LETTER

Is there an antagonistic pleiotropic effect of a *LRRK2* mutation on leprosy and Parkinson's disease?

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Neurodegeneration is a shared feature of some infectious diseases, such as leprosy, and noninfectious conditions, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (1). The type-1 reaction (T1R), a nerve damaging process seen in leprosy and caused by chronic *Mycobacterium leprae* infection (2), is a natural model for the study of the relationship between infection and neuronal loss. Fava et al. (3) have analyzed the genetic predisposition of T1R in 237 T1R-affected and 237 T1R-free leprosy patients from Vietnam. They find that *Parkin* mutations are shared risk factors for T1R and PD, whereas *LRRK2* mutation p.R1628P is protective for T1R but a risk for PD (3–5). Importantly, they find no association for leprosy per se and claim a T1R-specific effect of *Parkin* and *LRRK2*.

We and others have previously shown that common variants in *LRRK2* and *Parkin* were associated with leprosy per se and were shared by leprosy and PD (1, 4, 6). The lack of association of PD/T1R-related rare coding variants in these two genes for leprosy per se in Fava et al.'s study (3) is thus open for discussion, especially considering their relatively small sample size. We analyzed coding variants of *LRRK2* and *Parkin* in 798 leprosy patients and 990 healthy controls from Wenshan, Yunnan Province, China, by using next-generation sequencing technology as previously described (7). Three mutations (*LRRK2* p.N551K, *Parkin* p.S167L, and p.V380L) Fava et al. highlighted in T1R show significant associations with leprosy per se in our sample (Table 1), with the same effect direction as observed in T1R (3). However, the T1R-protective *LRRK2* allele p.R1628P show a significant association with risk of leprosy per se (adjusted $P = 0.0081$, odds ratio [OR] = 1.5962; Table 1). The risk effect is even stronger ($P = 7.4 \times 10^{-10}$, OR = 2.3629) when East Asians ($n = 9{,}977$) from the Genome Aggregation Database (gnomAD; https://gnomad.broadinstitute.org/) are used as a population control for comparison. As T1R arises mainly in borderline leprosy (2), we analyzed patients with borderline leprosy and found a similar risk effect of p.R1628P (Table 1). We speculate that the missed associations for leprosy per se in Fava et al.'s (3) study might be caused by their limited sample size. To detect a moderate OR of 1.596 for an allele with a frequency of 4%, 760 pairs of samples are needed to reach a statistic power of 80% for leprosy. Note that the pleiotropic effect might be specific for leprosy and PD, as we observed no such association with AD (Table 1) (8, 9).

Besides the inconsistency of the significance level for the association of leprosy per se, another concern is the direction of the effect. A recent study has shown that *Mycobacterium tuberculosis* infection could induce neuroinflammation in astrocytes of PD-related brain regions in a *LRRK2*-dependent manner (10). It is therefore reasonable to speculate that *M. leprae* infection might have a similar effect. Under the condition of peripheral *M. leprae* infection, the genetic defect caused by *LRRK2* mutations, for example, p.R1628P, might be the agonist for neuroinflammation and neuronal loss; this effect may also apply to the development of PD. The mutation *LRRK2* p.R1628P should be considered a shared risk factor for leprosy per se and PD.

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Table 1. Association of coding in *LRRK2* and *Parkin* with variants T1R, leprosy, and AD

Phenotype	Gene information	Variants in *PRKN* (*Parkin*)		Variants in *LRRK2*				
Variants	Chromosome	6	6	12	12	12	12	12
	Position	162622197	161807855	40657700	40677699	40713845	40713901	40758652
	SNP ID	rs1801474	rs1801582	rs7308720	rs34410987	rs33949390	rs11564148	rs3761863
	Ref/alt	C/T	C/G	C/G	C/T	G/C	T/A	T/C
	Mutation	S167N	V380L	N551K	P755L	R1628P	S1647T	M2397T
T1R-affected vs. 1R-free*	MAF	0.3160	0.1160	0.0870	0.0110	0.0340	0.3360	0.4630
	P value	0.2200	0.0900	0.9000	0.1400	**0.0040**	0.3200	0.3300
	OR	0.8300	1.4400	0.9700	0.3700	0.2900	0.8700	0.8800
Leprosy per se (n = 798) vs. ctrl (n = 990)	Ctrl AC/AN	717/1980	200/1980	179/1980	12/1980	62/1980	627/1980	880/1980
	Leprosy AC/AN	498/1596	223/1596	102/1596	7/1596	76/1596	476/1596	684/1596
	P value	**0.0008**	**0.0005**	**0.0050**	0.4778	**0.0081**	0.1906	0.3179
	OR	0.7862	1.4409	0.6980	0.7103	1.5962	0.9082	0.9335
Leprosy per se vs. gnomAD (n = 9,977)	gnomAD AC/AN	7807/19950	1579/19952	2045/19912	185/19908	413/19932	6752/19856	9276/19798
	P value	$\mathbf{2.6\times10^{-10}}$	$\mathbf{5.4\times10^{-15}}$	$\mathbf{7.7\times10^{-07}}$	0.0510	$\mathbf{7.4\times10^{-10}}$	$\mathbf{6.0\times10^{-4}}$	$\mathbf{2.1\times10^{-3}}$
	OR	0.7055	1.8899	0.5965	0.4697	2.3629	0.8248	0.8508
Borderline leprosy (n = 593) vs. ctrl	Borderline AC/AN	383/1186	161/1186	73/1186	7/1186	56/1186	361/1186	519/1186
	P value	**0.0251**	**0.0029**	**0.0037**	1.0000	**0.0222**	0.4708	0.7083
	OR	0.8402	1.3980	0.6599	0.9737	1.5331	0.9442	0.9726
Alzheimer (n = 5,815) vs. ctrl (n = 4,755) in ADSP	MAF (AD)	0.0191	0.1681	0.0731	0.0	0.0003	0.2995	0.3421
	MAF (ctrl)	0.0220	0.1700	0.0674	0.0001	0.0003	0.2934	0.3447
	P value	0.1391	0.7049	0.1096	0.2687	0.9099	0.3324	0.6891
	OR	0.8659	0.9861	1.0910	NA	1.0900	1.0300	0.9883

Ctrl, control sample from Wang et al. (7); allele frequencies of East Asians were retrieved from https://gnomad.broadinstitute.org/; borderline leprosy includes borderline tuberculoid (BT), borderline borderline (BB), and borderline lepromatous (BL) leprosy; Alzheimer's and control were retrieved from the Alzheimer's Disease Sequencing Project (ADSP) (8) through dbGaP (phs000572.v7.p4); Ref/alt, reference allele and alternative allele based on human reference genome hg19; SNP ID, dbSNP access number of the single nucleotide polymorphism; ctrl, control subjects; MAF, minor allele frequency; AC/AN, allele count of alternative allele/total allele number of analyzed samples; NA, not available; *P* value for "Leprosy per se vs. ctrl" is adjusted by age and gender, calculated by plink/seq; *P* values for other comparisons are based on Fisher exact test; *P* values less than 0.05 are marked in bold.

*T1R data are from Fava et al. (3).

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