No genetic evidence for involvement of alcohol dehydrogenase genes in risk for Parkinson's disease

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Abstract

Multiple genes have been implicated in Parkinson's disease (PD), including causal gene variants and risk variants typically identified using genome-wide association studies (GWAS). Variants in the alcohol dehydrogenase genes *ADH1C* and *ADH1B* are among the genes that have been associated with PD, suggesting that this family of genes may be important in PD. As part of the International Parkinson's Disease Genomics Consortium's (IPDGC) efforts to scrutinize previously reported risk factors for PD, we explored genetic variation in the alcohol dehydrogenase genes *ADH1A*, *ADH1B*, *ADH1C*, *ADH4*, *ADH5*, *ADH6*, and *ADH7* using imputed GWAS data from 15,097 cases and 17,337 healthy controls. Rare-variant association tests and single-variant score tests did not show any statistically significant association of alcohol dehydrogenase genetic variation with the risk for PD.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder with a complex polygenic inheritance influenced by the interplay of genetic, aging and environmental factors. A variant in the gene encoding the Alcohol Dehydrogenase 1C (Class I) Gamma Polypeptide (*ADH1C*), an enzyme that catalyzes the oxidation of alcohol to acetaldehyde, was implicated as a potential risk factor involved in sporadic PD (Buervenich et al., 2005). Screening an international cohort of 1,076 PD patients of European ancestry and 940 matched controls, suggested that a rare nonsense variant (p.Gly78Ter) was significantly overrepresented in PD patients. Similarly, the variant p.His48Arg in the Alcohol Dehydrogenase 1B (Class I), Beta Polypeptide (*ADH1B*) was associated with PD in women in a cohort of 629 PD patients and 865 control participants (García-Martín et al., 2019). No additional studies on these genes have been performed, therefore the contribution of alcohol dehydrogenase genes to PD etiology has remained unclear. Here we investigate the potential association of common and rare variants in the alcohol dehydrogenase gene family with PD, in a large case-control series.

Methods

To investigate the role of alcohol dehydrogenase genes and the effects of their genetic variation on the risk of PD, we utilized the International Parkinson's Disease Genomics Consortium (IPDGC) genome-wide association study (GWAS) data consisting of 15,097 cases and 17,337 healthy controls (Supplementary

Table 1) (Nalls et al., n.d.). The data underwent standard quality control as previously described (Nalls et al., n.d.) and were annotated using KGGSeq (Li et al., 2012).

We analyzed both the whole IPDGC cohort as well as two sex-stratified subcohorts. Variant frequencies were determined using PLINK 1.9 (Chang et al., 2015). Gene-based burden analyses SKAT, SKAT-O, and CMC were performed by using RVTESTS (Zhan et al., 2016) to assess the cumulative effect of multiple rare variants (minor allele frequency ≤ 0.03) on the risk for PD according to default parameters. Single-variant score test was performed using RVTESTS to assess the association between single variants and PD. All analyses were adjusted by 10 principal components to account for population stratification, dataset, age at onset for cases or examination for controls, and sex. All results were corrected for multiple testing by Benjamini–Hochberg False Discovery Rate (FDR) correction.

Results

We identified 602 variants within the alcohol dehydrogenase gene loci, including 25 coding variants. Only two loss of function variants were identified: the previously reported p.Gly78Ter (rs283413) *ADH1C* variant, and the p.Tyr22Ter (rs3919370) of *ADH4*. The latter variant's minor allele frequency (MAF = 0.29) did not meet the threshold for inclusion in the gene-level burden analysis tests for rare variants. No evidence for an association between alcohol dehydrogenase rare genetic variation and PD was detected when gene-based burden analysis was performed.

At variant-level, single-score test analyses found no evidence for an association between alcohol dehydrogenase variants and PD (FDR corrected $p > 0.99$) (Supplementary Table 1). The *ADH1C* p.Gly78Ter variant was previously reported with a frequency of 0.020 in PD patients, and a frequency of 0.006 in controls (Buervenich et al., 2005). However, in our cohort this variant was not associated with PD, as the allele frequency in patients was 0.016, while frequency in controls was 0.012 ($p > 0.3$, FDR corrected $p > 0.99$, Table 2). This is consistent with the frequency reported in gnomAD European (non-Finnish) origin population (0.012) (Karczewski et al., 2019).

Similarly, *ADH1B* p.His48Arg was previously reported to be associated with PD in women, with a frequency of 0.015 in PD patients and a frequency of 0.006 in controls (García-Martín et al., 2019). However, analysis

of the IPDGC female subcohort showed no association with PD, as the effect allele frequency was 0.053 in patients and 0.040 in controls ($P > 0.16$, FDR corrected $p > 0.89$) (Table 2).

