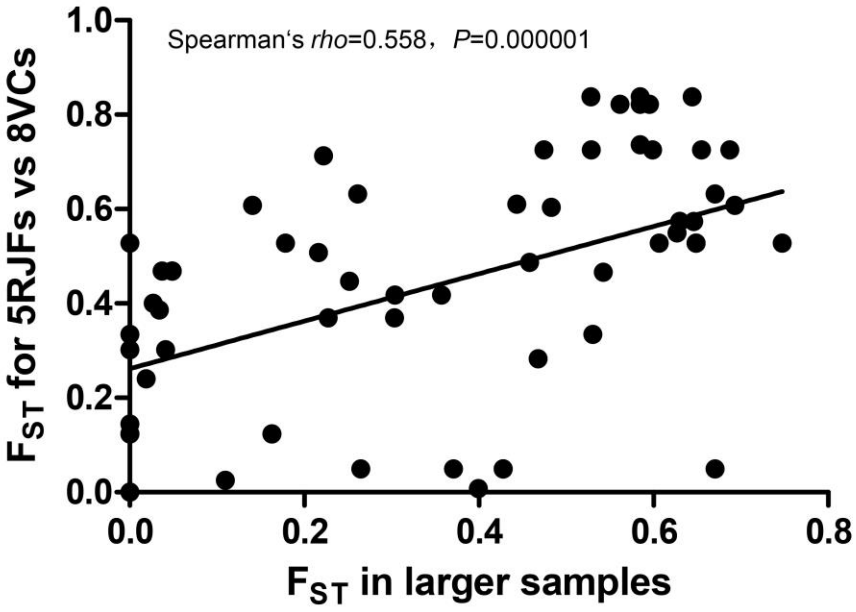
(**Supplementary information** is linked to the online version of the paper on the *Cell Research* website.)



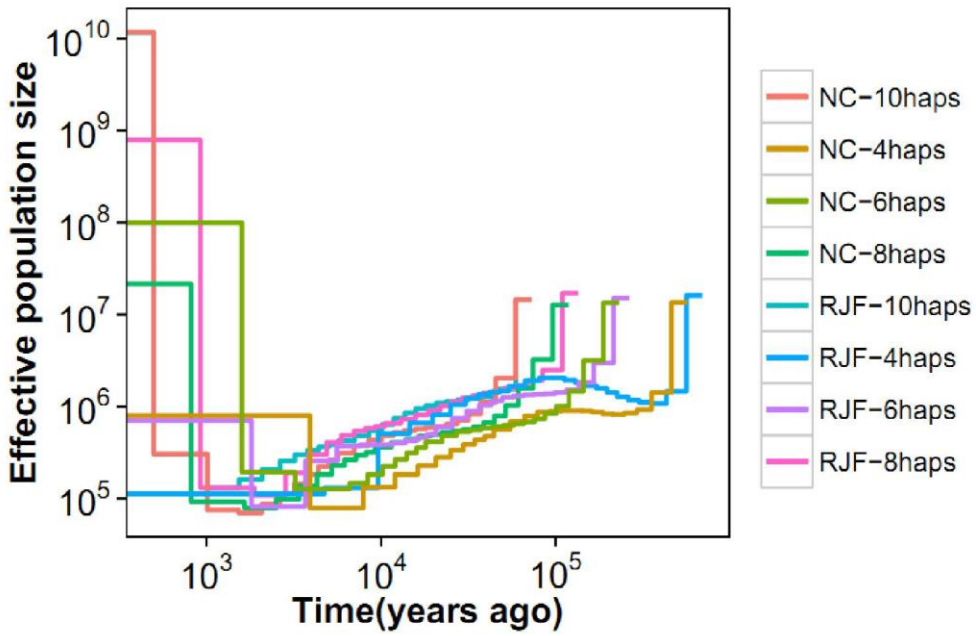
Supplementary information, Figure S1 Genomic landscape of the F_{ST} values (**A**) and △Pi values (**B**) in the genomes of the domestic chickens.



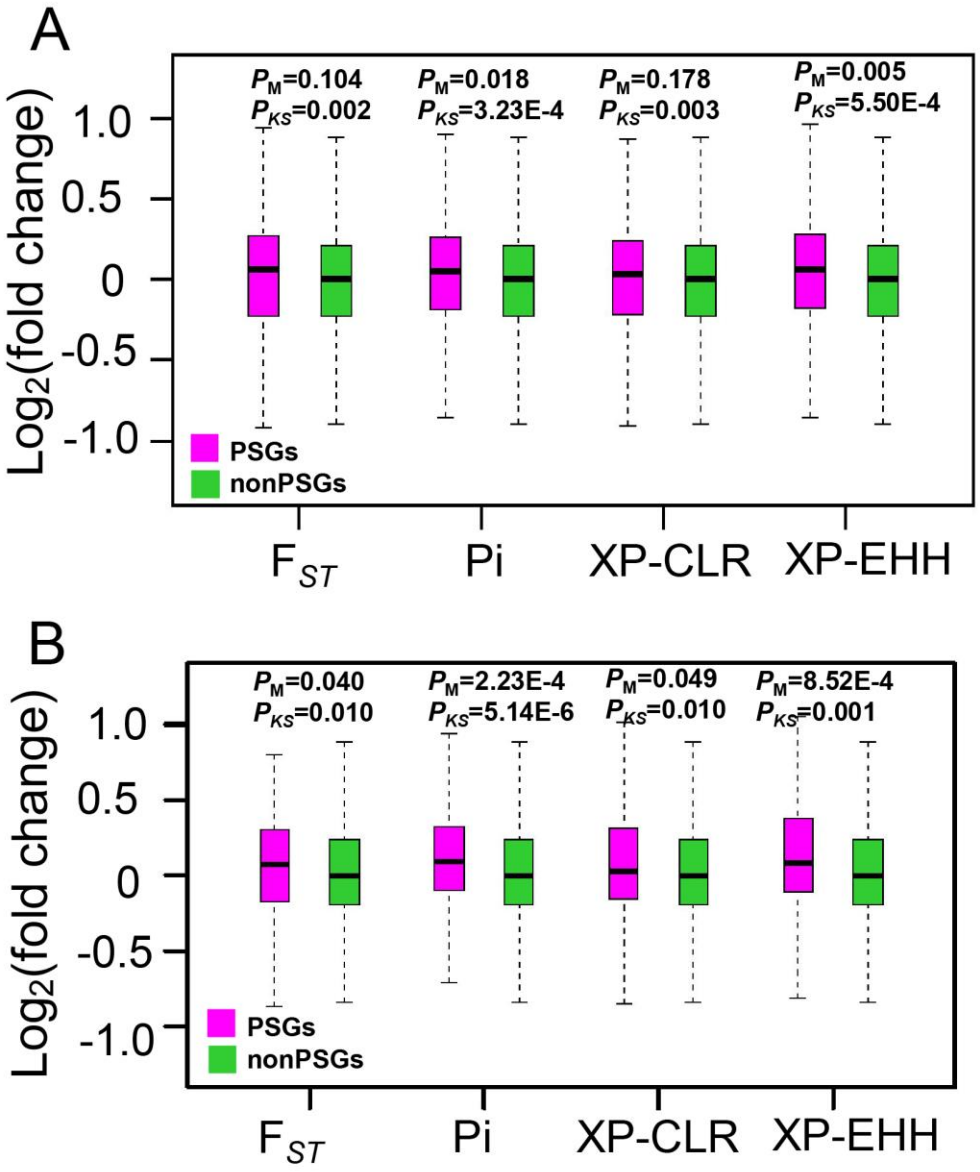
Supplementary information, Figure S2 Genomic landscape of the XP-CLR values using grid size 2Kb (**A**) and 5 Kb (**B**).



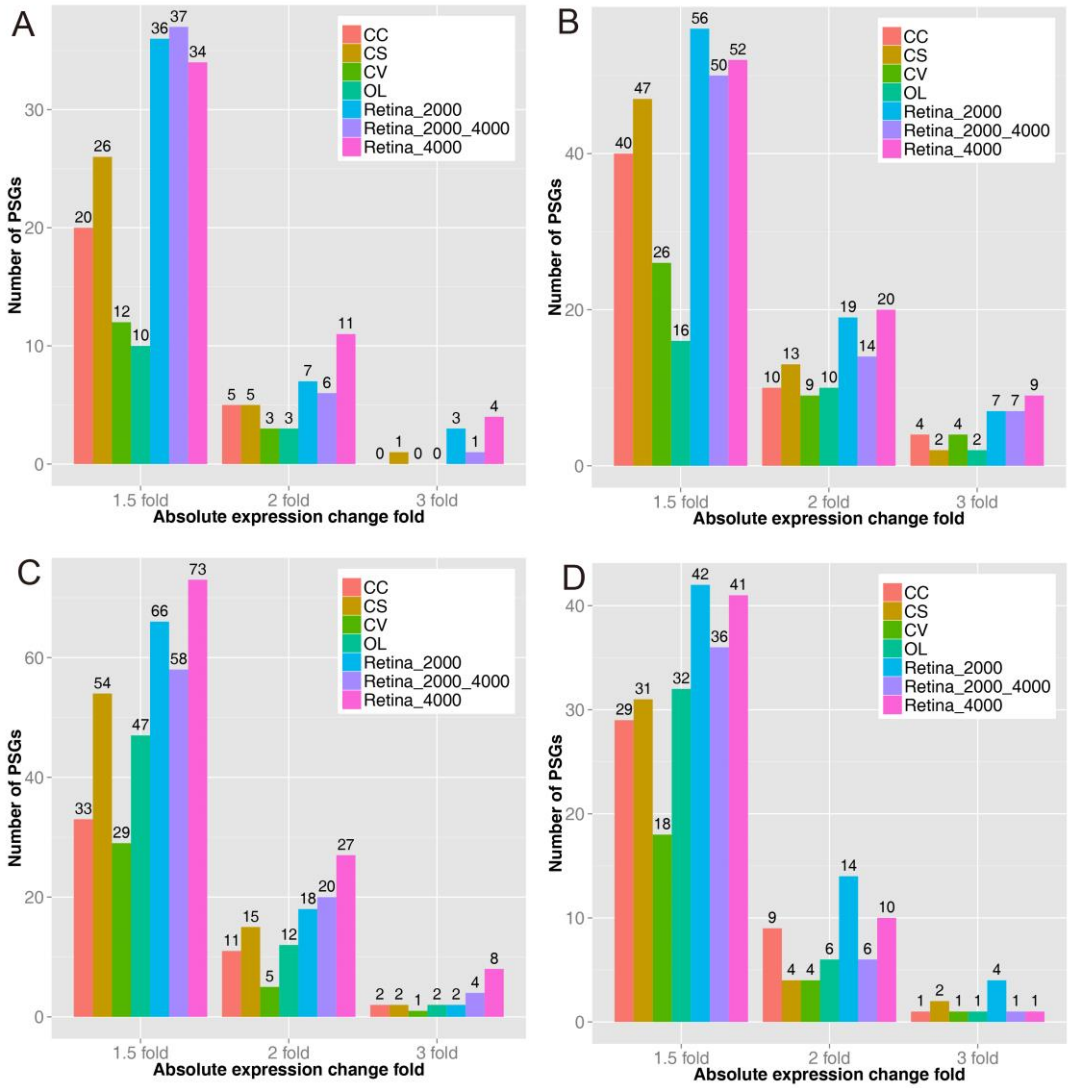
Supplementary information, Figure S3 Correlation for F_{ST} computed in (5RJFs vs 8VCs) and larger population (~25 RJFs vs ~20 VCs).



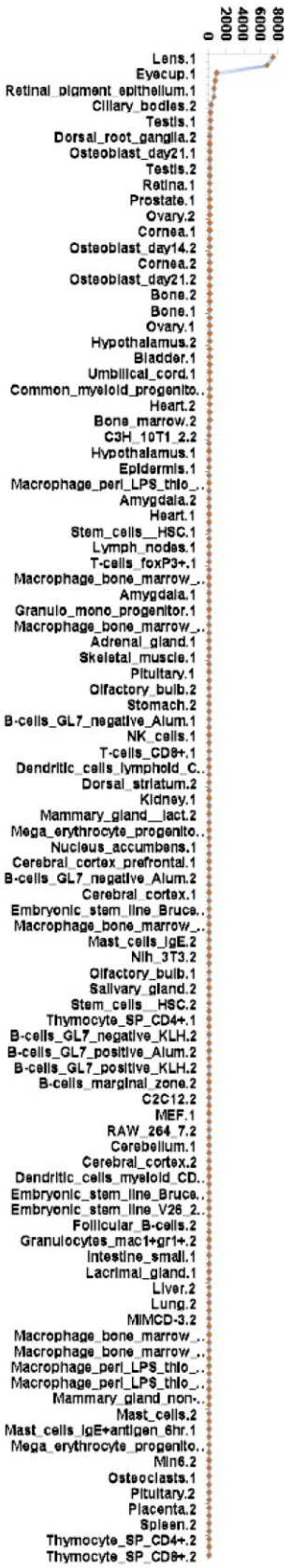
Supplementary information, Figure S4 Demographic history for Red Junglefowl and village chicken inferred by MSMC.



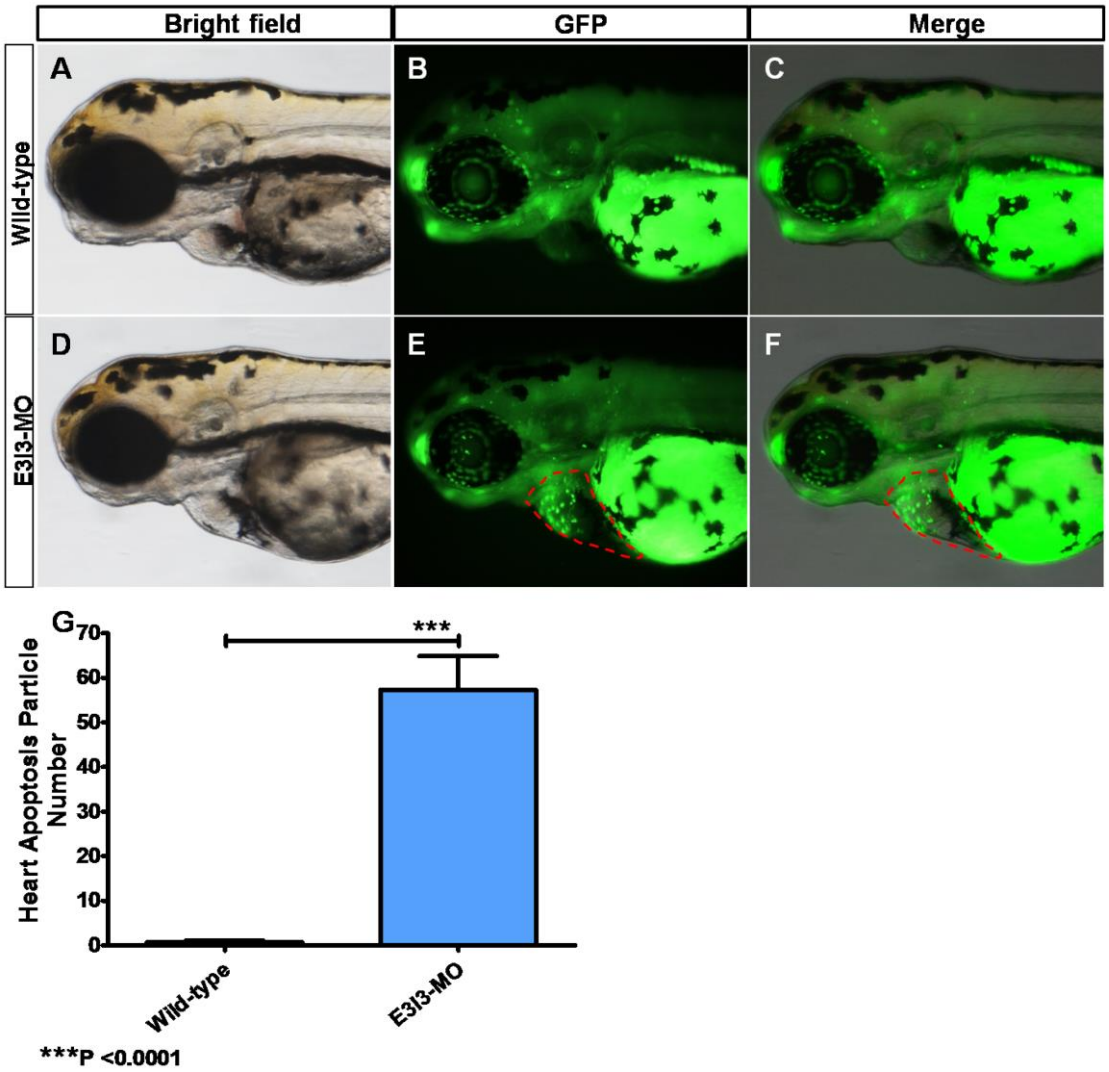
Supplementary information, Figure S5 Differences in gene expression in eye for PSGs identified by F_{ST}, Pi, XP-CLR and XP-EHH compared with non-PSGs based on transcriptomes generated on Hiseq4000 platform (**A**) and combining Hiseq 2000 platform and Hiseq4000 platform together (**B**). P_M and P_{KS} mean values were calculated by Mann-Whitney U test and Kolmogorov-Smirnov test, respectively.



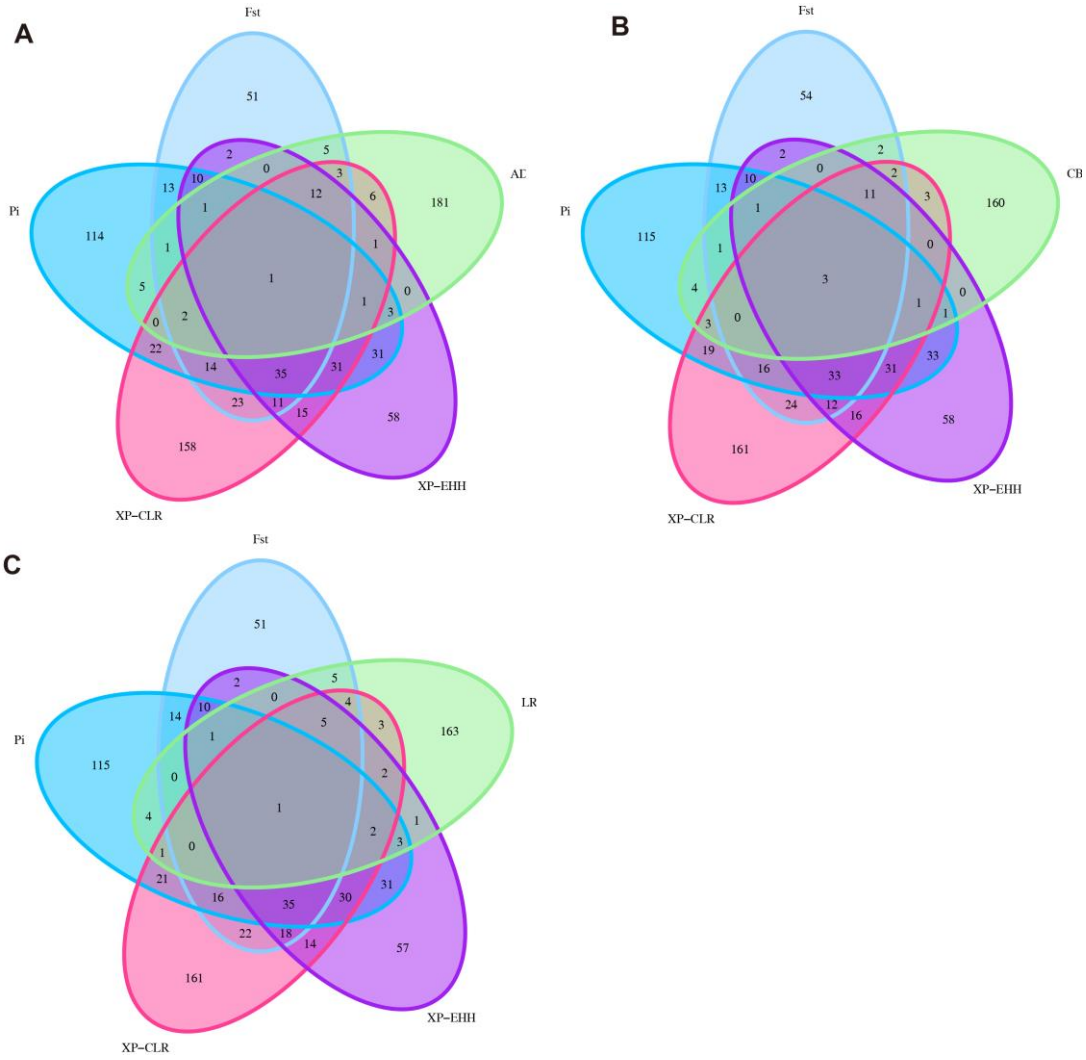
Supplementary information, Figure S6 Number of PSGs genes exhibiting different expression level changes between Red Junglefowl and village chicken in the eye and 4 brain regions. Retina_2000, analysis performed based on eye transcriptomes generated by Hiseq 2000 platform; Retina_4000, analysis performed based on eye transcriptomes generated by Hiseq4000 platform; Retina_2000_4000, analysis performed based on eye transcriptomes generated by Hiseq 2000 platform and 4000 platform together; CC, cerebral cortex; CS, corpus striatum;CV, cerebellar vermis; OL, optic lobe.



