HHS Public Access

Author manuscript

Mov Disord. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

Mov Disord. 2022 November ; 37(11): 2312–2314. doi:10.1002/mds.29207.

Evaluation of SORL1 in Lewy body dementia identifies no significant associations

Anindita Ray, PhD[1], **Paolo Reho, PhD**[1], **Zalak Shah, PhD**[1],
International LBD Genomics Consortium,
Sonja W. Scholz, MD, PhD[1,2,*]

[1]Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

[2]Department of Neurology, Johns Hopkins University Medical Center, Baltimore, MD, USA

Lewy body dementia (LBD) is a clinically heterogeneous neurodegenerative disorder characterized by parkinsonism, visual hallucinations, fluctuating mental status, and REM sleep behavior disorder[1,2]. LBD lies along a spectrum between Parkinson's disease and Alzheimer's disease, and recent evidence suggests that the genetic architectures of these age-related syndromes are intersecting[3].

Numerous investigations into the role of amyloid precursor protein (APP) pathway genes have implicated an intracellular transmembrane protein, sortilin-related receptor 1 (encoded by the *SORL1* gene), to be associated with an increased risk of Alzheimer's disease. Pathogenic loss-of-function and missense mutations in *SORL1* have been postulated to affect APP shuttling between the trans-Golgi network and early endosomes, leading to disease[4]. Interestingly, several studies have also found rare *SORL1* mutations in patients with Alzheimer's disease with concomitant LBD, suggesting that *SORL1* may be a pleiotropic risk gene[4–6]. Here, we assessed the possible association of *SORL1* variants with risk for LBD.

We used our previously published whole-genome sequencing data generated on 2,591 European-ancestry LBD patients and 4,027 neurologically healthy individuals[3], which has good coverage of the *SORL1* gene (mean coverage 38x, range=22x–83x). Patients with LBD included in this dataset were diagnosed with pathologically definite or clinically probable disease according to consensus criteria.[1,3] Controls were selected based on a lack of evidence of cognitive decline in their clinical history and absence of neurological deficits on neurological examination. We first reviewed a common *SORL1* risk variant for Alzheimer's disease (rs74685827) in our previous LBD GWAS data,[3] which found no association (beta=0.02, standard error=0.14, *p*-value=0.90). Next, we extracted 6,617 rare variants in *SORL1* (minor allele frequency ≤0.01 in the European, non-Finnish population; Supplementary Table 1) and annotated them with variant effect predictor[7], then filtered the data to only include loss-of-function and missense mutations. This step identified 167

[*]**Corresponding author:** Sonja W. Scholz, M.D., Ph.D., Neurodegenerative Diseases Research Unit, National Institutes of Health | NINDS, Bethesda, MD 20892-3707, USA. Tel.: +1 (301) 496-0013 | Fax: +1 (301) 451-7295 | sonja.scholz@nih.gov.

variants on which we performed a gene burden analysis using SKAT-O, as implemented in RVTests (v.2.1.0)[8]. The model included age, sex, and four principal components as covariates. We also explored the rare single-variant association tests for each observed missense and loss-of-function mutation using Fisher's exact tests, as implemented in PLINK (v.1.9) (Supplementary Table 2).

Our gene burden analysis did not identify a significant association of rare damaging variants with an increased risk of developing LBD (SKAT-O *p*-value=0.24). Additionally, none of the single-variant associations were significant after correction for multiple testing (Supplementary Table 2). We observed eight missense mutations that have been previously described in patients with mixed dementias[4–6]. However, these mutations were either found in cases and controls or were more frequent in controls. None of these variants were nominally associated with disease (Table 1). Furthermore, a recent report examining *SORL1* mutations in a large Greek family with Parkinson's disease, Parkinson's disease dementia and mixed dementia reported a rare missense variant (p.G379W) segregating with disease[6]. We observed the same mutation in one LBD patient of Greek ancestry. From our data, we cannot conclude that this mutation is disease-causing or simply a variant present in the Greek population.

In summary, we did not find a significant enrichment of rare, damaging *SORL1* mutations in our well-powered LBD cohort. Our dataset is, to our knowledge, the largest genome-sequence cohort in this understudied disease. While it is possible that an association was missed due to allelic heterogeneity, our findings indicate that caution should be exercised when interpreting *SORL1* mutations in LBD, as current evidence does not conclusively support an association with disease risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding source:

This research was supported by the Intramural Research Program of the National Institutes of Health (National Institute of Neurological Disorders and Stroke; project number: 1ZIANS003154).

