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A paradoxical relationship between family history, onset age and genetic risk in Parkinson's disease

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Parkinson's disease; genetic risk score; age at onset; family history

About 10 % of patients with Parkinson's diesase (PD) report a positive family history.[1] Large meta-analyses of genome-wide association studies (GWAS) have identified an increasing number of common risk-variants, yet these do not fully account for familial clustering in PD.[2] A deeper understanding of the genetic profiles of individual patients,

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including cases of familial non-Mendelian PD, could have implications for prognosis and personalized therapy.

The cumulative burden of common GWAS variants has been associated with earlier PD onset[3-5] and higher rates of motor and cognitive progression.[6,7] Presuming that common risk loci contribute to familial clustering in non-Mendelian PD, one would expect cumulative genetic risk score (GRS) to be on average higher in patients with a positive family history. However, a recent study reported slower progression in patients with affected first degree relatives.[8]

To further explore the relationship between cumulative genetic risk, family history and age at onset in PD we generated a combined dataset from two Norwegian[9,10] (Oslo and ParkWest) and four US[11-14] (dbGAP phs000126.v1.p1, phs000089.v3.p2, phs000196.v2.p1 and PPMI) studies comprising a total of 4266 patients and calculated individual GRS. Methods and results are described in further detail in an online supplement. We found a significant, independent association of both lower GRS ($p=5.7*10^{-8}$, beta=−0.92, SE=0.17) and positive family history ($p=4.5*10^{-9}$,beta=2.25,SE=0.38) with higher age at onset in a linear regression model including sex, country and top five principal components as covariates. Next, we assessed association between GRS and family history by logistic regression, observing a significant association (p=0.00052, odds ratio 95% CI=1.05–1.19).

Taken together, the results indicate that familial PD is paradoxically associated with later age at onset, occuring not because of a lower GRS, but *in spite of* a higher GRS (Table 1). Consequently, one or more unknown mechanisms must be responsible for the observed association between family history and later age at onset. The previous report showing slower progression in familial cases is consistent with the notion of familial PD as paradoxically milder than what should be expected based on the genetic load.[8]

“False negative” family history, where siblings will later go on to develop PD, will plausibly be more frequent in early onset cases, as their siblings will also be younger. If this mechanism was driving the results, however, the same form of bias should also tend to give higher GRS in the non-familial PD group, not lower as we observed here. We note as a limitation that the included substudies were heterogeneous with respect to age at onset and the proportion of patients with positive family history.

We can currently only speculate about possible explanations behind the intriguing paradox this study uncovered, yet we note that our observations might be compatible with a scenario where the genetic risk factors that contribute to familial clustering *interact* with normal aging, having a disproportionately stronger effect in older individuals. Further studies are needed to map out how genetic profile contributes to different aspects of PD phenotype in the individual patient, which could ultimately have implications for prognosis and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Thomas B, Beal MF. Parkinson's disease. Hum Mol Genet 2007;16 Spec No. 2:R183–194 [PubMed: 17911161]
2. Pihlstrom L, Toft M. Parkinson's disease: What remains of the "missing heritability"? Mov Disord 2011;26:1971–1973 [PubMed: 21812035]
3. Nalls MA, Escott-Price V, Williams NM, et al. Genetic risk and age in Parkinson's disease: Continuum not stratum. Mov Disord 2015;30:850–854 [PubMed: 25778492]

4. Pihlstrom L, Toft M. Cumulative genetic risk and age at onset in Parkinson's disease. Mov Disord 2015:30;1712–1713 [PubMed: 26234887]
5. Lill CM, Hansen J, Olsen JH, et al. Impact of Parkinson's disease risk loci on age at onset. Mov Disord 2015;30:847–850 [PubMed: 25914293]
6. Pihlstrom L, Morset KR, Grimstad E, et al. A cumulative genetic risk score predicts progression in Parkinson's disease. Mov Disord 2016;31:487–490 [PubMed: 26853697]
7. Paul KC, Schulz J, Bronstein JM, et al. Association of Polygenic Risk Score With Cognitive Decline and Motor Progression in Parkinson Disease. JAMA Neurol 2018;75:360–366 [PubMed: 29340614]
8. Gaare JJ, Skeie GO, Tzoulis C, et al. Familial aggregation of Parkinson's disease may affect progression of motor symptoms and dementia. Mov Disord 2017;32:241–245 [PubMed: 27862270]
9. Pihlstrom L, Axelsson G, Bjornara KA, et al. Supportive evidence for 11 loci from genome-wide association studies in Parkinson's disease. Neurobiol Aging 2013;34:1708 e1707–1713
10. Alves G, Muller B, Herlofson K, et al. Incidence of Parkinson's disease in Norway: the Norwegian ParkWest study. J Neurol Neurosurg Psychiatry 2009;80:851–857 [PubMed: 19246476]
11. Hamza TH, Zabetian CP, Tenesa A, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat Genet 2010;42:781–785 [PubMed: 20711177]
12. Maraganore DM, de Andrade M, Lesnick TG, et al. High-resolution whole-genome association study of Parkinson disease. Am J Hum Genet 2005;77:685–693 [PubMed: 16252231]
13. Pankratz N, Wilk JB, Latourelle JC, et al. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. Hum Genet 2009;124:593–605 [PubMed: 18985386]
14. Nalls MA, Keller MF, Hernandez DG, et al. Baseline genetic associations in the Parkinson's Progression Markers Initiative (PPMI). Mov Disord 2016;31:79–85 [PubMed: 26268663]

Table 1

The relationship between genetic risk, age at onset and family history

		Genetic risk score quintile				
		1	**2**	**3**	**4**	**5**
Mean age at onset	**Negative family history**	60.6	58.2	57.7	57.6	57.3
	Positive family history	61.9	61.1	61.1	59.8	59.4
		Age at onset quintile				
		1	**2**	**3**	**4**	**5**
Mean genetic risk Z-score	**Negative family history**	0.61	0.58	0.46	0.41	0.35
	Positive family history	0.70	0.68	0.63	0.52	0.46

The table shows mean age at onset across quintiles of genetic risk and vice versa, contrasting the groups of positive versus negative family history Parkinson's disease patients. Higher genetic risk is consistently seen with earlier onset. Yet with similar genetic burden, patients with family history have higher age at onset. Given similar age at onset, patients with family history have higher genetic risk score.