Supplementary information, Figure S7 The expression level of *VIT* in different tissues in the mouse.



Supplementary information, Figure S8 Morpholino knock down of *VIT* induces potent apoptosis in heart. Wild-type control embryos and embryos injected with *VIT*-e3i3-MO (E3I3-MO) were stained with acridine orange (AO) at 80hpf. Apoptotic cells are visible as bright green spots, and less bright homogenous green staining is unspecific background staining. (**A-C**) Uninjected wild-type control zebrafish exhibited few or no apoptotic cells in heart. In contrast, significantly increased staining was observed throughout the heart in zebrafish injected with 4ng VIT-e3i3-MO (**D-F**, red circled area). (**G**) Quantification of apoptosis particle number at heart shows a 81-fold increased in *VIT* morphants (n = 10) at 80hpf. A-F: lateral view, anterior, left.



Supplementary information, Figure S9 Overlap of PSGs identified in our study compared with the report by Rubin and colleagues (2010) in domestic lines (AD), commercial broiler lines (CB) and layer lines (LR).

Supplementary information, Table S1 Village chicken and Red Junglefowl genome sequence information

Breeds	NO. runs	No. reads	Data size (Gbp)	Sequence depth
village chicken1	2	231220158	17.28	15.3291
village chicken2	2	206893558	17.81	16.5434
village chicken3	3	266469886	29.69	19.5379
village chicken4	3	301822858	26.72	18.6694
village chicken5	2	269483358	17.81	10.8655
village chicken6	2	235001290	23.75	19.2231
village chicken7	2	178477396	17.81	14.5754
village chicken8	3	508596074	55.31	31.95
Red Junglefowl1	3	177458494	26.18	11.6534
Red Junglefowl2	2	286042830	17.81	23.3578
Red Junglefowl3	2	186436306	17.28	14.1309
Red Junglefowl4	2	223851144	17.28	17.2666
Red Junglefowl5	2	402348272	37.5	32.4167

Supplementary information, Table S2 RNA-seq sequence information for village chicken and Red Junglefowl

Breeds	**Tissues**	**Sample ID (replicates)**	**Experimental replicates**	**Length of reads (bp)**	**Number of reads**
RJF	retina	RJF-Ypt540	RJF-Ypt540-1	2X101bp	64579522
			RJF-Ypt540-2	2X150bp	15396330
			RJF-Ypt540-3	2X150bp	19503196
RJF	retina	RJF-Ypt570	RJF-Ypt570-1	2X101bp	64248596
			RJF-Ypt570-2	2X150bp	16106488
			RJF-Ypt570-3	2X150bp	18176038
RJF	retina	RJF-Ypt2828	RJF-Ypt2828-1	2X150bp	15047342
			RJF-Ypt2828-2	2X150bp	17508200
VC	retina	VC-Ypt583	VC-Ypt583-1	2X101bp	64609196
			VC-Ypt583-2	2X150bp	17069300
			VC-Ypt583-3	2X150bp	18036884
VC	retina	VC-Ypt593	VC-Ypt593-1	2X101bp	78844344
			VC-Ypt593-2	2X150bp	16642708
			VC-Ypt593-3	2X150bp	17039632
VC	retina	VC-Ypt592	VC-Ypt592-1	2X101bp	87378940
RJF	cerebellar vermis	RJF-Ypt540	RJF-Ypt540-1	2X101bp	41282982
VC	cerebellar vermis	VC-527YB-500	VC-527YB-500	2X101bp	26318676
VC	cerebellar vermis	VC-530YB-500	VC-530YB-500	2X101bp	38305844
RJF	cerebral cortex	RJF-540PC-700	RJF-540PC-700	2X101bp	48235898
VC	cerebral cortex	VC-527PC-500	VC-527PC-500	2X101bp	49914452
VC	cerebral cortex	VC-530PC-500	VC-530PC-500	2X101bp	30256168
RJF	optic lobe	RJF-540SY-500	RJF-540SY-500	2X101bp	39525596
VC	optic lobe	VC-527SY-500	VC-527SY-500	2X101bp	48003780
VC	optic lobe	VC-530SY-500	VC-530SY-500	2X101bp	27969846
RJF	corpus striatum	RJF-540WZ-500	RJF-540WZ-500	2X101bp	46601142
VC	corpus striatum	VC-530WZ-500	VC-530WZ-500	2X101bp	33906634

Supplementary information, Table S3 Distribution of SNPs

Terms	Number	Proportion
exonic	246336	1.44%
intronic	7367199	43.04%
intergenic	8823233	51.55%
UTRs	213394	1.25%
others	465213	2.72%
Total	17115375	100.00%

Supplementary information, Table S4 Distribution of SNPs located in protein coding regions

	Synonymous	**Nonsynonymous**	**Stop gain**	**Stop loss**
Number of SNV	174748	70990	506	58
Number of genes	13779	11531	445	57
Number of transcripts	563	12111	446	57

Supplementary information, Table S5 Results for 67 SNPs validated in larger population

Chr	Position	Ref allele	Alt allele	Number of RJF	Number of VC	FST in larger samples	FST for 5RJFs vs 8VCs	Overlapped genes
2	80326793	C	T	31	26	0.629903087	0.574021614	intergenic
2	80326818	T	C	31	26	0.629903087	0.574021614	intergenic
2	80326839	A	C	31	26	0.629903087	0.574021614	intergenic
2	80326840	A	T	31	26	0.629903087	0.574021614	intergenic
2	80326866	G	C	31	25	0.645921577	0.574021614	intergenic
5	40092110	G	C	27	20	0.747457033	0.528023599	TSHR(downstream)
5	40092012	G	A	25	20	0.606600372	0.528023599	TSHR(downstream)
5	40092286	G	A	25	20	0.64881475	0.528023599	TSHR(downstream)
5	40092309	G	A	25	20	0.64881475	0.528023599	TSHR(downstream)
5	40092338	A	G	25	20	0.64881475	0.528023599	TSHR(downstream)
9	12584591	T	C	30	24	0.303592891	0.418181818	ATP13A4
9	12584847	T	G	29	24	0.670237929	0.632183908	ATP13A4
9	12584853	T	G	29	24	0.357273768	0.418181818	ATP13A4
9	12584874	G	A	29	24	0.670237929	0.04950495	ATP13A4
11	4363346	T	G	28	20	0.626972457	0.549295775	RPGRIP1L
11	4363390	C	T	28	20	0	0	RPGRIP1L
11	4363778	C	T	28	20	0.542398101	0.466282144	RPGRIP1L
11	4363787	G	A	28	20	0.467915606	0.283267457	RPGRIP1L
7	6649854	C	A	28	22	0.443423046	0.610705596	COL18A1 (upstream)
7	6649878	A	G	28	22	0.227269817	0.369853204	COL18A1 (upstream)
7	6650054	G	A	27	22	0.371091062	0.04950495	COL18A1 (upstream)
7	6650120	T	C	27	22	0.427655161	0.04950495	COL18A1 (upstream)
7	6650129	G	A	27	22	0.303552043	0.369853204	COL18A1 (upstream)
7	6650196	C	T	27	22	0.427655161	0.04950495	COL18A1 (upstream)
7	6650160	A	T	27	22	0.427655161	0.04950495	COL18A1 (upstream)
9	12546345	A	G	31	23	0.02676464	0.400749064	OPA1
9	12546387	A	G	31	23	0.048581794	0.468942627	OPA1
9	12546416	C	G	31	23	0.048581794	0.468942627	OPA1

9	12546421	G	T	31	23	0.037141971	0.468942627	OPA1
9	12546426	C	T	31	23	0.048581794	0.468942627	OPA1
9	12546495	C	T	31	23	0.034167181	0.386518244	OPA1
9	12546566	T	G	31	23	0	0.334257975	OPA1
9	12546613	C	A	31	23	0.178307316	0.528023599	OPA1
9	12546701	G	A	31	23	0.109406819	0.025239339	OPA1
9	12546702	C	T	31	33	0	0.144385027	OPA1
3	31539842	G	A	16	6	0.216048287	0.508301223	VIT
3	31539574	T	C	32	19	0.221907599	0.712722298	VIT
2	31291843	C	T	30	24	0.264609324	0.04950495	IGF2BP3
2	31291844	C	T	30	25	0.041190935	0.302180685	IGF2BP3
2	31291910	A	G	30	24	0	0.302180685	IGF2BP3
2	31291931	G	A	29	24	0.474355677	0.725166099	IGF2BP3
2	31292042	G	A	29	23	0.260988811	0.632183908	IGF2BP3
2	31292094	C	T	29	23	0	0.528023599	IGF2BP3
2	31292233	T	C	30	21	0.59886167	0.725166099	IGF2BP3
2	31292359	A	G	29	22	0.399202476	0.008092839	IGF2BP3
2	31290728	A	G	30	23	0	0.124028388	IGF2BP3
2	31290818	C	T	30	23	0.482820252	0.603851444	IGF2BP3
2	31290904	G	A	31	24	0.528317897	0.837892604	IGF2BP3
2	31290970	A	C	31	24	0.530306533	0.334916865	IGF2BP3
2	31291039	C	T	31	24	0.018775131	0.240011176	IGF2BP3
2	31290675	C	T	29	21	0.644305664	0.837892604	IGF2BP3
2	31290672	C	A	29	21	0	0.124028388	IGF2BP3
2	31290665	A	C	29	21	0	0.124028388	IGF2BP3
3	54316468	A	G	24	14	0.561601858	0.822335025	MAP3K5
3	54316446	A	G	27	14	0.595234855	0.822335025	MAP3K5
3	54316289	G	A	26	14	0.584725202	0.837892604	MAP3K5
3	54316272	T	C	26	14	0.584725202	0.822335025	MAP3K5
3	54316232	T	C	26	14	0.584725202	0.73651192	MAP3K5
3	54316242	T	C	25	14	0.251641276	0.44735208	MAP3K5
3	54316350	A	G	26	14	0.140856889	0.607972207	MAP3K5
3	54316094	G	T	24	14	0.162825692	0.124028388	MAP3K5
3	54316098	G	A	24	14	0.162825692	0.124028388	MAP3K5
1	63172968	C	T	30	23	0.528863839	0.725166099	intergenic
1	63172991	A	G	29	23	0.693279086	0.607972207	intergenic
1	63173097	C	T	20	23	0.457792875	0.4869873	intergenic
1	63173216	C	T	18	23	0.655093741	0.725166099	intergenic
1	63173227	C	T	18	23	0.687342389	0.725166099	intergenic

Supplementary information, Table S6 Primers used for SNP validation in larger samples.

Primers	**sequences**	**length(bp)**	**Tm(℃）**
Chr1.1-3F	AAAGCAGCAGTGTTGTAAGC	20	54℃
Chr1.1-3R	CCTGTATGGAGTGGGAGATA	20	54℃
Chr2-1F	GAAATGGCAGTGAGAATT	18	54℃
Chr2-1R	GTGGGATATGTTGAGGAT	18	54℃
Chr3-3F	GGGTCAAAGAACAAACTC	18	54℃
Chr3-3R	GAGAAGACAAGGTAGGGA	18	54℃
Chr5-1F	GCATCTACCCTTAAACAA	18	54℃
Chr5-1R	GTACATGGCATTCACAAT	18	54℃
2-ATP13A4-1-1F	GGGTCTACAGGAAATGGA	18	54℃
2-ATP13A4-1-1R	AAGGTACTGAATGGTGCT	18	54℃
3-RPGRIP1L-1-1F	GCTCTACCGCTCTGAATA	18	54℃
3-RPGRIP1L-1-1R	ATGGGTTTTAGGGATAAG	18	54℃
5-COL18A1-1-1F	TGCTGGTTTCCATTTGGTTG	20	54℃
5-COL18A1-1-1R	ATGGCAAAGGCGGTGTCT	18	54℃
6-OPA1-1-3F	CCTTGGTTCCTTCCGCTAT	19	54℃
6-OPA1-1-3R	GGTTTAGTTTCGCTTGTATCTT	22	54℃
4-IGF2BP3-2-1F	ATTCTCCCTTGAGCCTAC	18	54℃
4-IGF2BP3-2-1R	CATCTTCTGATGCCCATA	18	54℃
7-VIT-2-5F	ATAAGCACTCGGCACAAA	18	54℃
7-VIT-2-5R	AAACACCCAGGAAGATGA	18	54℃
4-IGF2BP3-1-1F	ATACTCCACAACACCCAA	18	54℃
4-IGF2BP3-1-1R	TAGCCTTTAAGACCTGCT	18	54℃

Supplementary information, Table S7 Primers for qPCR to measure gene expression in the chicken retina of vision functionally related genes

Primer	**Sequence (5'-3')**	**Product length (bp)**	**Annealing temperatures (ºC)**
cGUCAIA F	CCAGTAAACCCCAGGACAC	168	58
cGUCAIA R	GTGTTCGGAGGGACATCG		
cTRPM1 F	GGCAAGCAGAACAGAAACAG	89	58
cTRPM1 R	CATAGAGGCGTAAGAGGCAC		
cPDE6B F	TGCCTGGACTGATTACCTG	80	58
cPDE6B R	ACAAGTCACACGCAGTCA		
cRHO F	CTGTAGTGGCATTCTGGATC	142	58
cRHO R	CAATTACGGAACTGCTTGTT		
cNR2E3 F	TGTCAAGTGGGCAAAGAACC	103	56
cNR2E3 R	GGCACAGAGCAGGAACAG		
cGAPDH F	AGGACCAGGTTGTCTCCTGT	153	62
cGAPDH R	CCATCAAGTCCACAACACGG		
cRPGR F	TACTTTTGGGGAACCTGAGA	77	56
cRPGR R	CTGGCTGTGGGACTCTAC		
cVIT F	GGTGATGGTGGATGGGTG	191	56
cVIT R	TGG GCACAGTGATGGAATAG		

Note*: GAPDH* primer sequence is got from Feng et al (2013).[1]

References:

1 Feng ZQ, Lian T, Huang Y, Zhu Q, Liu YP. Expression pattern of genes of RLR-mediated antiviral pathway in different-breed chicken response to Marek's disease virus infection. *Biomed Res Int* 2013; **2013**:419256.

Supplementary information, Table S8 Functional enrichment categories of PSGs detected by XP-EHH

Term	Term ID	P-value	Gene number	Description
BP	GO:0007218	0.05	6	neuropeptide signaling pathway
hp	HP:0000707	0.05	31	Abnormality of the nervous system
hp	HP:0002011	0.0487	30	Abnormality of the central nervous system
hp	HP:0000608	0.0429	3	Macular degeneration
hp	HP:0004298	0.0238	9	Abnormality of the abdominal wall
hp	HP:0001551	0.0456	6	Abnormality of the umbilicus
hp	HP:0100656	0.028	8	Thoracoabdominal wall defects
hp	HP:0010866	0.028	8	Abdominal wall defect
hp	HP:0004299	0.026	8	Hernia of the abdominal wall
hp	HP:0001537	0.0397	6	Umbilical hernia
hp	HP:0100543	0.0222	25	Cognitive impairment
ke	KEGG:04144	0.05	6	Endocytosis

Supplementary information, Table S9 Functional enrichment categories of PSGs detected by F_{ST}

Term	term ID	P-value	Gene number	Description
MF	GO:0004767	5.00E-02	3	sphingomyelin phosphodiesterase activity
hp	HP:0011282	5.00E-02	15	Abnormality of the hindbrain
hp	HP:0011283	5.00E-02	15	Abnormality of the metencephalon
hp	HP:0001317	5.00E-02	15	Abnormality of the cerebellum
ke	KEGG:04260	1.51E-02	2	Cardiac muscle contraction
ke	KEGG:00600	1.40E-02	2	Sphingolipid metabolism
ke	KEGG:04060	3.13E-02	3	Cytokine-cytokine receptor interaction
ke	KEGG:04144	3.90E-02	3	Endocytosis
ke	KEGG:00510	1.34E-02	2	N-Glycan biosynthesis
ke	KEGG:04080	1.67E-02	5	Neuroactive ligand-receptor interaction

Supplementary information, Table S10 Functional enrichment categories of PSGs detected by *Pi*

Term	Term ID	p-value	Gene number	Description
MF	GO:0016894	0.0209	3	endonuclease activity, active with either ribo- or deoxyribonucleic acids and producing 3'-phosphomonoesters
MF	GO:0016892	0.0106	3	endoribonuclease activity, producing 3'-phosphomonoesters
MF	GO:0008009	0.05	4	chemokine activity
hp	HP:0000707	0.05	40	Abnormality of the nervous system
hp	HP:0011442	0.0147	24	Abnormality of central motor function
hp	HP:0000572	0.0268	5	Visual loss
hp	HP:0003146	0.012	2	Hypocholesterolemia
hp	HP:0000519	0.0084	4	Congenital cataract
hp	HP:0004329	0.0184	19	Abnormality of the posterior segment of the eye
hp	HP:0001098	0.0394	18	Abnormality of the fundus
hp	HP:0001103	0.0175	5	Abnormality of the macula
hp	HP:0008059	0.0408	2	Aplasia/Hypoplasia of the macula
hp	HP:0011446	0.0294	34	Abnormality of higher mental function
ke	KEGG:00650	0.05	2	Butanoate metabolism
ke	KEGG:00770	0.0195	2	Pantothenate and CoA biosynthesis
ke	KEGG:00020	0.05	2	Citrate cycle (TCA cycle)

Supplementary information, Table S11 Functional enrichment categories of PSGs detected by XP-CLR

Term	Term ID	P-value	Gene number	Description
hp	HP:0012232	1.05E-02	2	Shortened QT interval
hp	HP:0001279	2.20E-03	4	Syncope
hp	HP:0001634	3.26E-02	3	Mitral valve prolapse
hp	HP:0002297	1.05E-02	2	Red hair
hp	HP:0100678	2.13E-02	2	Premature skin wrinkling
hp	HP:0002213	2.63E-02	4	Fine hair
hp	HP:0000591	2.63E-02	4	Abnormality of the sclera
hp	HP:0000592	1.63E-02	4	Blue sclerae
hp	HP:0005115	1.03E-02	4	Supraventricular arrhythmia
hp	HP:0001649	1.75E-02	5	Tachycardia
hp	HP:0004755	9.13E-03	4	Supraventricular tachycardia
hp	HP:0001692	9.13E-03	4	Primary atrial arrhythmia
hp	HP:0005110	6.99E-03	4	Atrial fibrillation
hp	HP:0000639	1.09E-02	18	Nystagmus
hp	HP:0010647	1.81E-02	6	Abnormal elasticity of skin
hp	HP:0008067	1.50E-02	5	Abnormally lax or hyperextensible skin
hp	HP:0000977	4.90E-03	3	Soft skin
hp	HP:0002047	3.54E-02	2	Malignant hyperthermia
hp	HP:0000993	6.39E-03	2	Molluscoid pseudotumors
hp	HP:0008056	1.18E-02	10	Aplasia/Hypoplasia affecting the eye
hp	HP:0008062	2.71E-02	5	Aplasia/Hypoplasia affecting the anterior segment of the eye
hp	HP:0008055	4.60E-02	4	Aplasia/Hypoplasia affecting the uvea
hp	HP:0008053	4.28E-02	4	Aplasia/Hypoplasia of the iris
hp	HP:0001788	2.13E-02	2	Premature rupture of membranes
hp	HP:0002445	3.54E-02	2	Tetraplegia
hp	HP:0001250	3.65E-02	23	Seizures
hp	HP:0000963	4.23E-03	5	Thin skin
hp	HP:0004329	2.66E-02	20	Abnormality of the posterior segment of the eye
hp	HP:0001252	5.00E-02	19	Muscular hypotonia
hp	HP:0100738	3.54E-02	2	Abnormal eating behavior
hp	HP:0001103	2.04E-02	5	Abnormality of the macula
hp	HP:0000493	1.55E-02	2	Abnormality of the fovea
hp	HP:0008061	2.77E-03	3	Aplasia/Hypoplasia affecting the retina
hp	HP:0008059	1.97E-03	3	Aplasia/Hypoplasia of the macula
hp	HP:0008060	1.05E-02	2	Aplasia/Hypoplasia of the fovea
hp	HP:0007750	1.05E-02	2	Hypoplasia of the fovea
hp	HP:0001030	4.36E-02	2	Fragile skin

hp	HP:0002085	4.36E-02	2	Occipital encephalocele
ke	KEGG:04144	1.27E-02	7	Endocytosis
ke	KEGG:04020	1.79E-02	6	Calcium signaling pathway
ke	KEGG:04270	6.05E-03	5	Vascular smooth muscle contraction
ke	KEGG:00230	3.49E-02	5	Purine metabolism
ke	KEGG:04916	4.73E-02	3	Melanogenesis
ke	KEGG:00565	2.88E-02	2	Ether lipid metabolism
ke	KEGG:00520	1.45E-02	3	Amino sugar and nucleotide sugar metabolism
ke	KEGG:00650	1.76E-02	2	Butanoate metabolism
ke	KEGG:04060	4.09E-02	5	Cytokine-cytokine receptor interaction
ke	KEGG:04350	2.81E-03	5	TGF-beta signaling pathway
ke	KEGG:00410	1.63E-02	2	beta-Alanine metabolism
ke	KEGG:04260	1.69E-02	3	Cardiac muscle contraction
ke	KEGG:04010	4.69E-02	6	MAPK signaling pathway
ke	KEGG:00280	3.93E-02	2	Valine, leucine and isoleucine degradation
ke	KEGG:04510	3.22E-02	6	Focal adhesion
ke	KEGG:04110	3.52E-02	4	Cell cycle
ke	KEGG:04210	2.89E-02	3	Apoptosis
ke	KEGG:00983	2.16E-02	2	Drug metabolism - other enzymes