Financial Disclosure/Conflicts of Interest:

We thank the International LBD Genomics Consortium. A complete list of acknowledgments for individual site investigators is provided in the supplementary materials. Data used in the preparation of this letter were obtained from the Accelerating Medicine Partnership (AMP) Parkinson's Disease (AMP PD) Knowledge Platform. For up-to-date information on the study, visit https://www.amp-pd.org. A complete list of acknowledgments for individual studies/contributors to the AMP PD platform is given in the supplementary materials. S.W.S. serves on the Scientific Advisory Council of the Lewy Body Dementia Association and receives grant support from Cerevel Therapeutics.

Author Roles:

A.R. wrote the first draft. A.R., P.R., Z.S. performed or contributed to the statistical analysis. S.W.S. conceptualized, designed and supervised the project. All authors edited and reviewed the final manuscript.

References

1. Emre M. et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 22, 1689–1707; quiz 1837, doi:10.1002/mds.21507 (2007). [PubMed: 17542011]
2. McKeith IG et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89, 88–100, doi:10.1212/WNL.0000000000004058 (2017). [PubMed: 28592453]
3. Chia R. et al. Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture. Nat Genet 53, 294–303, doi:10.1038/s41588-021-00785-3 (2021). [PubMed: 33589841]
4. Cuccaro ML et al. SORL1 mutations in early- and late-onset Alzheimer disease. Neurol Genet 2, e116, doi:10.1212/NXG.0000000000000116 (2016). [PubMed: 27822510]
5. Benussi L. et al. Investigating the Endo-Lysosomal System in Major Neurocognitive Disorders Due to Alzheimer's Disease, Frontotemporal Lobar Degeneration and Lewy Body Disease: Evidence for SORL1 as a Cross-Disease Gene. Int J Mol Sci 22, doi:10.3390/ijms222413633 (2021).
6. Xiromerisiou G. et al. SORL1 mutation in a Greek family with Parkinson's disease and dementia. Ann Clin Transl Neurol 8, 1961–1969, doi:10.1002/acn3.51433 (2021). [PubMed: 34506082]
7. McLaren W. et al. The Ensembl Variant Effect Predictor. Genome Biol 17, 122, doi:10.1186/s13059-016-0974-4 (2016). [PubMed: 27268795]
8. Zhan X, Hu Y, Li B, Abecasis GR & Liu DJ RVTESTS: an efficient and comprehensive tool for rare variant association analysis using sequence data. Bioinformatics 32, 1423–1426, doi:10.1093/bioinformatics/btw079 (2016). [PubMed: 27153000]

Table 1.

Single-variant associations of rare *SORL1* mutations reported in the literature in patients with dementia

Position (hg38)	REF	ALT	dbSNP	AA Change	gnomAD MAF (all population)	gnomAD MAF (NFE)	No. of LBD Patients	No. of Controls	*p*-value	Previous Reports
chr11:121514222	A	C	rs150609294	p.N371T	0.0014	0.0031	8	8	0.2458	Alzheimer's disease with FTLD
chr11:121514245	G	T	-	p.G379W	-	-	1	0	0.3915	Parkinson's disease and mixed dementia
chr11:121550604	G	A	rs148430425	p.D734N	0.0006	0.0002	0	3	0.2853	Alzheimer's disease with DLB
chr11:121558767	C	T	rs143571823	p.T947M	0.0042	0.00011	0	1	1	Late-onset Alzheimer's disease with DLB
chr11:121586253	C	G	rs1699102	p.N1246K	0.00002	0.00005	0	1	1	Alzheimer's disease
chr11:121595662	G	A	rs776117825	p.R1470Q	0.00001	0.00004	0	2	0.5235	Alzheimer's disease with DLB
chr11:121625107	A	T	rs140327834	p.D2065V	0.0022	0.0037	25	42	0.8029	Alzheimer's disease, DLB, FTLD
chr11:121627591	C	T	rs142884576	p.T2134M	0.0005	0.0008	4	5	0.7441	Early-onset Alzheimer's disease with DLB

Rare loss-of-function and missense mutations in *SORL1* reported in patients with mixed dementia. The minor allele frequencies (MAF) in non-Finnish European ancestry (NFE) population are reported from the Genome Aggregation Database v3.1.2 (gnomAD)(https://gnomad.broadinstitute.org/). Abbreviations: reference allele (REF), alternate allele (ALT), amino acid change (AA change), Frontotemporal dementia (FTLD), Dementia with Lewy bodies (DLB).