When summary statistics from 27,823 PD cases and 443,190 controls (Nalls et al., n.d.) were further assessed, no significant association was identified (Figure 1). These summary statistics included the cohort that was analyzed in this manuscript. Our results are based on the largest series of PD patients and controls to date with 100% statistical power to detect variants associated with PD at a MAF < 0.01 , odds ratio = 1.5 and an α of 0.05.

Discussion

Our analyses, based on the largest PD genetic dataset to date, do not support the hypothesis that alcohol dehydrogenase genetic variants, including the *ADH1C* p.Gly78Ter stop loss variant and the *ADH1B* p.His48Arg missense variant, are risk or disease-causing factors for PD in the European population. The originally described variant, as well as other identified variants in these genes, have similar frequencies in patients and controls, and are therefore likely benign. A series of gene-based burden analyses and single variant analyses also failed to show a cumulative effect of rare variation in these genes on the risk for PD in the European population. In conclusion, our results do not support a role for common and rare variants in genes encoding the family of alcohol dehydrogenases as genetic risk factors or causal variants in PD. We suggest that these results should be taken into consideration when performing functional work.

References

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Disclosure Statement:

Ziv Gan-Or is consulting for Lysosomal Therapeutics Inc., Denali, Idorsia, Prevail Therapeutics and Inception Sciences. These activities are all outside the scope of the current work. Jonggeol Jeffrey Kim, Sara Bandres-Ciga and Cornelis Blauwendraat report no disclosures.

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TABLE 1. Gene-based burden analysis of alcohol dehydrogenase variants and risk for Parkinson's disease

Gene	CHR	BP ranges	Cohort Sex	Number of Variants	P-value		
					CMC	SKAT	SKAT-O
ADH1A	4	100197522 - 100212185	All	10	0.303	0.318	0.455
			Female	10	0.307	0.574	0.675
			Male	10	0.542	0.914	0.707
ADH1B	4	100227526 - 100242572	All	13	0.657	0.562	0.631
			Female	13	0.968	0.385	0.596
			Male	13	0.643	0.977	0.842
ADH1C	4	100257648 - 100273917	All	15	0.898	0.442	0.618
			Female	15	0.619	0.276	0.454
			Male	14	0.338	0.903	0.365
ADH4	4	100044832 - 100065449	All	27	0.277	0.29	0.377
			Female	27	0.232	0.703	0.793
			Male	27	0.743	0.95	0.536
ADH5	4	99992129 - 100009931	All	19	0.892	0.521	0.601
			Female	19	0.657	0.703	0.862
			Male	18	0.568	0.988	0.597
ADH6	4	100125878 - 100140403, 100123794 - 100140403	All	5	0.619	0.356	0.566
			Female	6	0.685	0.679	0.799
			Male	5	0.754	0.864	0.891
ADH7	4	100333417 - 100356667, 100333417 - 100356291	All	29	0.463	0.694	0.33
			Female	29	0.88	0.818	0.835
			Male	29	0.403	0.952	0.24

CHR, chromosome; BP, base pair; CMC, combined multivariate and collapsing; SKAT, sequence Kernel association tests; SKAT-O, optimized SKAT.

TABLE 2. Coding variants of alcohol dehydrogenase genes and risk for Parkinson's disease