Supplementary information, Table S12 Description for 36 PSGs detected by combining F_{ST}, *Pi*, XP-EHH and XP-CLR

Ensemble GeneID	Gene name	Discription
ENSGALG00000002789	MAP2	Microtubule-associated protein
ENSGALG00000002828	UNC80	Uncharacterized protein
ENSGALG00000003591	FTO	protein fto
ENSGALG00000003602	RPGRIP1L	RPGRIP1-like
ENSGALG00000003620	AKTIP	AKT-interacting protein
ENSGALG00000003663	RBL2	retinoblastoma-like protein 2
ENSGALG00000003719	CHD9	chromodomain helicase DNA binding protein 9
ENSGALG00000004322	N/A	Uncharacterized protein
ENSGALG00000004338	COL18A1	collagen, type XVIII, alpha 1 precursor
ENSGALG00000007150	OPA1	dynamin-like 120 kDa protein, mitochondrial precursor
ENSGALG00000007179	ATP13A5	ATPase type 13A5
ENSGALG00000007193	HRASLS	Uncharacterized protein
ENSGALG00000007208	N/A	N/A
ENSGALG00000008164	ADAMTS7	Uncharacterized protein
ENSGALG00000008526	BRD1	bromodomain-containing protein 1
ENSGALG00000008539	ALG12	alpha-1,6-mannosyltransferase ALG12 precursor
ENSGALG00000008547	ZBED4	zinc finger BED domain-containing protein 4
ENSGALG00000008551	CRELD2	cysteine-rich with EGF-like domain protein 2 precursor
ENSGALG00000009925	MTA3	metastasis associated 1 family, member 3
ENSGALG00000009926	HAAO	3-hydroxyanthranilate 3,4-dioxygenase
ENSGALG00000010391	MMRN1	multimerin 1
ENSGALG00000010572	TSHR	thyrotropin receptor isoform 1 precursor
ENSGALG00000010949	GPNMB	glycoprotein (transmembrane) nmb
ENSGALG00000010954	MALSU1	mitochondrial assembly of ribosomal large subunit 1
ENSGALG00000010961	IGF2BP3	Insulin-like growth factor 2 mRNA-binding protein 3
ENSGALG00000013521	TBC1D1	TBC1 (tre-2/USP6, BUB2, cdc16) domain family, member 1
ENSGALG00000013576	MEL1A	Melatonin receptor type 1A
ENSGALG00000014421	LCORL	Ligand-dependent nuclear receptor corepressor-like protein
ENSGALG00000014425	NCAPG	non-SMC condensin I complex, subunit G
ENSGALG00000016157	UMODL1	Uncharacterized protein
ENSGALG00000016183	EYS	Uncharacterized protein
ENSGALG00000016460	NBAS	neuroblastoma amplified sequence
ENSGALG00000020827	ATP13A4	probable cation-transporting ATPase 13A4
ENSGALG00000022827	SDR16C5	short chain dehydrogenase/reductase family 16C, member 5
ENSGALG00000023731	N/A	N/A
ENSGALG00000023742	N/A	N/A

Supplementary information, Table S13 Functional enrichment categories of 36 PSGs detected shared by F_{ST}, Pi, XP-CLR and XP-EHH

Term	Term ID	P-value	Gene number	Description
hp	HP:0000006	5.00E-02	2	Autosomal dominant inheritance
hp	HP:0000005	4.91E-02	6	Mode of inheritance
hp	HP:0000951	4.85E-02	2	Abnormality of the skin
hp	HP:0000079	4.28E-02	2	Abnormality of the urinary system
hp	HP:0011354	4.13E-02	2	Generalized abnormality of skin
hp	HP:0001574	4.02E-02	3	Abnormality of the integument
hp	HP:0100022	3.66E-02	2	Abnormality of movement
hp	HP:0002814	3.61E-02	2	Abnormality of the lower limb
hp	HP:0000364	3.45E-02	2	Hearing abnormality
hp	HP:0000365	3.38E-02	2	Hearing impairment
hp	HP:0000478	3.38E-02	4	Abnormality of the eye
hp	HP:0012243	3.30E-02	2	Abnormal genital system morphology
hp	HP:0002817	3.29E-02	2	Abnormality of the upper limb
hp	HP:0001249	3.25E-02	2	Intellectual disability
hp	HP:0012759	3.24E-02	3	Neurodevelopmental abnormality
hp	HP:0000002	3.20E-02	2	Abnormality of body height
hp	HP:0011024	3.16E-02	2	Abnormality of the gastrointestinal tract
hp	HP:0000240	3.15E-02	2	Abnormality of skull size
hp	HP:0011805	3.13E-02	2	Abnormality of muscle morphology
hp	HP:0004323	3.11E-02	2	Abnormality of body weight
hp	HP:0002493	3.07E-02	2	Upper motor neuron dysfunction
hp	HP:0000598	3.07E-02	3	Abnormality of the ear
hp	HP:0002012	3.05E-02	3	Abnormality of the abdominal organs
hp	HP:0004328	3.03E-02	2	Abnormality of the anterior segment of the eye
hp	HP:0001155	3.02E-02	2	Abnormality of the hand
hp	HP:0004322	2.99E-02	2	Short stature
hp	HP:0010935	2.97E-02	2	Abnormality of the upper urinary tract
hp	HP:0002597	2.87E-02	2	Abnormality of the vasculature
hp	HP:0007364	2.87E-02	2	Aplasia/Hypoplasia of the cerebrum
hp	HP:0040064	2.85E-02	3	Abnormality of limbs
hp	HP:0000818	2.84E-02	2	Abnormality of the endocrine system
hp	HP:0012718	2.78E-02	2	Morphological abnormality of the gastrointestinal tract
hp	HP:0001392	2.78E-02	2	Abnormality of the liver
hp	HP:0001760	2.77E-02	2	Abnormality of the foot
hp	HP:0011458	2.71E-02	2	Abdominal symptom
hp	HP:0001263	2.66E-02	2	Global developmental delay

hp	HP:0003674	2.62E-02	2	Onset
hp	HP:0000811	2.49E-02	2	Abnormal external genitalia
hp	HP:0010461	2.47E-02	2	Abnormality of the male genitalia
hp	HP:0000032	2.40E-02	2	Abnormality of male external genitalia
hp	HP:0009115	2.35E-02	2	Aplasia/hypoplasia involving the skeleton
hp	HP:0001595	2.32E-02	2	Abnormality of the hair
hp	HP:0001438	2.29E-02	4	Abnormality of the abdomen
hp	HP:0011025	2.26E-02	2	Abnormality of cardiovascular system physiology
hp	HP:0000492	2.23E-02	2	Abnormality of the eyelid
hp	HP:0040195	2.16E-02	2	Decreased head circumference
hp	HP:0000252	2.16E-02	2	Microcephaly
hp	HP:0000007	2.11E-02	5	Autosomal recessive inheritance
hp	HP:0004325	2.09E-02	2	Decreased body weight
hp	HP:0100547	2.09E-02	3	Abnormality of forebrain morphology
hp	HP:0002664	2.08E-02	2	Neoplasm
hp	HP:0002060	2.08E-02	3	Abnormality of the cerebrum
hp	HP:0000707	2.07E-02	6	Abnormality of the nervous system
hp	HP:0000174	2.04E-02	2	Abnormality of the palate
hp	HP:0000163	2.03E-02	3	Abnormality of the oral cavity
hp	HP:0000315	2.02E-02	2	Abnormality of the orbital region
hp	HP:0001250	2.02E-02	3	Seizures
hp	HP:0001324	2.01E-02	2	Muscle weakness
hp	HP:0000119	1.99E-02	4	Abnormality of the genitourinary system
hp	HP:0000359	1.98E-02	2	Abnormality of the inner ear
hp	HP:0001626	1.98E-02	4	Abnormality of the cardiovascular system
hp	HP:0011389	1.96E-02	2	Functional abnormality of the inner ear
hp	HP:0001507	1.95E-02	4	Growth abnormality
hp	HP:0000035	1.92E-02	2	Abnormality of the testis
hp	HP:0002715	1.89E-02	3	Abnormality of the immune system
hp	HP:0000159	1.88E-02	2	Abnormality of the lip
hp	HP:0000479	1.87E-02	2	Abnormality of the retina
hp	HP:0000924	1.87E-02	5	Abnormality of the skeletal system
hp	HP:0000422	1.86E-02	2	Abnormality of the nasal bridge
hp	HP:0012372	1.85E-02	4	Abnormal eye morphology
hp	HP:0000407	1.84E-02	2	Sensorineural hearing impairment
hp	HP:0000152	1.79E-02	5	Abnormality of head or neck
hp	HP:0005105	1.78E-02	2	Abnormal nasal morphology
hp	HP:0012374	1.78E-02	4	Abnormality of the globe
hp	HP:0012373	1.78E-02	4	Abnormal eye physiology
hp	HP:0000277	1.75E-02	2	Abnormality of the mandible
hp	HP:0000517	1.73E-02	2	Abnormality of the lens
hp	HP:0000366	1.72E-02	3	Abnormality of the nose

hp	HP:0000234	1.71E-02	5	Abnormality of the head
hp	HP:0000078	1.70E-02	3	Abnormality of the genital system
hp	HP:0002977	1.68E-02	3	Aplasia/Hypoplasia involving the central nervous system
hp	HP:0011844	1.67E-02	3	Abnormal appendicular skeleton morphology
hp	HP:0000290	1.65E-02	2	Abnormality of the forehead
hp	HP:0000518	1.64E-02	2	Cataract
hp	HP:0001276	1.62E-02	2	Hypertonia
hp	HP:0003549	1.61E-02	3	Abnormality of connective tissue
hp	HP:0010938	1.59E-02	2	Abnormality of the external nose
hp	HP:0100886	1.59E-02	2	Abnormality of globe location
hp	HP:0000284	1.58E-02	3	Abnormality of the ocular region
hp	HP:0012758	1.58E-02	3	Neurodevelopmental delay
hp	HP:0011446	1.57E-02	4	Abnormality of higher mental function
hp	HP:0011842	1.57E-02	5	Abnormality of skeletal morphology
hp	HP:0040068	1.56E-02	3	Abnormality of limb bone
hp	HP:0012638	1.45E-02	6	Abnormality of nervous system physiology
hp	HP:0001627	1.42E-02	3	Abnormality of cardiac morphology
hp	HP:0002813	1.40E-02	3	Abnormality of limb bone morphology
hp	HP:0012639	1.36E-02	5	Abnormality of nervous system morphology
hp	HP:0002564	1.32E-02	3	Malformation of the heart and great vessels
hp	HP:0000481	1.31E-02	2	Abnormality of the cornea
ke	KEGG:01100	1.29E-02	2	Metabolic pathways
hp	HP:0011138	1.25E-02	3	Abnormality of skin adnexa
hp	HP:0000177	1.24E-02	2	Abnormality of upper lip
hp	HP:0100763	1.19E-02	2	Abnormality of the lymphatic system
hp	HP:0000028	1.16E-02	2	Cryptorchidism
hp	HP:0000925	1.16E-02	3	Abnormality of the vertebral column
hp	HP:0000271	1.11E-02	5	Abnormality of the face
hp	HP:0000202	1.08E-02	2	Oral cleft
hp	HP:0000153	1.08E-02	4	Abnormality of the mouth
hp	HP:0000508	1.06E-02	2	Ptosis
hp	HP:0000316	1.03E-02	2	Hypertelorism
hp	HP:0003812	1.03E-02	2	Phenotypic variability
hp	HP:0001780	1.01E-02	2	Abnormality of toe
hp	HP:0011297	1.01E-02	3	Abnormality of digit
hp	HP:0000429	9.59E-03	2	Abnormality of the nasal alae
hp	HP:0000606	9.32E-03	3	Abnormality of the periorbital region
hp	HP:0010936	9.20E-03	2	Abnormality of the lower urinary tract
hp	HP:0001197	9.20E-03	2	Abnormality of prenatal development or birth
hp	HP:0002011	9.20E-03	5	Morphological abnormality of the central nervous system
hp	HP:0011442	9.02E-03	4	Abnormality of central motor function

hp	HP:0100737	8.98E-03	2	Abnormality of the hard palate
hp	HP:0000175	8.87E-03	2	Cleft palate
hp	HP:0011843	8.65E-03	2	Abnormality of skeletal physiology
hp	HP:0000464	8.59E-03	2	Abnormality of the neck
hp	HP:0011821	8.30E-03	3	Abnormality of facial skeleton
hp	HP:0005288	8.16E-03	2	Abnormality of the nares
hp	HP:0012547	7.80E-03	3	Abnormal involuntary eye movements
hp	HP:0000639	7.72E-03	3	Nystagmus
hp	HP:0000463	7.69E-03	2	Anteverted nares
hp	HP:0009121	7.52E-03	5	Abnormal axial skeleton morphology
hp	HP:0011927	7.32E-03	2	Short digit
hp	HP:0000309	7.27E-03	2	Abnormality of the midface
hp	HP:0012823	6.90E-03	4	Clinical modifier
hp	HP:0012443	6.51E-03	5	Abnormality of brain morphology
hp	HP:0000534	6.46E-03	2	Abnormality of the eyebrow
hp	HP:0001510	6.38E-03	4	Growth delay
hp	HP:0003593	6.36E-03	2	Infantile onset
hp	HP:0000539	6.07E-03	2	Abnormality of refraction
hp	HP:0100543	5.95E-03	4	Cognitive impairment
hp	HP:0000496	5.37E-03	4	Abnormality of eye movement
hp	HP:0000286	5.26E-03	2	Epicanthus
hp	HP:0011443	5.02E-03	3	Abnormality of coordination
hp	HP:0001252	4.99E-03	4	Muscular hypotonia
hp	HP:0008056	4.94E-03	2	Aplasia/Hypoplasia affecting the eye
hp	HP:0000505	4.71E-03	3	Visual impairment
hp	HP:0001156	4.32E-03	2	Brachydactyly syndrome
hp	HP:0003319	3.90E-03	2	Abnormality of the cervical spine
hp	HP:0000545	3.81E-03	2	Myopia
hp	HP:0000929	3.48E-03	5	Abnormality of the skull
hp	HP:0000587	3.47E-03	3	Abnormality of the optic nerve
hp	HP:0000470	3.33E-03	2	Short neck
hp	HP:0007957	3.25E-03	2	Corneal opacity
hp	HP:0002648	3.17E-03	3	Abnormality of calvarial morphology
hp	HP:0000927	3.14E-03	2	Abnormality of skeletal maturation
hp	HP:0004329	2.90E-03	4	Abnormality of the posterior segment of the eye
hp	HP:0001098	2.87E-03	4	Abnormality of the fundus
hp	HP:0012795	2.86E-03	3	Abnormality of the optic disc
hp	HP:0003011	2.86E-03	6	Abnormality of the musculature
hp	HP:0000864	2.77E-03	2	Abnormality of the hypothalamus-pituitary axis
hp	HP:0001551	2.38E-03	2	Abnormality of the umbilicus
hp	HP:0001537	2.28E-03	2	Umbilical hernia

hp	HP:0003808	2.28E-03	5	Abnormal muscle tone
hp	HP:0000648	2.26E-03	3	Optic atrophy
hp	HP:0001251	2.22E-03	3	Ataxia
hp	HP:0002118	2.09E-03	3	Abnormality of the cerebral ventricles
hp	HP:0011603	1.98E-03	2	Congenital malformation of the great arteries
hp	HP:0002438	1.95E-03	2	Cerebellar malformation
hp	HP:0011282	1.88E-03	4	Abnormality of hindbrain morphology
hp	HP:0011283	1.88E-03	4	Abnormality of the metencephalon
hp	HP:0001317	1.87E-03	4	Abnormality of the cerebellum
hp	HP:0000280	1.83E-03	2	Coarse facial features
hp	HP:0001643	1.80E-03	2	Patent ductus arteriosus
hp	HP:0002538	1.68E-03	2	Abnormality of the cerebral cortex
hp	HP:0000504	1.58E-03	4	Abnormality of vision
hp	HP:0002536	1.42E-03	2	Abnormal cortical gyration
hp	HP:0100729	1.37E-03	2	Large face
hp	HP:0011804	1.36E-03	6	Abnormality of muscle physiology
hp	HP:0002334	1.34E-03	2	Abnormality of the cerebellar vermis
hp	HP:0006817	1.18E-03	2	Aplasia/Hypoplasia of the cerebellar vermis
hp	HP:0007663	1.13E-03	2	Reduced visual acuity
ke	KEGG:04080	1.08E-03	2	Neuroactive ligand-receptor interaction
hp	HP:0000276	1.06E-03	2	Long face
hp	HP:0001320	1.04E-03	2	Cerebellar vermis hypoplasia
hp	HP:0004298	1.00E-03	3	Abnormality of the abdominal wall
hp	HP:0002921	1.00E-03	3	Abnormality of the cerebrospinal fluid
hp	HP:0010576	9.65E-04	2	Intracranial cystic lesion
hp	HP:0100790	9.00E-04	3	Hernia
hp	HP:0002693	8.97E-04	2	Abnormality of the skull base
hp	HP:0002683	8.21E-04	4	Abnormality of the calvaria
hp	HP:0000932	7.67E-04	2	Abnormality of the posterior cranial fossa
hp	HP:0011815	7.67E-04	2	Cephalocele
hp	HP:0002084	7.67E-04	2	Encephalocele
hp	HP:0002119	7.55E-04	3	Ventriculomegaly
hp	HP:0001999	7.54E-04	4	Abnormal facial shape
hp	HP:0002350	7.26E-04	2	Cerebellar cyst
hp	HP:0010950	7.06E-04	2	Abnormality of the fourth ventricle
hp	HP:0002198	7.06E-04	2	Dilated fourth ventricle
hp	HP:0000341	6.47E-04	2	Narrow forehead
hp	HP:0010866	6.33E-04	3	Abdominal wall defect
hp	HP:0005445	6.28E-04	2	Widened posterior fossa
hp	HP:0004299	6.16E-04	3	Hernia of the abdominal wall
hp	HP:0001305	6.09E-04	2	Dandy-Walker malformation
hp	HP:0004307	5.19E-04	2	Abnormal anatomic location of the heart
hp	HP:0001651	5.19E-04	2	Dextrocardia

hp	HP:0000572	5.19E-04	2	Visual loss
hp	HP:0000549	4.81E-04	4	Abnormal conjugate eye movement
hp	HP:0000486	4.72E-04	4	Strabismus
hp	HP:0011534	4.51E-04	2	Abnormal spatial orientation of the cardiac segments
hp	HP:0001696	4.51E-04	2	Situs inversus totalis
hp	HP:0000238	4.28E-04	3	Hydrocephalus
hp	HP:0002269	3.75E-04	3	Abnormality of neuronal migration
hp	HP:0000157	2.70E-04	3	Abnormality of the tongue
hp	HP:0002085	1.82E-05	2	Occipital encephalocele

Supplementary information, Table S14 Functional enrichment categories of PSGs reported by Rubin and colleagues in all domestic lines(AD). Categories associated with vision-related function are marked in green.

Term	Term ID	P-value	Gene number	Descriptions
ke	KEGG:04621	2.59E-02	3	NOD-like receptor signaling pathway
ke	KEGG:00770	5.00E-02	2	Pantothenate and CoA biosynthesis
hp	HP:0410008	7.77E-03	4	Abnormality of the peripheral nervous system
hp	HP:0200013	3.59E-03	2	Neoplasm of fatty tissue
hp	HP:0200007	4.35E-02	2	Abnormal size of the palpebral fissures
hp	HP:0100886	3.77E-02	7	Abnormality of globe location
hp	HP:0100851	4.28E-02	4	Abnormal emotion/affect behavior
hp	HP:0100790	1.22E-02	6	Hernia
hp	HP:0100755	1.88E-03	3	Abnormality of salivation
hp	HP:0100729	4.35E-02	2	Large face
hp	HP:0100691	2.26E-02	2	Abnormality of the curvature of the cornea
hp	HP:0100689	3.41E-02	2	Decreased corneal thickness
hp	HP:0100659	4.46E-02	2	Abnormality of the cerebral vasculature
hp	HP:0100615	1.43E-02	2	Ovarian neoplasm
hp	HP:0100589	7.64E-03	3	Urogenital fistula
hp	HP:0100547	1.36E-02	16	Abnormality of forebrain morphology
hp	HP:0100543	3.66E-02	13	Cognitive impairment
hp	HP:0100540	2.65E-03	2	Palpebral edema
hp	HP:0100539	4.29E-03	2	Periorbital edema
hp	HP:0100335	7.49E-03	2	Non-midline cleft lip
hp	HP:0100259	3.63E-02	2	Postaxial polydactyly
hp	HP:0100022	1.87E-02	14	Abnormality of movement
hp	HP:0040195	2.92E-02	9	Decreased head circumference
hp	HP:0040075	2.37E-02	2	Hypopituitarism
hp	HP:0030311	3.63E-02	2	Lower extremity joint dislocation
hp	HP:0030182	3.59E-03	2	Tetraplegia/tetraparesis
hp	HP:0012874	2.49E-02	2	Abnormal male reproductive system physiology
hp	HP:0012823	3.13E-02	14	Clinical modifier
hp	HP:0012758	3.81E-02	12	Neurodevelopmental delay
hp	HP:0012640	6.63E-03	2	Abnormality of intracranial pressure
hp	HP:0012639	4.18E-02	22	Abnormality of nervous system morphology
hp	HP:0012575	4.24E-02	2	Abnormality of the nephron
hp	HP:0012547	1.44E-02	11	Abnormal involuntary eye movements
hp	HP:0012531	2.24E-02	3	Pain
hp	HP:0012503	1.76E-02	3	Abnormality of the pituitary gland
hp	HP:0012443	1.47E-02	21	Abnormality of brain morphology
hp	HP:0012387	6.63E-03	2	Bronchitis

hp	HP:0012331	1.09E-02	3	Abnormal autonomic nervous system morphology
hp	HP:0012210	4.76E-02	7	Abnormal renal morphology
hp	HP:0012130	4.81E-02	5	Abnormality of cells of the erythroid lineage
hp	HP:0012103	1.98E-02	2	Abnormality of the mitochondrion
hp	HP:0012031	3.59E-03	2	Lipomatous tumor
hp	HP:0011815	9.07E-03	3	Cephalocele
hp	HP:0011804	4.76E-02	18	Abnormality of muscle physiology
hp	HP:0011799	1.59E-02	4	Abnormality of facial soft tissue
hp	HP:0011772	1.98E-02	2	Abnormality of thyroid morphology
hp	HP:0011747	1.65E-02	3	Abnormality of the anterior pituitary
hp	HP:0011733	2.72E-02	2	Abnormality of adrenal physiology
hp	HP:0011732	9.31E-03	2	Abnormality of adrenal morphology
hp	HP:0011486	3.52E-02	2	Abnormality of corneal thickness
hp	HP:0011458	5.00E-02	9	Abdominal symptom
hp	HP:0011446	1.29E-02	20	Abnormality of higher mental function
hp	HP:0011443	1.06E-02	10	Abnormality of coordination
hp	HP:0011442	2.19E-02	16	Abnormality of central motor function
hp	HP:0011355	4.83E-02	6	Localized skin lesion
hp	HP:0011338	3.69E-02	2	Abnormality of mouth shape
hp	HP:0011334	9.35E-04	2	Facial shape deformation
hp	HP:0011329	3.37E-02	3	Abnormality of cranial sutures
hp	HP:0011328	1.06E-02	3	Abnormality of fontanelles
hp	HP:0011283	2.97E-02	10	Abnormality of the metencephalon
hp	HP:0011282	2.97E-02	10	Abnormality of hindbrain morphology
hp	HP:0011025	3.29E-02	9	Abnormality of cardiovascular system physiology
hp	HP:0011017	4.03E-02	4	Abnormality of cell physiology
hp	HP:0011014	4.49E-02	5	Abnormal glucose homeostasis
hp	HP:0010950	2.78E-02	2	Abnormality of the fourth ventricle
hp	HP:0010866	7.61E-03	6	Abdominal wall defect
hp	HP:0010864	1.87E-02	2	Intellectual disability, severe
hp	HP:0010787	2.78E-02	2	Genital neoplasm
hp	HP:0010785	1.98E-02	2	Gonadal neoplasm
hp	HP:0010647	4.24E-02	2	Abnormal elasticity of skin
hp	HP:0010576	1.19E-02	3	Intracranial cystic lesion
hp	HP:0010460	2.78E-02	7	Abnormality of the female genitalia
hp	HP:0010161	1.81E-02	2	Abnormality of the phalanges of the toes
hp	HP:0009774	3.52E-02	2	Triangular shaped phalanges of the hand
hp	HP:0009602	3.24E-02	2	Abnormality of thumb phalanx
hp	HP:0009136	2.95E-02	2	Duplication involving bones of the feet
hp	HP:0009124	1.80E-02	3	Abnormality of adipose tissue
hp	HP:0009121	1.98E-02	21	Abnormal axial skeleton morphology
hp	HP:0009118	4.19E-02	6	Aplasia/Hypoplasia of the mandible
hp	HP:0009116	4.34E-02	6	Aplasia/Hypoplasia involving bones of the skull

hp	HP:0008872	4.46E-02	4	Feeding difficulties in infancy
hp	HP:0008678	3.20E-02	3	Renal hypoplasia/aplasia
hp	HP:0008572	2.26E-02	2	External ear malformation
hp	HP:0008316	3.26E-03	2	Abnormal mitochondria in muscle tissue
hp	HP:0008067	2.37E-02	2	Abnormally lax or hyperextensible skin
hp	HP:0008056	3.35E-02	4	Aplasia/Hypoplasia affecting the eye
hp	HP:0008047	2.36E-02	3	Abnormality of the vasculature of the eye
hp	HP:0008046	2.04E-02	3	Abnormality of the retinal vasculature
hp	HP:0007379	4.19E-02	2	Neoplasm of the genitourinary tract
hp	HP:0007364	1.67E-02	12	Aplasia/Hypoplasia of the cerebrum
hp	HP:0007360	1.65E-02	5	Aplasia/Hypoplasia of the cerebellum
hp	HP:0007256	4.48E-02	3	Abnormal pyramidal signs
hp	HP:0006817	1.50E-02	3	Aplasia/Hypoplasia of the cerebellar vermis
hp	HP:0006703	3.06E-02	2	Aplasia/Hypoplasia of the lungs
hp	HP:0005750	2.37E-02	2	Contractures of the joints of the lower limbs
hp	HP:0005607	6.91E-03	5	Abnormality of the tracheobronchial system
hp	HP:0005445	2.55E-02	2	Widened posterior fossa
hp	HP:0005262	4.67E-02	2	Abnormality of the synovia
hp	HP:0005107	2.37E-02	2	Abnormality of the sacrum
hp	HP:0004426	4.62E-02	2	Abnormality of the cheek
hp	HP:0004372	3.05E-03	6	Reduced consciousness/confusion
hp	HP:0004362	1.09E-02	3	Abnormality of the enteric ganglia
hp	HP:0004360	2.13E-02	5	Abnormality of acid-base homeostasis
hp	HP:0004329	4.61E-02	10	Abnormality of the posterior segment of the eye
hp	HP:0004325	2.68E-02	9	Decreased body weight
hp	HP:0004323	3.54E-02	11	Abnormality of body weight
hp	HP:0004305	1.60E-02	5	Involuntary movements
hp	HP:0004302	2.52E-02	3	Functional motor problems
hp	HP:0004299	7.32E-03	6	Hernia of the abdominal wall
hp	HP:0004298	5.93E-03	7	Abnormality of the abdominal wall
hp	HP:0003812	1.51E-02	7	Phenotypic variability
hp	HP:0003808	2.35E-02	16	Abnormal muscle tone
hp	HP:0003781	5.20E-04	3	Excessive salivation
hp	HP:0003677	3.91E-02	2	Slow progression
hp	HP:0003593	1.59E-03	8	Infantile onset
hp	HP:0003549	3.94E-02	12	Abnormality of connective tissue
hp	HP:0003546	1.87E-02	2	Exercise intolerance
hp	HP:0003487	2.90E-02	3	Babinski sign
hp	HP:0003457	4.78E-02	2	EMG abnormality
hp	HP:0003287	1.87E-02	2	Abnormality of mitochondrial metabolism
hp	HP:0003128	5.83E-03	4	Lactic acidosis
hp	HP:0003119	4.57E-02	2	Abnormality of lipid metabolism
hp	HP:0003117	3.59E-02	3	Abnormality of circulating hormone level

hp	HP:0003011	4.22E-02	21	Abnormality of the musculature
hp	HP:0002977	1.12E-02	15	Aplasia/Hypoplasia involving the central nervous system
hp	HP:0002921	4.88E-02	4	Abnormality of the cerebrospinal fluid
hp	HP:0002837	2.36E-03	2	Recurrent bronchitis
hp	HP:0002827	2.83E-02	2	Hip dislocation
hp	HP:0002804	2.20E-02	2	Arthrogryposis multiplex congenita
hp	HP:0002803	2.66E-02	2	Congenital contracture
hp	HP:0002795	3.62E-02	8	Functional respiratory abnormality
hp	HP:0002793	4.18E-02	3	Abnormal pattern of respiration
hp	HP:0002788	2.37E-02	2	Recurrent upper respiratory tract infections
hp	HP:0002778	1.22E-02	3	Abnormality of the trachea
hp	HP:0002693	3.29E-02	2	Abnormality of the skull base
hp	HP:0002683	4.84E-02	7	Abnormality of the calvaria
hp	HP:0002634	2.09E-02	2	Arteriosclerosis
hp	HP:0002621	1.98E-02	2	Atherosclerosis
hp	HP:0002575	1.70E-02	2	Tracheoesophageal fistula
hp	HP:0002553	2.60E-02	2	Highly arched eyebrow
hp	HP:0002539	2.08E-03	2	Cortical dysplasia
hp	HP:0002538	4.93E-02	2	Abnormality of the cerebral cortex
hp	HP:0002516	6.63E-03	2	Increased intracranial pressure
hp	HP:0002510	1.28E-02	2	Spastic tetraplegia
hp	HP:0002493	1.30E-02	13	Upper motor neuron dysfunction
hp	HP:0002465	4.29E-03	2	Poor speech
hp	HP:0002445	1.82E-03	2	Tetraplegia
hp	HP:0002438	2.57E-02	3	Cerebellar malformation
hp	HP:0002360	2.16E-02	3	Sleep disturbance
hp	HP:0002354	1.76E-02	2	Memory impairment
hp	HP:0002350	8.48E-03	3	Cerebellar cyst
hp	HP:0002344	3.59E-03	2	Progressive neurologic deterioration
hp	HP:0002334	1.72E-02	3	Abnormality of the cerebellar vermis
hp	HP:0002315	3.91E-02	2	Headache
hp	HP:0002311	3.96E-02	4	Incoordination
hp	HP:0002307	3.94E-03	2	Drooling
hp	HP:0002270	7.57E-03	4	Abnormality of the autonomic nervous system
hp	HP:0002251	1.09E-02	3	Aganglionic megacolon
hp	HP:0002244	3.69E-02	2	Abnormality of the small intestine
hp	HP:0002198	2.78E-02	2	Dilated fourth ventricle
hp	HP:0002194	2.95E-03	2	Delayed gross motor development
hp	HP:0002186	7.91E-03	3	Apraxia
hp	HP:0002119	4.07E-02	4	Ventriculomegaly
hp	HP:0002109	2.55E-02	2	Abnormality of the bronchi
hp	HP:0002104	2.32E-02	3	Apnea

hp	HP:0002089	1.87E-02	2	Pulmonary hypoplasia
hp	HP:0002087	7.61E-03	6	Abnormality of the upper respiratory tract
hp	HP:0002084	9.07E-03	3	Encephalocele
hp	HP:0002072	8.19E-03	3	Chorea
hp	HP:0002071	4.14E-02	2	Abnormality of extrapyramidal motor function
hp	HP:0002060	1.32E-02	16	Abnormality of the cerebrum
hp	HP:0002031	2.53E-02	5	Abnormality of the esophagus
hp	HP:0002027	1.29E-02	3	Abdominal pain
hp	HP:0002017	9.57E-03	5	Nausea and vomiting
hp	HP:0002013	1.61E-02	3	Vomiting
hp	HP:0002011	2.92E-02	21	Morphological abnormality of the central nervous system
hp	HP:0002009	9.35E-04	2	Potter facies
hp	HP:0001999	2.96E-02	8	Abnormal facial shape
hp	HP:0001943	4.57E-02	2	Hypoglycemia
hp	HP:0001941	1.73E-02	5	Acidosis
hp	HP:0001939	4.05E-02	20	Abnormality of metabolism/homeostasis
hp	HP:0001877	4.81E-02	5	Abnormality of erythrocytes
hp	HP:0001829	2.89E-02	2	Foot polydactyly
hp	HP:0001824	1.69E-02	3	Weight loss
hp	HP:0001770	4.46E-02	2	Toe syndactyly
hp	HP:0001763	3.91E-02	2	Pes planus
hp	HP:0001739	3.01E-02	2	Abnormality of the nasopharynx
hp	HP:0001710	2.60E-02	2	Conotruncal defect
hp	HP:0001695	3.75E-02	2	Cardiac arrest
hp	HP:0001649	7.36E-03	3	Tachycardia
hp	HP:0001645	3.58E-02	2	Sudden cardiac death
hp	HP:0001636	2.55E-02	2	Tetralogy of Fallot
hp	HP:0001626	3.63E-02	19	Abnormality of the cardiovascular system
hp	HP:0001622	9.07E-03	3	Premature birth
hp	HP:0001600	3.47E-02	2	Abnormality of the larynx
hp	HP:0001562	7.36E-03	3	Oligohydramnios
hp	HP:0001561	3.86E-02	2	Polyhydramnios
hp	HP:0001560	1.73E-02	4	Abnormality of the amniotic fluid
hp	HP:0001551	4.23E-03	5	Abnormality of the umbilicus
hp	HP:0001537	3.88E-03	5	Umbilical hernia
hp	HP:0001518	2.37E-02	2	Small for gestational age
hp	HP:0001438	4.93E-02	19	Abnormality of the abdomen
hp	HP:0001384	4.57E-02	2	Abnormality of the hip joint
hp	HP:0001347	6.72E-03	9	Hyperreflexia
hp	HP:0001337	1.67E-02	5	Tremor
hp	HP:0001336	3.12E-02	2	Myoclonus
hp	HP:0001332	1.98E-03	6	Dystonia

hp	HP:0001320	1.29E-02	3	Cerebellar vermis hypoplasia
hp	HP:0001319	2.72E-02	2	Neonatal hypotonia
hp	HP:0001317	2.95E-02	10	Abnormality of the cerebellum
hp	HP:0001305	2.49E-02	2	Dandy-Walker malformation
hp	HP:0001276	2.37E-02	8	Hypertonia
hp	HP:0001274	1.47E-02	3	Agenesis of corpus callosum
hp	HP:0001270	9.18E-03	5	Motor delay
hp	HP:0001266	8.39E-03	2	Choreoathetosis
hp	HP:0001257	4.40E-02	5	Spasticity
hp	HP:0001254	3.06E-02	2	Lethargy
hp	HP:0001252	2.86E-02	13	Muscular hypotonia
hp	HP:0001251	1.94E-02	7	Ataxia
hp	HP:0001250	6.64E-03	17	Seizures
hp	HP:0001199	9.31E-03	2	Triphalangeal thumb
hp	HP:0001197	4.11E-02	5	Abnormality of prenatal development or birth
hp	HP:0001123	3.18E-02	2	Visual field defect
hp	HP:0001120	4.19E-02	2	Abnormality of corneal size
hp	HP:0001098	4.56E-02	10	Abnormality of the fundus
hp	HP:0001053	1.54E-02	3	Hypopigmented skin patches
hp	HP:0001012	3.26E-03	2	Multiple lipomas
hp	HP:0001010	2.82E-02	3	Hypopigmentation of the skin
hp	HP:0001005	2.24E-02	3	Dermatological manifestations of systemic disorders
hp	HP:0000957	2.55E-02	2	Cafe-au-lait spot
hp	HP:0000932	2.95E-02	2	Abnormality of the posterior cranial fossa
hp	HP:0000929	1.12E-02	19	Abnormality of the skull
hp	HP:0000889	2.78E-02	2	Abnormality of the clavicle
hp	HP:0000864	1.69E-03	6	Abnormality of the hypothalamus-pituitary axis
hp	HP:0000853	5.41E-03	2	Goiter
hp	HP:0000834	5.65E-03	4	Abnormality of the adrenal glands
hp	HP:0000830	2.32E-02	2	Anterior hypopituitarism
hp	HP:0000822	8.45E-03	5	Hypertension
hp	HP:0000818	1.58E-02	12	Abnormality of the endocrine system
hp	HP:0000812	2.14E-02	7	Abnormal internal genitalia
hp	HP:0000752	1.88E-02	3	Hyperactivity
hp	HP:0000738	2.89E-02	2	Hallucinations
hp	HP:0000737	1.87E-02	2	Irritability
hp	HP:0000729	4.19E-03	4	Autistic behavior
hp	HP:0000717	2.66E-02	2	Autism
hp	HP:0000708	1.94E-03	15	Behavioral abnormality
hp	HP:0000657	3.29E-03	3	Oculomotor apraxia
hp	HP:0000639	1.41E-02	11	Nystagmus
hp	HP:0000617	6.63E-03	2	Abnormality of ocular smooth pursuit

hp	HP:0000612	1.76E-02	3	Iris coloboma
hp	HP:0000610	4.98E-02	2	Abnormality of the choroid
hp	HP:0000600	3.75E-02	2	Abnormality of the pharynx
hp	HP:0000589	1.28E-02	4	Coloboma
hp	HP:0000582	4.72E-02	2	Upslanted palpebral fissure
hp	HP:0000581	3.24E-02	2	Blepharophimosis
hp	HP:0000568	4.41E-02	2	Microphthalmos
hp	HP:0000553	3.20E-02	5	Abnormality of the uvea
hp	HP:0000551	2.43E-02	2	Abnormality of color vision
hp	HP:0000545	2.44E-02	4	Myopia
hp	HP:0000543	2.49E-02	2	Optic disc pallor
hp	HP:0000539	2.27E-02	5	Abnormality of refraction
hp	HP:0000532	4.57E-02	2	Chorioretinal abnormality
hp	HP:0000525	1.94E-02	5	Abnormality of the iris
hp	HP:0000508	1.63E-02	7	Ptosis
hp	HP:0000505	4.65E-02	7	Visual impairment
hp	HP:0000499	4.19E-02	2	Abnormality of the eyelashes
hp	HP:0000496	3.18E-02	13	Abnormality of eye movement
hp	HP:0000492	4.75E-02	8	Abnormality of the eyelid
hp	HP:0000490	2.55E-02	2	Deeply set eye
hp	HP:0000482	3.75E-02	2	Microcornea
hp	HP:0000479	4.95E-02	7	Abnormality of the retina
hp	HP:0000453	2.03E-02	2	Choanal atresia
hp	HP:0000426	3.97E-02	2	Prominent nasal bridge
hp	HP:0000415	2.32E-02	2	Abnormality of the choanae
hp	HP:0000383	1.65E-02	2	Abnormality of periauricular region
hp	HP:0000368	3.99E-02	4	Low-set, posteriorly rotated ears
hp	HP:0000347	4.16E-02	6	Micrognathia
hp	HP:0000341	2.60E-02	2	Narrow forehead
hp	HP:0000340	3.29E-02	2	Sloping forehead
hp	HP:0000337	2.03E-02	2	Broad forehead
hp	HP:0000322	2.37E-02	2	Short philtrum
hp	HP:0000316	1.53E-02	7	Hypertelorism
hp	HP:0000315	3.89E-02	8	Abnormality of the orbital region
hp	HP:0000308	1.58E-03	2	Microretrognathia
hp	HP:0000286	1.80E-02	5	Epicanthus
hp	HP:0000282	4.29E-03	2	Facial edema
hp	HP:0000278	2.43E-02	2	Retrognathia
hp	HP:0000276	3.69E-02	2	Long face
hp	HP:0000268	4.24E-02	2	Dolichocephaly
hp	HP:0000260	7.06E-03	2	Wide anterior fontanel
hp	HP:0000252	2.92E-02	9	Microcephaly
hp	HP:0000240	2.43E-02	12	Abnormality of skull size