Gene	CHR	BP	rsID	Consequence	A1	A2	Frequency (cases)	Frequency (control)	Frequency (All)	Frequency (gnomAD) ^a	Nalls et. al 2019							Score Test	
											Frequency	Effect	Odds Ratio	Standard Error	95% Upper CI	95% Lower CI	P value	P value	FDR
ADH1B	4	100229017	rs2066702	missense	A	G	0.002979	0.001945	0.002373	0.0013	0.004	0.0753	1.07820756	0.3613	0.4366	-0.286	0.8349	0.477	0.994
	4	100235053	rs1789882	synonymous	A	G	0.1632	0.17	0.1669	0.1691	0.1677	0.0377	1.03841966	0.0268	0.0645	0.0109	0.1603	0.463	0.994
	4	100235140	rs2018417	synonymous	A	C	0.03057	0.03108	0.03085	0.0324	0.0311	-0.0495	0.95170516	0.0652	0.0157	-0.1147	0.4483	0.153	0.994
	4	100239284	rs6413413	missense	A	T	0.007197	0.007616	0.007435	0.0077	0.0115	-0.0014	0.99860098	0.114	0.1126	-0.1154	0.9902	0.342	0.994
	4	100239319	rs1229984^b	missense	T	C	0.05389	0.03961	0.04606	0.0374	0.063	0.0851	1.08882594	0.0453	0.1304	0.0398	0.06053	0.162	0.994
	4	100240002	rs1229983	synonymous	T	C	0.96357	0.96246	0.96296	0.9614	0.9633	0.0421	1.04299877	0.0529	0.095	-0.0108	0.4267	0.693	0.994
ADH1C	4	100260783	rs35719513	missense	T	G	0.00273	0.003168	0.00297	0.0031	0.0034	-0.0704	0.93202094	0.1839	0.1135	-0.2543	0.702	0.154	0.994
	4	100260789	rs698	missense	T	C	0.6168	0.6018	0.6086	0.5689	0.6116	-0.0014	0.99860098	0.0173	0.0159	-0.0187	0.9359	0.918	0.994
	4	100263965	rs1693482	missense	T	C	0.3832	0.3982	0.3914	0.431	0.3884	7.00E-04	1.00070025	0.0173	0.018	-0.0166	0.9659	0.911	0.994
	4	100264102	rs6413444	synonymous	A	G	0.01498	0.01468	0.01482	0.014	0.0161	0.0456	1.04665566	0.0784	0.124	-0.0328	0.5611	0.549	0.994
	4	100266112	rs1693425	synonymous	T	C	0.3832	0.3982	0.3914	0.4316	0.3883	8.00E-04	1.00080032	0.0173	0.0181	-0.0165	0.9648	0.911	0.994
	4	100266133	rs2241894	synonymous	T	C	0.7771	0.7735	0.7751	0.7772	0.7729	-0.0026	0.99740338	0.0231	0.0205	-0.0257	0.9089	0.162	0.994
	4	100266157	rs79372027	synonymous	A	G	0.002479	0.002931	0.002727	0.0027	0.0028	-0.1105	0.89538633	0.2233	0.1128	-0.3338	0.6207	0.14	0.994
	4	100266371	rs1789915	synonymous	A	G	0.6989	0.6938	0.6961	0.6781	0.7017	-0.0078	0.99223034	0.019	0.0112	-0.0268	0.6838	0.428	0.994
	4	100268190	rs283413^c	stop lost	A	C	0.01609	0.01178	0.01373	0.0117	0.0201	0.1061	1.11193306	0.1025	0.2086	0.0036	0.3006	0.344	0.994
ADH4	4	100045616	rs1126673	missense	T	C	0.6761	0.6843	0.6806	0.6785	0.6814	0.0167	1.01684022	0.018	0.0347	-0.0013	0.3533	0.974	0.994
	4	100047812	rs1126672	synonymous	A	G	0.2938	0.2863	0.2897	0.2882	0.291	-0.0146	0.98550606	0.0189	0.0043	-0.0335	0.4403	0.798	0.994
	4	100048414	rs1126671	missense	T	C	0.3239	0.3157	0.3194	0.3127	0.3186	-0.0165	0.98363538	0.0181	0.0016	-0.0346	0.3621	0.965	0.994
	4	100052733	rs1126670	synonymous	A	C	0.6766	0.685	0.6812	0.6881	0.6821	0.0164	1.01653522	0.0181	0.0345	-0.0017	0.3659	0.921	0.994
	4	100062819	rs2032349	synonymous	A	G	0.03	0.0294	0.02967	0.0283	0.03	-0.0291	0.97131933	0.0598	0.0307	-0.0889	0.6261	0.447	0.994
	4	100064326	rs3919370	stopgain	A	T	0.7063	0.7138	0.7104	0.7126	0.7092	0.0159	1.01602708	0.0191	0.035	-0.0032	0.4036	0.786	0.994
ADH5	4	99993833	rs28730643	synonymous	A	G	0.96429	0.96294	0.96355	0.9618	0.9639	0.0391	1.03987447	0.0603	0.0994	-0.0212	0.5167	0.958	0.994
ADH7	4	100341839	rs59534319	missense	T	C	0.997829	0.998209	0.998041	0.9994	0.9952	0.1836	1.20153511	0.3409	0.5245	-0.1573	0.5902	0.254	0.994
	4	100341861	rs971074	synonymous	T	C	0.1131	0.1139	0.1135	0.1262	0.1224	-0.0295	0.97093088	0.0265	-0.003	-0.056	0.2651	0.743	0.994
	4	100349669	rs1573496	missense	C	G	0.8984	0.8974	0.8978	0.8846	0.8895	0.0252	1.0255202	0.0271	0.0523	-0.0019	0.3528	0.969	0.994

All frequencies refer to Allele 1. CHR, chromosome; BP, base pair; CI, confidence interval; FDR, false discovery rate

^a refers to frequency of Allele 1 found in European (non-Finnish) population according to gnomAD

^b Variant identified by García-Martín et al. 2019 (in bold).

^c Variant identified by Buervenich et al. 2005 (in bold).

Plotted SNPs

Figure 1. Locus zoom plot of the locus including the alcohol dehydrogenase genes, demonstrating lack of association with Parkinson's disease risk. The violet circle with red arrow denotes the p.Gly78Ter variant of *ADH1C* (rs283413).