hp	HP:0000239	6.83E-03	3	Large fontanelles
hp	HP:0000236	1.38E-02	2	Abnormality of the anterior fontanelle
hp	HP:0000235	1.60E-02	5	Abnormality of the fontanelles or cranial sutures
hp	HP:0000234	3.44E-02	24	Abnormality of the head
hp	HP:0000204	4.98E-02	2	Cleft upper lip
hp	HP:0000194	1.28E-02	2	Open mouth
hp	HP:0000157	1.83E-02	4	Abnormality of the tongue
hp	HP:0000152	3.77E-02	24	Abnormality of head or neck
hp	HP:0000137	4.93E-02	2	Abnormality of the ovary
hp	HP:0000112	2.83E-02	2	Nephropathy
hp	HP:0000091	1.54E-02	2	Abnormality of the renal tubule
hp	HP:0000025	2.15E-02	2	Functional abnormality of male internal genitalia
hp	HP:0000023	8.77E-03	3	Inguinal hernia
hp	HP:0000008	1.77E-02	7	Abnormality of female internal genitalia
hp	HP:0000007	2.77E-02	26	Autosomal recessive inheritance
hp	HP:0000006	5.00E-02	16	Autosomal dominant inheritance
hp	HP:0000005	3.78E-02	38	Mode of inheritance
BP	GO:2001022	3.99E-02	2	positive regulation of response to DNA damage stimulus
BP	GO:2000377	4.21E-02	3	regulation of reactive oxygen species metabolic process
BP	GO:1990778	4.64E-02	4	protein localization to cell periphery
BP	GO:1990542	1.36E-02	2	mitochondrial transmembrane transport
BP	GO:1904591	1.63E-02	3	positive regulation of protein import
BP	GO:1903522	3.20E-02	4	regulation of blood circulation
BP	GO:1901990	4.54E-02	4	regulation of mitotic cell cycle phase transition
MF	GO:1901981	3.87E-02	3	phosphatidylinositol phosphate binding
MF	GO:1901618	4.77E-03	3	organic hydroxy compound transmembrane transporter activity
BP	GO:1900182	2.02E-02	3	positive regulation of protein localization to nucleus
CC	GO:0098798	4.57E-02	3	mitochondrial protein complex
CC	GO:0098794	2.74E-02	5	postsynapse
MF	GO:0098772	2.50E-02	14	molecular function regulator
CC	GO:0098590	2.33E-02	9	plasma membrane region
BP	GO:0097306	1.28E-02	3	cellular response to alcohol
BP	GO:0097305	4.45E-02	3	response to alcohol
BP	GO:0097031	7.12E-03	2	mitochondrial respiratory chain complex I biogenesis
BP	GO:0090659	2.78E-02	2	walking behavior
BP	GO:0090075	9.08E-03	2	relaxation of muscle
BP	GO:0090002	4.93E-02	3	establishment of protein localization to plasma membrane

BP	GO:0072661	4.58E-03	2	protein targeting to plasma membrane
BP	GO:0072659	4.54E-02	4	protein localization to plasma membrane
BP	GO:0072593	4.10E-02	4	reactive oxygen species metabolic process
BP	GO:0071806	4.41E-03	3	protein transmembrane transport
BP	GO:0071805	4.27E-02	4	potassium ion transmembrane transport
BP	GO:0071804	4.27E-02	4	cellular potassium ion transport
BP	GO:0071514	8.07E-03	2	genetic imprinting
BP	GO:0071407	1.63E-02	6	cellular response to organic cyclic compound
BP	GO:0071396	4.76E-02	5	cellular response to lipid
BP	GO:0071383	4.81E-02	3	cellular response to steroid hormone stimulus
BP	GO:0070482	2.83E-02	4	response to oxygen levels
BP	GO:0065002	3.28E-02	2	intracellular protein transmembrane transport
BP	GO:0061647	1.88E-02	2	histone H3-K9 modification
BP	GO:0061384	9.08E-03	2	heart trabecula morphogenesis
BP	GO:0061383	2.47E-02	2	trabecula morphogenesis
BP	GO:0061061	1.89E-02	9	muscle structure development
BP	GO:0060537	4.53E-02	6	muscle tissue development
BP	GO:0060420	1.61E-02	2	regulation of heart growth
BP	GO:0060419	3.74E-03	3	heart growth
BP	GO:0060122	1.88E-02	2	inner ear receptor stereocilium organization
BP	GO:0060119	3.81E-02	2	inner ear receptor cell development
BP	GO:0060113	1.70E-02	3	inner ear receptor cell differentiation
MF	GO:0060089	5.00E-02	16	molecular transducer activity
BP	GO:0060043	1.12E-02	2	regulation of cardiac muscle cell proliferation
BP	GO:0060038	1.88E-02	2	cardiac muscle cell proliferation
BP	GO:0055117	4.93E-02	2	regulation of cardiac muscle contraction
BP	GO:0055114	4.95E-02	12	oxidation-reduction process
BP	GO:0055085	4.29E-02	16	transmembrane transport
BP	GO:0055024	3.11E-02	2	regulation of cardiac muscle tissue development
BP	GO:0055021	1.36E-02	2	regulation of cardiac muscle tissue growth
BP	GO:0055017	2.86E-03	3	cardiac muscle tissue growth
BP	GO:0055013	3.63E-02	2	cardiac muscle cell development
BP	GO:0055008	3.81E-02	2	cardiac muscle tissue morphogenesis
BP	GO:0055006	4.36E-02	2	cardiac cell development
BP	GO:0055001	2.62E-02	4	muscle cell development
MF	GO:0052689	3.76E-02	3	carboxylic ester hydrolase activity
BP	GO:0051937	2.62E-02	2	catecholamine transport
BP	GO:0051649	3.92E-02	24	establishment of localization in cell
BP	GO:0051567	1.01E-02	2	histone H3-K9 methylation
BP	GO:0051482	2.01E-03	2	positive regulation of cytosolic calcium ion concentration involved in phospholipase C-activating G-protein coupled signaling pathway
BP	GO:0051297	3.87E-02	3	centrosome organization

MF	GO:0051213	7.76E-03	3	dioxygenase activity
BP	GO:0051188	3.33E-02	3	cofactor biosynthetic process
MF	GO:0051117	3.99E-02	2	ATPase binding
BP	GO:0051049	4.83E-02	17	regulation of transport
BP	GO:0051046	3.55E-02	8	regulation of secretion
MF	GO:0051015	4.93E-02	3	actin filament binding
BP	GO:0050906	3.22E-02	3	detection of stimulus involved in sensory perception
BP	GO:0050821	2.18E-02	3	protein stabilization
BP	GO:0048771	1.13E-02	4	tissue remodeling
BP	GO:0048738	3.27E-02	4	cardiac muscle tissue development
BP	GO:0048545	3.93E-02	4	response to steroid hormone
BP	GO:0048514	4.93E-02	7	blood vessel morphogenesis
MF	GO:0046914	4.15E-02	18	transition metal ion binding
BP	GO:0046824	2.63E-02	3	positive regulation of nucleocytoplasmic transport
BP	GO:0046785	2.78E-02	2	microtubule polymerization
BP	GO:0045739	1.36E-02	2	positive regulation of DNA repair
CC	GO:0045202	5.65E-03	10	synapse
BP	GO:0044763	2.06E-02	106	single-organism cellular process
BP	GO:0044743	2.62E-02	2	intracellular protein transmembrane import
BP	GO:0044708	9.53E-03	8	single-organism behavior
BP	GO:0044700	1.96E-02	53	single organism signaling
CC	GO:0044463	3.61E-02	9	cell projection part
CC	GO:0044459	3.75E-02	23	plasma membrane part
CC	GO:0044456	1.45E-02	7	synapse part
CC	GO:0044306	2.32E-02	2	neuron projection terminus
CC	GO:0044291	3.81E-02	2	cell-cell contact zone
BP	GO:0044057	1.38E-03	9	regulation of system process
CC	GO:0043679	1.48E-02	2	axon terminus
BP	GO:0043502	3.11E-02	2	regulation of muscle adaptation
BP	GO:0043500	8.77E-03	3	muscle adaptation
BP	GO:0043200	4.74E-02	2	response to amino acid
MF	GO:0043167	4.13E-02	55	ion binding
BP	GO:0043087	3.20E-02	8	regulation of GTPase activity
BP	GO:0042692	3.96E-02	6	muscle cell differentiation
BP	GO:0042594	4.21E-02	3	response to starvation
BP	GO:0042490	2.10E-02	3	mechanoreceptor differentiation
BP	GO:0042472	4.81E-02	3	inner ear morphogenesis
BP	GO:0042391	4.02E-02	6	regulation of membrane potential
BP	GO:0042307	1.56E-02	3	positive regulation of protein import into nucleus
MF	GO:0038023	2.81E-02	13	signaling receptor activity
BP	GO:0036293	2.42E-02	4	response to decreased oxygen levels
BP	GO:0035873	1.52E-03	2	lactate transmembrane transport

CC	GO:0035032	1.09E-03	2	phosphatidylinositol 3-kinase complex, class III
BP	GO:0034770	1.09E-03	2	histone H4-K20 methylation
CC	GO:0033267	1.94E-02	3	axon part
BP	GO:0033108	1.48E-02	2	mitochondrial respiratory chain complex assembly
BP	GO:0032981	7.12E-03	2	mitochondrial respiratory chain complex I assembly
BP	GO:0032924	2.02E-02	2	activin receptor signaling pathway
BP	GO:0031669	4.69E-02	3	cellular response to nutrient levels
BP	GO:0031644	1.74E-02	2	regulation of neurological system process
CC	GO:0031300	2.97E-02	5	intrinsic component of organelle membrane
CC	GO:0031226	1.06E-02	17	intrinsic component of plasma membrane
BP	GO:0031214	3.12E-02	3	biomineral tissue development
BP	GO:0031023	4.81E-02	3	microtubule organizing center organization
BP	GO:0030534	2.42E-02	4	adult behavior
MF	GO:0030507	7.12E-03	2	spectrin binding
BP	GO:0030282	2.45E-02	3	bone mineralization
BP	GO:0030150	3.17E-03	2	protein import into mitochondrial matrix
BP	GO:0023052	1.39E-02	54	signaling
MF	GO:0022884	2.01E-03	2	macromolecule transmembrane transporter activity
BP	GO:0021591	1.74E-02	2	ventricular system development
MF	GO:0019842	4.93E-02	2	vitamin binding
BP	GO:0019722	3.33E-02	3	calcium-mediated signaling
BP	GO:0018345	1.61E-02	2	protein palmitoylation
BP	GO:0018231	8.07E-03	2	peptidyl-S-diacylglycerol-L-cysteine biosynthetic process from peptidyl-cysteine
BP	GO:0018230	8.07E-03	2	peptidyl-L-cysteine S-palmitoylation
BP	GO:0018198	2.17E-02	2	peptidyl-cysteine modification
BP	GO:0017038	4.45E-02	5	protein import
MF	GO:0016747	4.18E-02	4	transferase activity, transferring acyl groups other than amino-acyl groups
MF	GO:0016746	2.68E-02	5	transferase activity, transferring acyl groups
MF	GO:0016706	2.62E-02	2	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, 2-oxoglutarate as one donor, and incorporation of one atom each of oxygen into both donors
MF	GO:0016627	4.54E-02	2	oxidoreductase activity, acting on the CH-CH group of donors
MF	GO:0016500	3.85E-03	2	protein-hormone receptor activity
MF	GO:0016417	2.02E-02	2	S-acyltransferase activity
MF	GO:0016248	1.48E-02	2	channel inhibitor activity
MF	GO:0016247	5.50E-03	4	channel regulator activity
BP	GO:0015850	1.27E-02	5	organic hydroxy compound transport

BP	GO:0015844	4.17E-02	2	monoamine transport
BP	GO:0015727	1.52E-03	2	lactate transport
BP	GO:0015672	4.21E-02	8	monovalent inorganic cation transport
MF	GO:0015450	7.34E-04	2	P-P-bond-hydrolysis-driven protein transmembrane transporter activity
MF	GO:0015129	1.52E-03	2	lactate transmembrane transporter activity
BP	GO:0014898	2.56E-03	2	cardiac muscle hypertrophy in response to stress
BP	GO:0014897	3.14E-03	3	striated muscle hypertrophy
BP	GO:0014896	3.14E-03	3	muscle hypertrophy
BP	GO:0014888	1.61E-02	2	striated muscle adaptation
BP	GO:0014887	2.56E-03	2	cardiac muscle adaptation
BP	GO:0014855	3.99E-02	2	striated muscle cell proliferation
BP	GO:0014743	1.36E-02	2	regulation of muscle hypertrophy
BP	GO:0014742	3.85E-03	2	positive regulation of muscle hypertrophy
BP	GO:0014706	3.55E-02	6	striated muscle tissue development
CC	GO:0014069	1.26E-02	4	postsynaptic density
BP	GO:0010633	3.45E-02	2	negative regulation of epithelial cell migration
BP	GO:0010613	3.85E-03	2	positive regulation of cardiac muscle hypertrophy
BP	GO:0010611	1.24E-02	2	regulation of cardiac muscle hypertrophy
BP	GO:0010596	1.48E-02	2	negative regulation of endothelial cell migration
BP	GO:0010501	2.95E-02	2	RNA secondary structure unwinding
CC	GO:0010494	1.36E-02	2	cytoplasmic stress granule
BP	GO:0010257	7.12E-03	2	NADH dehydrogenase complex assembly
BP	GO:0009987	3.15E-02	128	cellular process
BP	GO:0009755	9.69E-03	4	hormone-mediated signaling pathway
BP	GO:0009653	3.10E-02	28	anatomical structure morphogenesis
BP	GO:0009628	2.87E-02	11	response to abiotic stimulus
BP	GO:0009267	3.54E-02	3	cellular response to starvation
BP	GO:0009108	2.10E-02	3	coenzyme biosynthetic process
BP	GO:0008344	2.63E-02	3	adult locomotory behavior
MF	GO:0008320	1.09E-03	2	protein transmembrane transporter activity
MF	GO:0008270	1.67E-02	17	zinc ion binding
MF	GO:0008200	1.36E-02	2	ion channel inhibitor activity
MF	GO:0008092	4.03E-02	11	cytoskeletal protein binding
MF	GO:0008083	4.93E-02	3	growth factor activity
MF	GO:0008028	3.63E-02	2	monocarboxylic acid transmembrane transporter activity
BP	GO:0007628	2.78E-02	2	adult walking behavior
BP	GO:0007626	7.73E-03	6	locomotory behavior
BP	GO:0007528	3.28E-02	2	neuromuscular junction development
BP	GO:0007270	1.35E-02	4	neuron-neuron synaptic transmission
BP	GO:0007215	4.74E-02	2	glutamate receptor signaling pathway
BP	GO:0007204	4.81E-02	3	positive regulation of cytosolic calcium ion

				concentration
BP	GO:0007200	1.70E-03	4	phospholipase C-activating G-protein coupled receptor signaling pathway
BP	GO:0007165	2.45E-02	49	signal transduction
BP	GO:0007154	2.77E-02	53	cell communication
BP	GO:0007098	1.94E-02	3	centrosome cycle
BP	GO:0007009	4.16E-02	5	plasma membrane organization
BP	GO:0006914	4.02E-02	6	autophagy
BP	GO:0006893	3.11E-02	2	Golgi to plasma membrane transport
BP	GO:0006886	4.00E-02	12	intracellular protein transport
BP	GO:0006821	3.87E-02	3	chloride transport
BP	GO:0006612	2.54E-02	3	protein targeting to membrane
BP	GO:0006605	6.88E-03	10	protein targeting
BP	GO:0006400	4.36E-02	2	tRNA modification
BP	GO:0006349	3.85E-03	2	regulation of gene expression by genetic imprinting
BP	GO:0006275	2.36E-02	3	regulation of DNA replication
CC	GO:0005942	1.24E-02	2	phosphatidylinositol 3-kinase complex
CC	GO:0005887	1.42E-02	16	integral component of plasma membrane
CC	GO:0005776	4.17E-02	2	autophagosome
MF	GO:0005251	2.17E-02	2	delayed rectifier potassium channel activity
MF	GO:0005057	3.22E-02	3	receptor signaling protein activity
MF	GO:0004930	4.02E-02	8	G-protein coupled receptor activity
MF	GO:0004871	1.86E-02	16	signal transducer activity
MF	GO:0003725	3.99E-02	2	double-stranded RNA binding
BP	GO:0003300	2.60E-03	3	cardiac muscle hypertrophy
BP	GO:0003299	2.56E-03	2	muscle hypertrophy in response to stress
BP	GO:0003230	1.36E-02	2	cardiac atrium development
BP	GO:0003012	1.37E-02	6	muscle system process
BP	GO:0003008	2.18E-02	17	system process
BP	GO:0002066	4.74E-02	2	columnar/cuboidal epithelial cell development
BP	GO:0001881	1.48E-02	2	receptor recycling
BP	GO:0001666	2.42E-02	4	response to hypoxia
CC	GO:0000407	1.88E-02	2	pre-autophagosomal structure
BP	GO:0000186	3.28E-02	2	activation of MAPKK activity

Supplementary information, Table S15 Functional enrichment categories of PSGs reported by Rubin and colleagues in commercial broiler lines (CB). Categories associated with vision-related function are marked in green.

Term	Term ID	P-value	Gene number	Descriptions
ke	KEGG:04620	5.00E-02	6	Toll-like receptor signaling pathway
ke	KEGG:04068	9.27E-03	8	FoxO signaling pathway
hp	HP:3000001	4.42E-02	2	Abnormal heart morphology
hp	HP:0100790	1.24E-02	7	Hernia
hp	HP:0100787	9.32E-04	2	Prostate neoplasm
hp	HP:0100742	2.90E-02	2	Vascular neoplasm
hp	HP:0100711	4.86E-03	2	Abnormality of the thoracic spine
hp	HP:0100691	4.53E-02	2	Abnormality of the curvature of the cornea
hp	HP:0100491	3.71E-02	6	Abnormality of lower limb joint
hp	HP:0100490	3.53E-02	3	Camptodactyly of finger
hp	HP:0100360	3.42E-02	4	Contractures of the joints of the upper limbs
hp	HP:0040075	4.76E-02	2	Hypopituitarism
hp	HP:0040068	2.58E-02	15	Abnormality of limb bone
hp	HP:0040064	4.79E-02	18	Abnormality of limbs
hp	HP:0040063	2.78E-03	2	Decreased adipose tissue
hp	HP:0030311	7.85E-03	4	Lower extremity joint dislocation
hp	HP:0012785	3.83E-02	3	Flexion contracture of finger
hp	HP:0012614	4.64E-02	2	Abnormal urine cytology
hp	HP:0012503	1.22E-02	4	Abnormality of the pituitary gland
hp	HP:0012387	1.36E-02	2	Bronchitis
hp	HP:0012179	1.53E-02	2	Craniofacial dystonia
hp	HP:0012125	6.73E-04	2	Prostate cancer
hp	HP:0012084	2.34E-03	2	Abnormality of skeletal muscle fiber size
hp	HP:0011947	1.92E-02	7	Respiratory tract infection
hp	HP:0011893	4.47E-02	3	Abnormal leukocyte count
hp	HP:0011844	3.16E-02	15	Abnormal appendicular skeleton morphology
hp	HP:0011843	4.70E-02	6	Abnormality of skeletal physiology
hp	HP:0011830	4.71E-02	3	Abnormality of oral mucosa
hp	HP:0011799	3.42E-02	4	Abnormality of facial soft tissue
hp	HP:0011772	3.98E-02	2	Abnormality of thyroid morphology
hp	HP:0011747	1.11E-02	4	Abnormality of the anterior pituitary
hp	HP:0011675	3.52E-02	6	Arrhythmia
hp	HP:0011458	1.98E-02	13	Abdominal symptom
hp	HP:0011368	3.43E-02	6	Epidermal thickening
hp	HP:0011355	1.09E-02	10	Localized skin lesion
hp	HP:0011121	3.58E-02	11	Abnormality of skin morphology
hp	HP:0011119	4.95E-02	3	Abnormality of the nasal dorsum

hp	HP:0011006	3.87E-02	2	Abnormality of the musculature of the neck
hp	HP:0011003	5.45E-03	2	Severe Myopia
hp	HP:0010991	3.01E-04	5	Abnormality of the abdominal musculature
hp	HP:0010866	6.98E-03	7	Abdominal wall defect
hp	HP:0010864	3.76E-02	2	Intellectual disability, severe
hp	HP:0010719	3.83E-02	3	Abnormality of hair texture
hp	HP:0010669	3.00E-02	2	Hypoplasia of the zygomatic bone
hp	HP:0010647	3.53E-02	3	Abnormal elasticity of skin
hp	HP:0010514	1.44E-02	2	Hyperpituitarism
hp	HP:0010438	4.83E-02	4	Abnormality of the ventricular septum
hp	HP:0010318	1.16E-03	4	Aplasia/Hypoplasia of the abdominal wall musculature
hp	HP:0009811	2.51E-02	4	Abnormality of the elbow
hp	HP:0009810	3.21E-02	6	Abnormality of upper limb joint
hp	HP:0009484	4.31E-02	5	Deviation of the hand or of fingers of the hand
hp	HP:0009125	4.20E-02	2	Lipodystrophy
hp	HP:0009124	3.76E-02	3	Abnormality of adipose tissue
hp	HP:0008887	1.57E-03	2	Adipose tissue loss
hp	HP:0008872	2.69E-02	6	Feeding difficulties in infancy
hp	HP:0008775	1.94E-03	2	Abnormality of the prostate
hp	HP:0008366	1.53E-02	2	Contractures involving the joints of the feet
hp	HP:0008365	6.36E-03	3	Abnormality of the talus
hp	HP:0008188	4.53E-04	2	Thyroid dysgenesis
hp	HP:0008180	3.26E-03	2	Mildly elevated creatine phosphokinase
hp	HP:0008067	4.76E-02	2	Abnormally lax or hyperextensible skin
hp	HP:0008065	1.95E-02	4	Aplasia/Hypoplasia of the skin
hp	HP:0007550	2.35E-02	4	Hypohidrosis or hyperhidrosis
hp	HP:0007502	0.00157	2	Follicular hyperkeratosis
hp	HP:0007495	1.30E-02	3	Prematurely aged appearance
hp	HP:0006705	2.38E-02	3	Abnormality of the atrioventricular valves
hp	HP:0006532	1.03E-02	2	Recurrent pneumonia
hp	HP:0006466	1.94E-03	2	Ankle contracture
hp	HP:0006460	1.39E-04	2	Increased laxity of ankles
hp	HP:0006261	1.38E-02	4	Abnormality of phalangeal joints of the hand
hp	HP:0006256	2.34E-03	2	Abnormality of hand joint mobility
hp	HP:0006149	1.39E-04	2	Increased laxity of fingers
hp	HP:0006094	2.34E-03	2	Finger joint hypermobility
hp	HP:0005990	2.75E-04	2	Thyroid hypoplasia
hp	HP:0005988	6.73E-04	2	Congenital muscular torticollis
hp	HP:0005750	2.88E-03	4	Contractures of the joints of the lower limbs
hp	HP:0005656	1.51E-02	6	Positional foot deformity
hp	HP:0005616	1.36E-02	2	Accelerated skeletal maturation
hp	HP:0005262	1.46E-02	4	Abnormality of the synovia

hp	HP:0005115	2.19E-02	2	Supraventricular arrhythmia
hp	HP:0005110	1.90E-02	2	Atrial fibrillation
hp	HP:0005072	1.39E-04	2	Hyperextensibility at wrists
hp	HP:0004755	2.09E-02	2	Supraventricular tachycardia
hp	HP:0004415	2.78E-03	2	Pulmonary artery stenosis
hp	HP:0004414	4.71E-02	3	Abnormality of the pulmonary artery
hp	HP:0004404	3.15E-02	3	Abnormality of the nipple
hp	HP:0004373	1.62E-02	2	Focal dystonia
hp	HP:0004372	4.70E-02	4	Reduced consciousness/confusion
hp	HP:0004347	2.49E-02	2	Weakness of muscles of respiration
hp	HP:0004325	1.14E-02	12	Decreased body weight
hp	HP:0004323	2.21E-02	14	Abnormality of body weight
hp	HP:0004299	6.66E-03	7	Hernia of the abdominal wall
hp	HP:0004298	2.02E-03	9	Abnormality of the abdominal wall
hp	HP:0004097	3.81E-02	5	Deviation of finger
hp	HP:0003803	6.73E-04	2	Type 1 muscle fiber predominance
hp	HP:0003741	2.34E-03	2	Congenital muscular dystrophy
hp	HP:0003713	4.53E-04	2	Muscle fiber necrosis
hp	HP:0003701	4.79E-02	3	Proximal muscle weakness
hp	HP:0003700	8.81E-03	2	Generalized amyotrophy
hp	HP:0003677	9.41E-03	4	Slow progression
hp	HP:0003560	3.00E-02	2	Muscular dystrophy
hp	HP:0003557	1.94E-03	2	Increased variability in muscle fiber diameter
hp	HP:0003325	6.07E-03	2	Limb-girdle muscle weakness
hp	HP:0003306	3.76E-03	2	Spinal rigidity
hp	HP:0003272	1.21E-02	7	Abnormality of the hip bone
hp	HP:0003270	1.60E-03	3	Abdominal distention
hp	HP:0003115	1.62E-02	2	Abnormal EKG
hp	HP:0003110	1.55E-02	8	Abnormality of urine homeostasis
hp	HP:0003028	1.90E-02	2	Abnormality of the ankles
hp	HP:0002996	1.30E-02	3	Limited elbow movement
hp	HP:0002987	2.79E-03	3	Elbow flexion contracture
hp	HP:0002944	1.57E-03	2	Thoracolumbar scoliosis
hp	HP:0002938	1.62E-02	2	Lumbar hyperlordosis
hp	HP:0002926	3.37E-02	3	Abnormality of thyroid physiology
hp	HP:0002877	4.53E-04	2	Nocturnal hypoventilation
hp	HP:0002837	4.86E-03	2	Recurrent bronchitis
hp	HP:0002827	4.34E-03	4	Hip dislocation
hp	HP:0002814	1.72E-02	16	Abnormality of the lower limb
hp	HP:0002813	3.15E-02	14	Abnormality of limb bone morphology
hp	HP:0002808	2.89E-02	5	Kyphosis
hp	HP:0002804	4.42E-02	2	Arthrogryposis multiplex congenita
hp	HP:0002791	3.76E-03	2	Hypoventilation

hp	HP:0002788	4.76E-02	2	Recurrent upper respiratory tract infections
hp	HP:0002783	4.35E-04	4	Recurrent lower respiratory tract infections
hp	HP:0002747	2.29E-02	2	Respiratory insufficiency due to muscle weakness
hp	HP:0002692	3.43E-02	2	Hypoplastic facial bones
hp	HP:0002686	1.03E-02	2	Prenatal maternal abnormality
hp	HP:0002644	1.13E-02	8	Abnormality of pelvic girdle bone morphology
hp	HP:0002634	4.20E-02	2	Arteriosclerosis
hp	HP:0002621	3.98E-02	2	Atherosclerosis
hp	HP:0002460	2.24E-02	3	Distal muscle weakness
hp	HP:0002360	4.47E-02	3	Sleep disturbance
hp	HP:0002208	1.71E-02	2	Coarse hair
hp	HP:0002205	1.49E-02	7	Recurrent respiratory infections
hp	HP:0002090	3.76E-02	2	Pneumonia
hp	HP:0002019	3.07E-02	4	Constipation
hp	HP:0002017	4.90E-02	4	Nausea and vomiting
hp	HP:0002013	3.37E-02	3	Vomiting
hp	HP:0001883	1.48E-02	6	Talipes
hp	HP:0001882	1.69E-02	3	Leukopenia
hp	HP:0001850	1.99E-02	3	Abnormality of the tarsal bones
hp	HP:0001838	6.00E-03	3	Rocker bottom foot
hp	HP:0001824	3.53E-02	3	Weight loss
hp	HP:0001762	3.69E-03	6	Talipes equinovarus
hp	HP:0001760	2.20E-02	13	Abnormality of the foot
hp	HP:0001714	3.28E-03	3	Ventricular hypertrophy
hp	HP:0001713	1.90E-02	6	Abnormality of cardiac ventricle
hp	HP:0001712	1.11E-02	2	Left ventricular hypertrophy
hp	HP:0001711	2.09E-02	2	Abnormality of the left ventricle
hp	HP:0001695	2.86E-02	3	Cardiac arrest
hp	HP:0001692	2.09E-02	2	Primary atrial arrhythmia
hp	HP:0001659	4.30E-03	2	Aortic regurgitation
hp	HP:0001654	2.66E-02	5	Abnormality of the heart valves
hp	HP:0001649	3.56E-03	4	Tachycardia
hp	HP:0001646	3.01E-02	3	Abnormality of the aortic valve
hp	HP:0001645	2.65E-02	3	Sudden cardiac death
hp	HP:0001633	1.74E-02	3	Abnormality of the mitral valve
hp	HP:0001629	4.57E-02	4	Ventricular septal defect
hp	HP:0001608	3.86E-02	4	Abnormality of the voice
hp	HP:0001558	2.90E-02	2	Decreased fetal movement
hp	HP:0001557	1.20E-02	3	Prenatal movement abnormality
hp	HP:0001551	9.89E-03	5	Abnormality of the umbilicus
hp	HP:0001538	4.30E-03	2	Protuberant abdomen
hp	HP:0001537	9.09E-03	5	Umbilical hernia

hp	HP:0001533	6.73E-04	2	Slender build
hp	HP:0001518	1.35E-02	3	Small for gestational age
hp	HP:0001508	2.25E-02	8	Failure to thrive
hp	HP:0001428	4.76E-02	2	Somatic mutation
hp	HP:0001395	4.42E-02	2	Hepatic fibrosis
hp	HP:0001388	1.15E-02	3	Joint laxity
hp	HP:0001384	1.38E-02	4	Abnormality of the hip joint
hp	HP:0001373	3.13E-02	4	Joint dislocation
hp	HP:0001319	3.94E-03	4	Neonatal hypotonia
hp	HP:0001310	3.98E-02	2	Dysmetria
hp	HP:0001270	2.09E-02	5	Motor delay
hp	HP:0001259	4.42E-02	2	Coma
hp	HP:0001238	3.98E-02	2	Slender finger
hp	HP:0001231	4.31E-02	3	Abnormality of the fingernails
hp	HP:0001220	3.68E-02	3	Interphalangeal joint contracture of finger
hp	HP:0001197	2.78E-02	7	Abnormality of prenatal development or birth
hp	HP:0001166	3.43E-02	2	Arachnodactyly
hp	HP:0001072	2.18E-02	7	Thickened skin
hp	HP:0001028	2.79E-02	2	Hemangioma
hp	HP:0000989	4.76E-02	2	Pruritus
hp	HP:0000975	2.86E-02	3	Hyperhidrosis
hp	HP:0000974	1.71E-02	2	Hyperextensible skin
hp	HP:0000971	9.89E-03	5	Abnormality of the sweat gland
hp	HP:0000964	4.53E-02	2	Eczema
hp	HP:0000963	3.04E-03	4	Thin skin
hp	HP:0000962	2.43E-02	5	Hyperkeratosis
hp	HP:0000951	2.40E-02	20	Abnormality of the skin
hp	HP:0000938	5.22E-03	4	Osteopenia
hp	HP:0000927	4.05E-02	4	Abnormality of skeletal maturation
hp	HP:0000864	3.42E-02	4	Abnormality of the hypothalamus-pituitary axis
hp	HP:0000851	1.57E-03	2	Congenital hypothyroidism
hp	HP:0000830	4.64E-02	2	Anterior hypopituitarism
hp	HP:0000823	1.11E-02	2	Delayed puberty
hp	HP:0000822	4.50E-02	4	Hypertension
hp	HP:0000821	3.15E-02	3	Hypothyroidism
hp	HP:0000820	2.95E-02	4	Abnormality of the thyroid gland
hp	HP:0000812	4.89E-02	7	Abnormal internal genitalia
hp	HP:0000790	4.64E-02	2	Hematuria
hp	HP:0000771	3.32E-02	2	Gynecomastia
hp	HP:0000768	1.93E-02	3	Pectus carinatum
hp	HP:0000551	4.87E-02	2	Abnormality of color vision
hp	HP:0000539	4.94E-02	5	Abnormality of refraction

hp	HP:0000473	8.81E-03	2	Torticollis
hp	HP:0000444	2.39E-02	2	Convex nasal ridge
hp	HP:0000411	1.62E-02	2	Protruding ear
hp	HP:0000383	3.32E-02	2	Abnormality of periauricular region
hp	HP:0000322	4.76E-02	2	Short philtrum
hp	HP:0000311	3.11E-02	2	Round face
hp	HP:0000301	3.53E-02	3	Abnormality of facial musculature
hp	HP:0000280	1.90E-02	4	Coarse facial features
hp	HP:0000235	3.55E-02	5	Abnormality of the fontanelles or cranial sutures
hp	HP:0000218	1.26E-02	6	High palate
hp	HP:0000212	2.39E-02	2	Gingival overgrowth
hp	HP:0000194	2.59E-02	2	Open mouth
hp	HP:0000168	2.72E-02	3	Abnormality of the gingiva
hp	HP:0000157	1.59E-02	5	Abnormality of the tongue
hp	HP:0000142	3.43E-02	2	Abnormality of the vagina
hp	HP:0000098	1.30E-02	3	Tall stature
hp	HP:0000093	2.72E-02	3	Proteinuria
hp	HP:0000076	3.76E-02	2	Vesicoureteral reflux
hp	HP:0000023	1.86E-02	3	Inguinal hernia
hp	HP:0000022	5.45E-03	2	Abnormality of male internal genitalia
hp	HP:0000006	5.00E-02	19	Autosomal dominant inheritance
BP	GO:2001256	1.21E-03	2	regulation of store-operated calcium entry
BP	GO:2001237	1.51E-02	3	negative regulation of extrinsic apoptotic signaling pathway
BP	GO:2001057	2.29E-02	2	reactive nitrogen species metabolic process
BP	GO:2001022	3.31E-02	2	positive regulation of response to DNA damage stimulus
BP	GO:2001020	4.09E-02	3	regulation of response to DNA damage stimulus
BP	GO:2000736	2.77E-02	3	regulation of stem cell differentiation
BP	GO:2000379	3.79E-02	2	positive regulation of reactive oxygen species metabolic process
BP	GO:2000377	3.12E-02	3	regulation of reactive oxygen species metabolic process
BP	GO:2000045	1.64E-02	3	regulation of G1/S transition of mitotic cell cycle
BP	GO:1904407	6.52E-03	2	positive regulation of nitric oxide metabolic process
BP	GO:1904031	1.78E-02	2	positive regulation of cyclin-dependent protein kinase activity
BP	GO:1904029	2.05E-02	3	regulation of cyclin-dependent protein kinase activity

BP	GO:1903649	2.93E-02	6	regulation of cytoplasmic transport
BP	GO:1903580	3.68E-03	2	positive regulation of ATP metabolic process
BP	GO:1903578	2.16E-02	2	regulation of ATP metabolic process
BP	GO:1903428	1.01E-02	2	positive regulation of reactive oxygen species biosynthetic process
BP	GO:1903426	1.78E-02	2	regulation of reactive oxygen species biosynthetic process
BP	GO:1903409	3.79E-02	2	reactive oxygen species biosynthetic process
BP	GO:1903018	1.65E-02	2	regulation of glycoprotein metabolic process
BP	GO:1902806	2.05E-02	3	regulation of cell cycle G1/S phase transition
BP	GO:1901990	3.05E-02	4	regulation of mitotic cell cycle phase transition
BP	GO:1901987	3.90E-02	4	regulation of cell cycle phase transition
MF	GO:1901981	2.85E-02	3	phosphatidylinositol phosphate binding
BP	GO:1901701	4.04E-02	8	cellular response to oxygen-containing compound
MF	GO:1901682	1.54E-02	2	sulfur compound transmembrane transporter activity
BP	GO:1901606	6.79E-04	4	alpha-amino acid catabolic process
BP	GO:1901605	1.05E-02	5	alpha-amino acid metabolic process
BP	GO:1901565	4.13E-02	4	organonitrogen compound catabolic process
MF	GO:1901363	2.26E-03	54	heterocyclic compound binding
BP	GO:1901361	9.41E-03	6	organic cyclic compound catabolic process
BP	GO:1901292	4.81E-02	2	nucleoside phosphate catabolic process
MF	GO:1901265	4.48E-03	28	nucleoside phosphate binding
BP	GO:1900544	1.70E-02	3	positive regulation of purine nucleotide metabolic process
CC	GO:0098852	2.55E-02	4	lytic vacuole membrane
CC	GO:0098590	2.45E-02	8	plasma membrane region
MF	GO:0098531	3.01E-02	2	transcription factor activity, direct ligand regulated sequence-specific DNA binding
MF	GO:0097367	1.69E-02	24	carbohydrate derivative binding
BP	GO:0097306	1.08E-03	4	cellular response to alcohol
BP	GO:0097305	1.02E-03	5	response to alcohol
MF	GO:0097159	2.92E-03	54	organic cyclic compound binding
BP	GO:0090596	3.63E-03	7	sensory organ morphogenesis
BP	GO:0090103	4.30E-04	3	cochlea morphogenesis
BP	GO:0090102	1.47E-04	4	cochlea development
BP	GO:0072666	1.54E-02	2	establishment of protein localization to vacuole
BP	GO:0072665	1.78E-02	2	protein localization to vacuole
BP	GO:0072524	3.34E-03	4	pyridine-containing compound metabolic process
BP	GO:0072348	2.03E-02	2	sulfur compound transport

CC	GO:0071944	8.21E-03	36	cell periphery
BP	GO:0071902	2.00E-02	5	positive regulation of protein serine/threonine kinase activity
BP	GO:0071542	2.54E-03	2	dopaminergic neuron differentiation
BP	GO:0071417	4.27E-02	5	cellular response to organonitrogen compound
BP	GO:0071407	2.83E-02	5	cellular response to organic cyclic compound
BP	GO:0071396	8.79E-03	6	cellular response to lipid
BP	GO:0071383	3.59E-02	3	cellular response to steroid hormone stimulus
BP	GO:0071356	2.85E-02	3	cellular response to tumor necrosis factor
BP	GO:0071230	2.29E-02	2	cellular response to amino acid stimulus
BP	GO:0071229	2.68E-02	3	cellular response to acid chemical
BP	GO:0070972	2.29E-02	2	protein localization to endoplasmic reticulum
BP	GO:0070875	2.54E-03	2	positive regulation of glycogen metabolic process
BP	GO:0070873	7.34E-03	2	regulation of glycogen metabolic process
BP	GO:0070208	2.05E-03	2	protein heterotrimerization
BP	GO:0070206	1.10E-02	2	protein trimerization
BP	GO:0065007	1.24E-02	82	biological regulation
BP	GO:0061061	2.01E-02	8	muscle structure development
BP	GO:0060628	3.09E-03	2	regulation of ER to Golgi vesicle-mediated transport
BP	GO:0060563	2.28E-02	3	neuroepithelial cell differentiation
BP	GO:0060122	1.54E-02	2	inner ear receptor stereocilium organization
BP	GO:0060119	2.95E-04	4	inner ear receptor cell development
BP	GO:0060117	6.86E-04	3	auditory receptor cell development
BP	GO:0060113	1.61E-03	4	inner ear receptor cell differentiation
MF	GO:0060089	5.00E-02	14	molecular transducer activity
BP	GO:0060005	3.53E-04	2	vestibular reflex
BP	GO:0060004	5.74E-03	2	reflex
BP	GO:0055123	4.62E-02	3	digestive system development
BP	GO:0055114	1.83E-02	12	oxidation-reduction process
BP	GO:0055002	2.15E-03	5	striated muscle cell development
BP	GO:0055001	6.24E-04	6	muscle cell development
BP	GO:0051924	4.51E-02	3	regulation of calcium ion transport
BP	GO:0051897	1.06E-02	3	positive regulation of protein kinase B signaling
BP	GO:0051896	3.59E-02	3	regulation of protein kinase B signaling
BP	GO:0051785	2.71E-02	2	positive regulation of nuclear division
BP	GO:0051783	4.95E-02	3	regulation of nuclear division
BP	GO:0051716	2.99E-02	50	cellular response to stimulus
BP	GO:0051347	3.21E-02	7	positive regulation of transferase activity
BP	GO:0051302	2.78E-02	5	regulation of cell division
BP	GO:0051291	1.29E-03	3	protein heterooligomerization

BP	GO:0051259	1.45E-02	6	protein oligomerization
BP	GO:0051239	3.81E-02	22	regulation of multicellular organismal process
MF	GO:0051213	4.12E-02	2	dioxygenase activity
BP	GO:0051197	1.21E-03	2	positive regulation of coenzyme metabolic process
BP	GO:0051196	1.42E-02	2	regulation of coenzyme metabolic process
BP	GO:0051194	1.21E-03	2	positive regulation of cofactor metabolic process
BP	GO:0051193	1.42E-02	2	regulation of cofactor metabolic process
BP	GO:0051188	2.44E-02	3	cofactor biosynthetic process
BP	GO:0051186	1.17E-03	7	cofactor metabolic process
BP	GO:0051146	3.57E-03	6	striated muscle cell differentiation
BP	GO:0051054	2.28E-02	3	positive regulation of DNA metabolic process
BP	GO:0051052	1.54E-02	5	regulation of DNA metabolic process
BP	GO:0050896	2.28E-02	58	response to stimulus
BP	GO:0050794	2.27E-02	73	regulation of cellular process
BP	GO:0050789	4.19E-02	75	regulation of biological process
BP	GO:0050679	3.88E-02	3	positive regulation of epithelial cell proliferation
BP	GO:0050654	1.21E-02	2	chondroitin sulfate proteoglycan metabolic process
BP	GO:0048878	3.22E-02	10	chemical homeostasis
BP	GO:0048873	1.31E-02	2	homeostasis of number of cells within a tissue
BP	GO:0048872	4.69E-02	4	homeostasis of number of cells
BP	GO:0048839	2.47E-03	6	inner ear development
BP	GO:0048771	3.49E-02	3	tissue remodeling
BP	GO:0048747	4.46E-02	2	muscle fiber development
BP	GO:0048741	1.42E-02	2	skeletal muscle fiber development
BP	GO:0048732	1.27E-02	6	gland development
BP	GO:0048729	2.04E-02	9	tissue morphogenesis
BP	GO:0048661	6.52E-03	2	positive regulation of smooth muscle cell proliferation
BP	GO:0048660	2.43E-02	2	regulation of smooth muscle cell proliferation
BP	GO:0048659	2.71E-02	2	smooth muscle cell proliferation
BP	GO:0048639	1.15E-02	4	positive regulation of developmental growth
BP	GO:0048638	3.77E-02	5	regulation of developmental growth
BP	GO:0048598	4.43E-02	8	embryonic morphogenesis
BP	GO:0048568	3.35E-02	6	embryonic organ development
BP	GO:0048562	1.40E-02	6	embryonic organ morphogenesis
BP	GO:0048545	2.61E-02	4	response to steroid hormone
BP	GO:0048538	2.43E-02	2	thymus development
BP	GO:0048525	3.47E-02	2	negative regulation of viral process
CC	GO:0048471	4.12E-02	6	perinuclear region of cytoplasm

BP	GO:0048278	4.99E-02	2	vesicle docking
BP	GO:0048146	2.71E-02	2	positive regulation of fibroblast proliferation
BP	GO:0048016	1.90E-02	2	inositol phosphate-mediated signaling
BP	GO:0046777	4.21E-02	4	protein autophosphorylation
BP	GO:0046700	5.84E-03	6	heterocycle catabolic process
BP	GO:0046496	2.71E-03	4	nicotinamide nucleotide metabolic process
BP	GO:0046395	1.35E-02	4	carboxylic acid catabolic process
BP	GO:0046394	4.45E-02	4	carboxylic acid biosynthetic process
BP	GO:0046323	4.99E-02	2	glucose import
BP	GO:0046209	2.29E-02	2	nitric oxide metabolic process
BP	GO:0046031	4.63E-02	2	ADP metabolic process
BP	GO:0045981	1.84E-02	3	positive regulation of nucleotide metabolic process
BP	GO:0045979	3.68E-03	2	positive regulation of nucleoside metabolic process
BP	GO:0045927	3.19E-02	4	positive regulation of growth
BP	GO:0045913	3.16E-02	2	positive regulation of carbohydrate metabolic process
BP	GO:0045860	4.12E-02	6	positive regulation of protein kinase activity
BP	GO:0045840	1.65E-02	2	positive regulation of mitotic nuclear division
BP	GO:0045821	1.21E-03	2	positive regulation of glycolytic process
BP	GO:0045787	3.57E-03	6	positive regulation of cell cycle
BP	GO:0045740	2.71E-02	2	positive regulation of DNA replication
BP	GO:0045739	1.10E-02	2	positive regulation of DNA repair
BP	GO:0045737	1.54E-02	2	positive regulation of cyclin-dependent protein serine/threonine kinase activity
BP	GO:0045725	2.05E-03	2	positive regulation of glycogen biosynthetic process
BP	GO:0045429	6.52E-03	2	positive regulation of nitric oxide biosynthetic process
BP	GO:0045428	1.10E-02	2	regulation of nitric oxide biosynthetic process
BP	GO:0044763	1.10E-02	91	single-organism cellular process
BP	GO:0044724	1.57E-02	3	single-organism carbohydrate catabolic process
BP	GO:0044723	2.87E-02	8	single-organism carbohydrate metabolic process
BP	GO:0044712	4.26E-02	10	single-organism catabolic process
BP	GO:0044710	3.88E-02	40	single-organism metabolic process
BP	GO:0044700	9.45E-03	47	single organism signaling
BP	GO:0044699	1.07E-02	100	single-organism process
CC	GO:0044464	1.48E-02	109	cell part
CC	GO:0044459	3.70E-02	20	plasma membrane part
CC	GO:0044437	4.78E-02	4	vacuolar part
BP	GO:0044419	4.37E-02	4	interspecies interaction between organisms

BP	GO:0044403	4.37E-02	4	symbiosis, encompassing mutualism through parasitism
BP	GO:0044282	1.05E-02	5	small molecule catabolic process
BP	GO:0044281	2.57E-02	18	small molecule metabolic process
BP	GO:0044275	2.57E-02	2	cellular carbohydrate catabolic process
BP	GO:0044270	5.55E-03	6	cellular nitrogen compound catabolic process
BP	GO:0044264	9.09E-03	3	cellular polysaccharide metabolic process
BP	GO:0044262	4.69E-02	4	cellular carbohydrate metabolic process
MF	GO:0044212	3.32E-02	9	transcription regulatory region DNA binding
BP	GO:0044093	4.40E-02	15	positive regulation of molecular function
BP	GO:0044057	2.09E-02	6	regulation of system process
BP	GO:0044042	4.75E-03	3	glucan metabolic process
BP	GO:0043967	4.46E-02	2	histone H4 acetylation
BP	GO:0043966	4.63E-02	2	histone H3 acetylation
BP	GO:0043903	4.19E-02	3	regulation of symbiosis, encompassing mutualism through parasitism
BP	GO:0043901	2.68E-02	3	negative regulation of multi-organism process
BP	GO:0043650	9.15E-05	3	dicarboxylic acid biosynthetic process
BP	GO:0043648	1.00E-03	4	dicarboxylic acid metabolic process
BP	GO:0043627	4.46E-02	2	response to estrogen
BP	GO:0043583	4.00E-03	6	ear development
BP	GO:0043500	4.46E-02	2	muscle adaptation
BP	GO:0043471	1.10E-02	2	regulation of cellular carbohydrate catabolic process
BP	GO:0043470	1.10E-02	2	regulation of carbohydrate catabolic process
BP	GO:0043467	4.99E-02	2	regulation of generation of precursor metabolites and energy
BP	GO:0043436	7.75E-03	12	oxoacid metabolic process
BP	GO:0043410	4.39E-02	6	positive regulation of MAPK cascade
BP	GO:0043406	2.10E-02	4	positive regulation of MAP kinase activity
BP	GO:0043255	3.96E-02	2	regulation of carbohydrate biosynthetic process
BP	GO:0043200	3.96E-02	2	response to amino acid
MF	GO:0043168	2.45E-03	31	anion binding
MF	GO:0043167	9.16E-04	55	ion binding
BP	GO:0043085	4.48E-02	13	positive regulation of catalytic activity
BP	GO:0042692	7.00E-03	7	muscle cell differentiation
BP	GO:0042592	5.14E-03	17	homeostatic process
BP	GO:0042537	1.21E-03	2	benzene-containing compound metabolic process
BP	GO:0042491	3.56E-03	3	auditory receptor cell differentiation
BP	GO:0042490	2.17E-03	4	mechanoreceptor differentiation
BP	GO:0042472	1.59E-04	6	inner ear morphogenesis
BP	GO:0042471	2.99E-04	6	ear morphogenesis

CC	GO:0042383	1.01E-02	3	sarcolemma
BP	GO:0042180	4.84E-02	3	cellular ketone metabolic process
BP	GO:0040014	1.16E-02	3	regulation of multicellular organism growth
BP	GO:0040008	1.73E-02	8	regulation of growth
MF	GO:0036094	4.55E-03	30	small molecule binding
MF	GO:0035639	5.31E-03	23	purine ribonucleoside triphosphate binding
BP	GO:0035556	4.68E-02	22	intracellular signal transduction
BP	GO:0035315	3.84E-03	3	hair cell differentiation
BP	GO:0035272	6.52E-03	3	exocrine system development
BP	GO:0035264	2.05E-02	4	multicellular organism growth
BP	GO:0034655	4.53E-02	4	nucleobase-containing compound catabolic process
BP	GO:0034637	2.36E-03	3	cellular carbohydrate biosynthetic process
BP	GO:0034612	3.59E-02	3	response to tumor necrosis factor
BP	GO:0033993	2.63E-02	7	response to lipid
BP	GO:0033692	1.78E-03	3	cellular polysaccharide biosynthetic process
BP	GO:0033674	2.22E-02	7	positive regulation of kinase activity
BP	GO:0033173	9.11E-03	2	calcineurin-NFAT signaling cascade
BP	GO:0033147	1.60E-03	2	negative regulation of intracellular estrogen receptor signaling pathway
BP	GO:0033146	1.10E-02	2	regulation of intracellular estrogen receptor signaling pathway
BP	GO:0033144	1.02E-03	3	negative regulation of intracellular steroid hormone receptor signaling pathway
BP	GO:0033143	5.08E-03	3	regulation of intracellular steroid hormone receptor signaling pathway
BP	GO:0032941	1.54E-02	2	secretion by tissue
BP	GO:0032885	5.01E-03	2	regulation of polysaccharide biosynthetic process
BP	GO:0032881	9.11E-03	2	regulation of polysaccharide metabolic process
BP	GO:0032870	3.44E-02	6	cellular response to hormone stimulus
BP	GO:0032787	1.77E-03	9	monocarboxylic acid metabolic process
MF	GO:0032559	2.27E-03	21	adenyl ribonucleotide binding
MF	GO:0032555	3.36E-03	24	purine ribonucleotide binding
MF	GO:0032553	3.74E-03	24	ribonucleotide binding
MF	GO:0032550	5.54E-03	23	purine ribonucleoside binding
MF	GO:0032549	5.68E-03	23	ribonucleoside binding
BP	GO:0032386	3.05E-02	7	regulation of intracellular transport
CC	GO:0031901	2.86E-02	2	early endosome membrane
BP	GO:0031659	1.21E-03	2	positive regulation of cyclin-dependent protein serine/threonine kinase activity involved in G1/S transition of mitotic cell cycle
BP	GO:0031657	1.60E-03	2	regulation of cyclin-dependent protein

				serine/threonine kinase activity involved in G1/S transition of mitotic cell cycle
BP	GO:0031329	3.64E-02	7	regulation of cellular catabolic process
CC	GO:0031226	1.04E-02	15	intrinsic component of plasma membrane
BP	GO:0031017	2.05E-03	2	exocrine pancreas development
BP	GO:0030813	1.60E-03	2	positive regulation of nucleotide catabolic process
BP	GO:0030811	8.21E-03	2	regulation of nucleotide catabolic process
MF	GO:0030594	1.39E-02	3	neurotransmitter receptor activity
MF	GO:0030554	2.37E-03	21	adenyl nucleotide binding
BP	GO:0030522	1.76E-03	6	intracellular receptor signaling pathway
BP	GO:0030520	2.03E-02	2	intracellular estrogen receptor signaling pathway
BP	GO:0030518	1.84E-02	3	intracellular steroid hormone receptor signaling pathway
BP	GO:0023052	9.84E-03	47	signaling
BP	GO:0023014	3.83E-02	9	signal transduction by protein phosphorylation
BP	GO:0022610	3.43E-02	13	biological adhesion
BP	GO:0022600	4.12E-02	2	digestive system process
BP	GO:0021795	3.63E-02	2	cerebral cortex cell migration
BP	GO:0021562	8.70E-04	2	vestibulocochlear nerve development
BP	GO:0021545	2.16E-02	2	cranial nerve development
MF	GO:0019842	5.42E-03	3	vitamin binding
MF	GO:0019838	2.68E-02	3	growth factor binding
BP	GO:0019752	3.71E-03	12	carboxylic acid metabolic process
BP	GO:0019722	2.44E-02	3	calcium-mediated signaling
BP	GO:0019439	6.30E-03	6	aromatic compound catabolic process
BP	GO:0019362	2.71E-03	4	pyridine nucleotide metabolic process
BP	GO:0019318	3.71E-03	5	hexose metabolic process
MF	GO:0019239	9.11E-03	2	deaminase activity
BP	GO:0019219	4.62E-02	28	regulation of nucleobase-containing compound metabolic process
BP	GO:0019217	2.43E-02	2	regulation of fatty acid metabolic process
BP	GO:0018393	4.95E-02	3	internal peptidyl-lysine acetylation
MF	GO:0017076	3.51E-03	24	purine nucleotide binding
MF	GO:0016864	5.01E-03	2	intramolecular oxidoreductase activity, transposing S-S bonds
MF	GO:0016860	1.60E-03	3	intramolecular oxidoreductase activity
MF	GO:0016853	2.06E-03	5	isomerase activity
MF	GO:0016773	3.55E-03	13	phosphotransferase activity, alcohol group as acceptor
MF	GO:0016772	3.55E-03	15	transferase activity, transferring phosphorus-containing groups

MF	GO:0016740	5.12E-03	26	transferase activity
BP	GO:0016573	4.95E-02	3	histone acetylation
BP	GO:0016310	4.81E-02	20	phosphorylation
MF	GO:0016301	6.98E-03	13	kinase activity
BP	GO:0016054	1.35E-02	4	organic acid catabolic process
BP	GO:0016053	4.45E-02	4	organic acid biosynthetic process
BP	GO:0016052	1.77E-02	3	carbohydrate catabolic process
BP	GO:0016051	2.43E-03	5	carbohydrate biosynthetic process
BP	GO:0015980	6.69E-03	5	energy derivation by oxidation of organic compounds
BP	GO:0015758	1.70E-02	3	glucose transport
BP	GO:0015749	1.91E-02	3	monosaccharide transport
BP	GO:0015698	4.73E-02	3	inorganic anion transport
BP	GO:0014904	1.78E-03	3	myotube cell development
BP	GO:0014902	1.57E-02	3	myotube differentiation
BP	GO:0014897	2.29E-02	2	striated muscle hypertrophy
BP	GO:0014896	2.29E-02	2	muscle hypertrophy
BP	GO:0010962	3.68E-03	2	regulation of glucan biosynthetic process
BP	GO:0010907	1.01E-02	2	positive regulation of glucose metabolic process
BP	GO:0010828	1.31E-02	2	positive regulation of glucose transport
BP	GO:0010827	3.16E-02	2	regulation of glucose transport
BP	GO:0010823	1.90E-02	2	negative regulation of mitochondrion organization
BP	GO:0010676	2.29E-02	2	positive regulation of cellular carbohydrate metabolic process
BP	GO:0010564	3.05E-02	7	regulation of cell cycle process
BP	GO:0010559	1.42E-02	2	regulation of glycoprotein biosynthetic process
BP	GO:0010107	1.54E-02	2	potassium ion import
BP	GO:0009987	3.16E-03	112	cellular process
BP	GO:0009894	3.46E-02	8	regulation of catabolic process
BP	GO:0009888	3.20E-02	18	tissue development
BP	GO:0009887	3.80E-02	11	organ morphogenesis
BP	GO:0009790	3.58E-02	10	embryo development
BP	GO:0009755	6.00E-03	4	hormone-mediated signaling pathway
BP	GO:0009725	1.13E-02	8	response to hormone
BP	GO:0009628	1.03E-02	11	response to abiotic stimulus
BP	GO:0009408	4.81E-02	2	response to heat
BP	GO:0009250	5.92E-04	3	glucan biosynthetic process
BP	GO:0009166	3.63E-02	2	nucleotide catabolic process
BP	GO:0009118	2.16E-02	2	regulation of nucleoside metabolic process
BP	GO:0009108	1.51E-02	3	coenzyme biosynthetic process

BP	GO:0009065	1.60E-03	2	glutamine family amino acid catabolic process
BP	GO:0009064	7.33E-03	3	glutamine family amino acid metabolic process
BP	GO:0009063	1.08E-03	4	cellular amino acid catabolic process
BP	GO:0008645	1.77E-02	3	hexose transport
BP	GO:0008643	3.03E-02	3	carbohydrate transport
BP	GO:0008544	6.89E-03	5	epidermis development
MF	GO:0008235	3.47E-02	2	metalloexopeptidase activity
MF	GO:0008188	4.63E-02	2	neuropeptide receptor activity
MF	GO:0008134	2.38E-02	7	transcription factor binding
BP	GO:0007589	1.78E-02	2	body fluid secretion
BP	GO:0007423	2.94E-02	8	sensory organ development
BP	GO:0007405	3.79E-02	2	neuroblast proliferation
BP	GO:0007346	4.12E-02	6	regulation of mitotic cell cycle
BP	GO:0007270	3.98E-02	3	neuron-neuron synaptic transmission
BP	GO:0007200	8.63E-03	3	phospholipase C-activating G-protein coupled receptor signaling pathway
BP	GO:0007165	2.40E-02	42	signal transduction
BP	GO:0007155	3.35E-02	13	cell adhesion
BP	GO:0007154	1.36E-02	47	cell communication
BP	GO:0007088	3.03E-02	3	regulation of mitotic nuclear division
BP	GO:0006970	1.78E-02	2	response to osmotic stress
BP	GO:0006835	4.63E-02	2	dicarboxylic acid transport
BP	GO:0006821	2.85E-02	3	chloride transport
BP	GO:0006809	2.03E-02	2	nitric oxide biosynthetic process
BP	GO:0006757	3.63E-02	2	ATP generation from ADP
BP	GO:0006733	4.05E-03	4	oxidoreduction coenzyme metabolic process
BP	GO:0006732	5.03E-04	7	coenzyme metabolic process
BP	GO:0006623	1.42E-02	2	protein targeting to vacuole
BP	GO:0006605	4.50E-02	7	protein targeting
BP	GO:0006536	4.30E-04	3	glutamate metabolic process
BP	GO:0006520	1.09E-02	6	cellular amino acid metabolic process
BP	GO:0006400	3.63E-02	2	tRNA modification
BP	GO:0006282	6.92E-03	3	regulation of DNA repair
BP	GO:0006112	6.92E-03	3	energy reserve metabolic process
BP	GO:0006110	7.34E-03	2	regulation of glycolytic process
BP	GO:0006096	3.47E-02	2	glycolytic process
BP	GO:0006091	2.12E-02	5	generation of precursor metabolites and energy
BP	GO:0006090	1.06E-02	3	pyruvate metabolic process
BP	GO:0006082	8.77E-03	12	organic acid metabolic process
BP	GO:0006073	4.75E-03	3	cellular glucan metabolic process
BP	GO:0006006	9.76E-03	4	glucose metabolic process

BP	GO:0005996	1.31E-03	6	monosaccharide metabolic process
BP	GO:0005979	3.68E-03	2	regulation of glycogen biosynthetic process
BP	GO:0005978	5.92E-04	3	glycogen biosynthetic process
BP	GO:0005977	4.75E-03	3	glycogen metabolic process
BP	GO:0005976	1.22E-02	3	polysaccharide metabolic process
CC	GO:0005887	7.19E-03	15	integral component of plasma membrane
CC	GO:0005886	2.26E-02	33	plasma membrane
CC	GO:0005829	1.12E-02	16	cytosol
CC	GO:0005774	4.45E-02	4	vacuolar membrane
CC	GO:0005773	2.09E-02	7	vacuole
CC	GO:0005765	2.55E-02	4	lysosomal membrane
CC	GO:0005764	2.31E-02	6	lysosome
CC	GO:0005643	3.47E-02	2	nuclear pore
CC	GO:0005623	1.82E-02	109	cell
CC	GO:0005581	4.63E-02	2	collagen trimer
MF	GO:0005547	1.42E-02	2	phosphatidylinositol-3,4,5-trisphosphate binding
MF	GO:0005524	4.09E-03	20	ATP binding
MF	GO:0005520	1.21E-02	2	insulin-like growth factor binding
MF	GO:0005310	1.90E-02	2	dicarboxylic acid transmembrane transporter activity
MF	GO:0005179	1.84E-02	3	hormone activity
MF	GO:0005159	3.09E-03	2	insulin-like growth factor receptor binding
MF	GO:0005057	5.52E-04	5	receptor signaling protein activity
MF	GO:0004879	3.01E-02	2	RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding
MF	GO:0004871	1.97E-02	14	signal transducer activity
MF	GO:0004716	3.53E-04	2	receptor signaling protein tyrosine kinase activity
MF	GO:0004707	3.68E-03	2	MAP kinase activity
MF	GO:0004702	6.14E-03	3	receptor signaling protein serine/threonine kinase activity
MF	GO:0004674	1.81E-03	9	protein serine/threonine kinase activity
MF	GO:0004672	6.49E-03	11	protein kinase activity
MF	GO:0003824	3.61E-02	50	catalytic activity
MF	GO:0003756	5.01E-03	2	protein disulfide isomerase activity
MF	GO:0003707	4.46E-02	2	steroid hormone receptor activity
BP	GO:0003300	2.03E-02	2	cardiac muscle hypertrophy
BP	GO:0003012	2.44E-02	5	muscle system process
BP	GO:0002115	3.09E-03	2	store-operated calcium entry
BP	GO:0002093	2.99E-04	3	auditory receptor cell morphogenesis
BP	GO:0002066	5.08E-03	3	columnar/cuboidal epithelial cell development

BP	GO:0001974	2.03E-02	2	blood vessel remodeling
MF	GO:0001883	5.59E-03	23	purine nucleoside binding
MF	GO:0001882	5.93E-03	23	nucleoside binding
CC	GO:0001726	2.77E-02	3	ruffle
BP	GO:0001704	3.59E-02	3	formation of primary germ layer
MF	GO:0001077	3.05E-02	4	transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding
MF	GO:0001067	3.46E-02	9	regulatory region nucleic acid binding
MF	GO:0001047	4.84E-02	3	core promoter binding
MF	GO:0000975	3.46E-02	9	regulatory region DNA binding
BP	GO:0000725	1.77E-02	3	recombinational repair
BP	GO:0000724	1.70E-02	3	double-strand break repair via homologous recombination
CC	GO:0000407	1.54E-02	2	pre-autophagosomal structure
CC	GO:0000323	2.35E-02	6	lytic vacuole
BP	GO:0000271	2.81E-03	3	polysaccharide biosynthetic process
BP	GO:0000187	3.21E-02	3	activation of MAPK activity
BP	GO:0000186	2.71E-02	2	activation of MAPKK activity
MF	GO:0000166	4.48E-03	28	nucleotide binding
BP	GO:0000165	2.96E-02	9	MAPK cascade

Supplementary information, Table S16 Functional enrichment categories of PSGs reported by Rubin and colleagues in layer lines(LR). Categories associated with vision-related function are marked in green.

Term	Term ID	P-value	Gene number	Descriptions
ke	KEGG:04020	5.00E-02	7	Calcium signaling pathway
hp	HP:0100699	4.36E-02	2	Scarring
hp	HP:0100689	2.51E-02	2	Decreased corneal thickness
hp	HP:0100659	1.15E-02	3	Abnormality of the cerebral vasculature
hp	HP:0100491	1.76E-02	5	Abnormality of lower limb joint
hp	HP:0040195	3.67E-02	7	Decreased head circumference
hp	HP:0030453	1.00E-02	4	Abnormal visual electrophysiology
hp	HP:0030319	8.98E-03	3	Weakness of facial musculature
hp	HP:0030311	2.69E-02	2	Lower extremity joint dislocation
hp	HP:0030178	8.04E-03	4	Abnormality of central nervous system electrophysiology
hp	HP:0012823	3.85E-02	11	Clinical modifier
hp	HP:0012758	3.58E-02	10	Neurodevelopmental delay
hp	HP:0012547	4.54E-02	7	Abnormal involuntary eye movements
hp	HP:0012503	3.29E-02	2	Abnormality of the pituitary gland
hp	HP:0012387	4.48E-03	2	Bronchitis
hp	HP:0012265	3.63E-03	2	Ciliary dyskinesia
hp	HP:0012262	3.91E-03	2	Abnormal ciliary motility
hp	HP:0012261	3.91E-03	2	Abnormal respiratory motile cilium physiology
hp	HP:0012223	4.29E-05	2	Splenic rupture
hp	HP:0011900	2.91E-04	2	Hypofibrinogenemia
hp	HP:0011898	2.91E-04	2	Abnormality of circulating fibrinogen
hp	HP:0011843	4.13E-02	4	Abnormality of skeletal physiology
hp	HP:0011842	8.18E-03	22	Abnormality of skeletal morphology
hp	HP:0011830	3.88E-02	2	Abnormality of oral mucosa
hp	HP:0011821	1.87E-02	9	Abnormality of facial skeleton
hp	HP:0011799	2.42E-02	3	Abnormality of facial soft tissue
hp	HP:0011747	3.15E-02	2	Abnormality of the anterior pituitary
hp	HP:0011733	1.96E-02	2	Abnormality of adrenal physiology
hp	HP:0011675	3.43E-02	4	Arrhythmia
hp	HP:0011492	4.31E-02	2	Abnormality of corneal stroma
hp	HP:0011486	2.60E-02	2	Abnormality of corneal thickness
hp	HP:0011463	9.18E-03	2	Childhood onset
hp	HP:0011389	1.66E-02	8	Functional abnormality of the inner ear
hp	HP:0011198	6.35E-03	2	EEG with generalized epileptiform discharges
hp	HP:0011182	6.69E-03	2	Epileptiform EEG discharges

hp	HP:0011039	1.96E-02	2	Abnormality of the helix
hp	HP:0011029	4.23E-02	2	Internal hemorrhage
hp	HP:0011028	4.23E-02	2	Abnormality of blood circulation
hp	HP:0011025	6.49E-03	10	Abnormality of cardiovascular system physiology
hp	HP:0010991	1.44E-02	2	Abnormality of the abdominal musculature
hp	HP:0010990	1.56E-03	2	Abnormality of the common coagulation pathway
hp	HP:0010827	8.74E-03	3	Abnormality of the seventh cranial nerve
hp	HP:0010696	3.11E-03	2	Polar cataract
hp	HP:0010628	8.74E-03	3	Facial palsy
hp	HP:0010549	4.66E-02	3	Weakness due to upper motor neuron dysfunction
hp	HP:0010490	3.24E-02	2	Abnormality of the palmar creases
hp	HP:0010460	4.34E-02	5	Abnormality of the female genitalia
hp	HP:0010318	1.11E-02	2	Aplasia/Hypoplasia of the abdominal wall musculature
hp	HP:0009122	3.44E-02	6	Aplasia/hypoplasia affecting bones of the axial skeleton
hp	HP:0009121	1.39E-02	18	Abnormal axial skeleton morphology
hp	HP:0009118	2.32E-02	6	Aplasia/Hypoplasia of the mandible
hp	HP:0009116	2.42E-02	6	Aplasia/Hypoplasia involving bones of the skull
hp	HP:0008736	2.61E-02	4	Hypoplasia of penis
hp	HP:0008678	4.82E-02	2	Renal hypoplasia/aplasia
hp	HP:0008373	4.59E-02	3	Puberty and gonadal disorders
hp	HP:0008064	3.43E-02	2	Ichthyosis
hp	HP:0008048	2.17E-03	2	Abnormality of the line of Schwalbe
hp	HP:0008047	3.97E-02	2	Abnormality of the vasculature of the eye
hp	HP:0008046	3.61E-02	2	Abnormality of the retinal vasculature
hp	HP:0008034	1.48E-02	2	Abnormal iris pigmentation
hp	HP:0007759	4.27E-02	2	Opacification of the corneal stroma
hp	HP:0007703	3.69E-02	4	Abnormality of retinal pigmentation
hp	HP:0007663	8.74E-03	3	Reduced visual acuity
hp	HP:0007477	4.49E-02	2	Abnormal dermatoglyphics
hp	HP:0006824	1.93E-02	3	Cranial nerve paralysis
hp	HP:0006703	2.23E-02	2	Aplasia/Hypoplasia of the lungs
hp	HP:0005978	2.78E-02	2	Type II diabetes mellitus
hp	HP:0005268	1.03E-03	2	Spontaneous abortion
hp	HP:0005262	1.26E-02	3	Abnormality of the synovia
hp	HP:0004936	7.72E-03	2	Venous thrombosis
hp	HP:0004418	3.37E-03	2	Thrombophlebitis
hp	HP:0004374	4.82E-02	2	Hemiplegia/hemiparesis

hp	HP:0004348	3.14E-02	5	Abnormality of bone mineral density
hp	HP:0004328	1.13E-02	11	Abnormality of the anterior segment of the eye
hp	HP:0004324	2.20E-02	4	Increased body weight
hp	HP:0003828	4.31E-02	2	Variable expressivity
hp	HP:0003745	1.31E-02	2	Sporadic
hp	HP:0003674	3.59E-02	8	Onset
hp	HP:0003577	4.61E-02	2	Congenital onset
hp	HP:0003457	3.65E-02	2	EMG abnormality
hp	HP:0003256	9.18E-03	2	Abnormality of the coagulation cascade
hp	HP:0003241	3.17E-02	4	External genital hypoplasia
hp	HP:0003117	2.42E-02	3	Abnormality of circulating hormone level
hp	HP:0002837	1.56E-03	2	Recurrent bronchitis
hp	HP:0002827	2.05E-02	2	Hip dislocation
hp	HP:0002817	4.24E-02	9	Abnormality of the upper limb
hp	HP:0002815	2.75E-02	3	Abnormality of the knees
hp	HP:0002808	3.75E-02	3	Kyphosis
hp	HP:0002804	1.57E-02	2	Arthrogryposis multiplex congenita
hp	HP:0002803	1.92E-02	2	Congenital contracture
hp	HP:0002795	1.65E-02	8	Functional respiratory abnormality
hp	HP:0002788	3.67E-03	3	Recurrent upper respiratory tract infections
hp	HP:0002750	4.70E-02	2	Delayed skeletal maturation
hp	HP:0002652	4.01E-02	2	Skeletal dysplasia
hp	HP:0002539	1.37E-03	2	Cortical dysplasia
hp	HP:0002538	3.79E-02	2	Abnormality of the cerebral cortex
hp	HP:0002521	6.02E-03	2	Hypsarrhythmia
hp	HP:0002510	8.81E-03	2	Spastic tetraplegia
hp	HP:0002360	3.74E-02	2	Sleep disturbance
hp	HP:0002353	6.27E-03	4	EEG abnormality
hp	HP:0002269	1.40E-02	4	Abnormality of neuronal migration
hp	HP:0002239	2.37E-02	2	Gastrointestinal hemorrhage
hp	HP:0002170	9.94E-03	2	Intracranial hemorrhage
hp	HP:0002110	8.08E-03	2	Bronchiectasis
hp	HP:0002109	1.83E-02	2	Abnormality of the bronchi
hp	HP:0002093	1.86E-02	6	Respiratory insufficiency
hp	HP:0002089	1.31E-02	2	Pulmonary hypoplasia
hp	HP:0002071	3.11E-02	2	Abnormality of extrapyramidal motor function
hp	HP:0001999	4.07E-02	6	Abnormal facial shape
hp	HP:0001977	1.27E-02	2	Abnormal thrombosis
hp	HP:0001933	4.01E-02	2	Subcutaneous hemorrhage
hp	HP:0001928	4.87E-03	4	Abnormality of coagulation
hp	HP:0001892	1.09E-02	5	Abnormal bleeding
hp	HP:0001850	2.19E-02	2	Abnormality of the tarsal bones
hp	HP:0001787	4.19E-03	2	Abnormal delivery

hp	HP:0001761	4.78E-02	2	Pes cavus
hp	HP:0001739	5.56E-03	3	Abnormality of the nasopharynx
hp	HP:0001710	1.87E-02	2	Conotruncal defect
hp	HP:0001695	2.78E-02	2	Cardiac arrest
hp	HP:0001649	4.31E-03	3	Tachycardia
hp	HP:0001645	2.65E-02	2	Sudden cardiac death
hp	HP:0001639	3.95E-02	3	Hypertrophic cardiomyopathy
hp	HP:0001636	1.83E-02	2	Tetralogy of Fallot
hp	HP:0001626	3.05E-02	16	Abnormality of the cardiovascular system
hp	HP:0001622	5.37E-03	3	Premature birth
hp	HP:0001608	1.00E-02	4	Abnormality of the voice
hp	HP:0001561	2.88E-02	2	Polyhydramnios
hp	HP:0001513	1.92E-02	4	Obesity
hp	HP:0001399	4.44E-02	2	Hepatic failure
hp	HP:0001386	3.37E-03	2	Joint swelling
hp	HP:0001384	1.20E-02	3	Abnormality of the hip joint
hp	HP:0001373	4.98E-02	2	Joint dislocation
hp	HP:0001367	3.29E-02	10	Abnormal joint morphology
hp	HP:0001347	4.16E-02	5	Hyperreflexia
hp	HP:0001324	4.91E-02	6	Muscle weakness
hp	HP:0001319	1.96E-02	2	Neonatal hypotonia
hp	HP:0001311	2.15E-02	4	Abnormal nervous system electrophysiology
hp	HP:0001291	2.38E-02	3	Abnormality of the cranial nerves
hp	HP:0001284	3.83E-02	2	Areflexia
hp	HP:0001279	2.62E-03	2	Syncope
hp	HP:0001270	1.29E-02	4	Motor delay
hp	HP:0001268	4.57E-02	2	Mental deterioration
hp	HP:0001256	1.74E-02	2	Intellectual disability, mild
hp	HP:0001250	3.80E-02	11	Seizures
hp	HP:0001249	2.65E-02	10	Intellectual disability
hp	HP:0001197	1.13E-02	6	Abnormality of prenatal development or birth
hp	HP:0001018	3.24E-02	2	Abnormal palmar dermatoglyphics
hp	HP:0000987	4.18E-02	2	Atypical scarring of skin
hp	HP:0000954	2.55E-02	2	Single transverse palmar crease
hp	HP:0000929	1.75E-02	15	Abnormality of the skull
hp	HP:0000927	2.75E-02	3	Abnormality of skeletal maturation
hp	HP:0000924	1.40E-02	22	Abnormality of the skeletal system
hp	HP:0000858	2.00E-02	3	Menstrual irregularities
hp	HP:0000842	2.60E-02	2	Hyperinsulinemia
hp	HP:0000834	3.34E-02	2	Abnormality of the adrenal glands
hp	HP:0000822	1.20E-02	4	Hypertension
hp	HP:0000819	3.71E-02	3	Diabetes mellitus
hp	HP:0000818	8.34E-03	11	Abnormality of the endocrine system

hp	HP:0000752	1.17E-02	3	Hyperactivity
hp	HP:0000750	2.52E-02	3	Delayed speech and language development
hp	HP:0000729	2.92E-02	2	Autistic behavior
hp	HP:0000708	4.26E-02	8	Behavioral abnormality
hp	HP:0000662	1.81E-02	3	Nyctalopia
hp	HP:0000639	4.49E-02	7	Nystagmus
hp	HP:0000627	1.95E-03	2	Posterior embryotoxon
hp	HP:0000613	4.53E-02	2	Photophobia
hp	HP:0000600	8.28E-03	3	Abnormality of the pharynx
hp	HP:0000598	3.21E-02	14	Abnormality of the ear
hp	HP:0000597	2.65E-02	3	Ophthalmoparesis
hp	HP:0000580	1.04E-02	4	Pigmentary retinopathy
hp	HP:0000556	1.31E-02	4	Retinal dystrophy
hp	HP:0000525	4.63E-02	3	Abnormality of the iris
hp	HP:0000518	3.56E-02	6	Cataract
hp	HP:0000517	2.26E-02	7	Abnormality of the lens
hp	HP:0000512	5.97E-03	4	Abnormal electroretinogram
hp	HP:0000510	3.14E-03	4	Rod-cone dystrophy
hp	HP:0000508	3.04E-02	5	Ptosis
hp	HP:0000505	2.49E-02	7	Visual impairment
hp	HP:0000504	4.47E-02	7	Abnormality of vision
hp	HP:0000501	7.52E-03	5	Glaucoma
hp	HP:0000481	4.13E-02	5	Abnormality of the cornea
hp	HP:0000421	1.20E-03	3	Epistaxis
hp	HP:0000407	2.60E-02	7	Sensorineural hearing impairment
hp	HP:0000403	6.35E-03	2	Recurrent otitis media
hp	HP:0000388	3.38E-02	2	Otitis media
hp	HP:0000370	3.20E-02	4	Abnormality of the middle ear
hp	HP:0000368	4.82E-02	3	Low-set, posteriorly rotated ears
hp	HP:0000366	2.73E-02	11	Abnormality of the nose
hp	HP:0000359	1.71E-02	8	Abnormality of the inner ear
hp	HP:0000358	3.46E-02	4	Posteriorly rotated ears
hp	HP:0000347	2.30E-02	6	Micrognathia
hp	HP:0000301	1.04E-02	3	Abnormality of facial musculature
hp	HP:0000280	4.01E-02	2	Coarse facial features
hp	HP:0000277	3.96E-02	6	Abnormality of the mandible
hp	HP:0000271	1.87E-02	19	Abnormality of the face
hp	HP:0000268	3.20E-02	2	Dolichocephaly
hp	HP:0000252	3.67E-02	7	Microcephaly
hp	HP:0000246	2.19E-02	2	Sinusitis
hp	HP:0000245	2.69E-02	2	Abnormality of the paranasal sinuses
hp	HP:0000240	3.75E-02	9	Abnormality of skull size
hp	HP:0000235	4.19E-02	3	Abnormality of the fontanelles or cranial

				sutures
hp	HP:0000234	1.08E-02	22	Abnormality of the head
hp	HP:0000225	1.95E-03	2	Gingival bleeding
hp	HP:0000168	2.69E-02	2	Abnormality of the gingiva
hp	HP:0000157	2.69E-02	3	Abnormality of the tongue
hp	HP:0000152	1.23E-02	22	Abnormality of head or neck
hp	HP:0000144	2.46E-02	2	Decreased fertility
hp	HP:0000140	1.81E-02	3	Abnormality of the menstrual cycle
hp	HP:0000113	1.23E-02	2	Polycystic kidney dysplasia
hp	HP:0000112	2.05E-02	2	Nephropathy
hp	HP:0000107	2.32E-02	3	Renal cyst
hp	HP:0000100	2.05E-02	2	Nephrotic syndrome
hp	HP:0000050	3.00E-02	4	Hypoplastic male external genitalia
hp	HP:0000036	4.52E-02	5	Abnormality of the penis
hp	HP:0000035	4.59E-02	6	Abnormality of the testis
hp	HP:0000014	4.65E-02	2	Abnormality of the bladder
hp	HP:0000007	2.00E-02	22	Autosomal recessive inheritance
hp	HP:0000006	5.00E-02	13	Autosomal dominant inheritance
hp	HP:0000005	1.77E-02	32	Mode of inheritance
hp	HP:0000003	2.92E-02	2	Multicystic kidney dysplasia
BP	GO:0051049	5.00E-02	27	regulation of transport
MF	GO:0004908	7.64E-03	4	interleukin-1 receptor activity