Genetic Variants in Sulfonylurea Targets Affect Parkinson's Disease Risk: A Two-Sample Mendelian Randomization Study

Disease-modifying drugs are urgently required for the treatment of Parkinson's disease (PD). Recent evidence suggests that overactivation of ATP-sensitive potassium (K_{ATP}) channels may be critically involved in PD pathogenesis.[1] Expression of the K_{ATP}-channel regulatory subunit that binds sulfonylurea (SUR1) is upregulated in the remaining dopaminergic neurons of PD patients.[1] Sulfonylureas are commonly used for the treatment of type II diabetes, a well-established risk factor for PD.[2,3] However, results regarding the relation between sulfonylurea use and PD risk are inconclusive, which might reflect the poor blood–brain barrier penetrance of commonly prescribed sulfonylureas, as well as confounding by indication.[4] Interestingly, mutations in *ABCC8* or *KCNJ11* genes that encode the SUR1 and Kir6.2 subunits of the K_{ATP}-channel, respectively, disrupt the potentiality of the channel and can cause neonatal diabetes. We, therefore, designed a two-sample Mendelian randomization (MR) study to assess whether variants in genes encoding sulfonylurea targets are causally related to PD risk.[4]

Methods

As instrumental variables for sulfonylurea targets we used five recently validated single nucleotide polymorphisms (SNPs) in the *ABCC8* and *KCNJ11* genes (Table 1).[4] Subsequently, we obtained effect estimates and the corresponding standard errors of these SNPs on PD risk from the largest genome-wide association study to date by the International Parkinson's Disease Genomics Consortium, including 33 674 cases and 449 056 controls.[5] The exposure and outcome SNP coefficients were then combined using MR regression based on the inverse variance weighting method. To assess specificity, we repeated the same analyses for other anti-glycemic drugs, including thiazolidinediones, as well as insulin and GLP-1 analogues (Table 1). The procedure for the curation of the specified SNPs as genetic instruments for different classes of antidiabetic drug targets has been extensively detailed before.[4] Programming was performed in R (version 4.0.2) using the 'TwoSampleMR' package.[6]

Results

Genetic variants in sulfonylurea targets were strongly associated with PD risk: every 1 mmol/L decrease in blood glucose lowered the risk of PD by more than 90% (odds ratio, 0.07 [95% confidence interval (CI), 0.01-0.39], $P = 0.002$) (Fig. 1). There was no evidence for heterogeneity (Cochran's Q, $P = 0.59$) or horizontal pleiotropy (MR Egger intercept 0.00 ± 0.04, $P = 0.99$). Leave-one-out analysis and other MR regression methods—including simple and weighted median, maximum likelihood and Egger regression—revealed both magnitudinal and directionally consistent estimates (Supplementary Tables S1 and S2). No variants in the targets of the other investigated anti-glycemic agents were associated with PD risk (all odds ratios, ≥2.10, all $P \geq 0.48$) (Fig. 1).

Discussion

We show that genetic variants in the *ABCC8* and *KCNJ11* genes that increase the affinity of the subunits of the K_{ATP}-channel to the effects of sulfonylureas are also associated with a markedly lower risk of PD. Conversely, variants in genes coding for targets of other widely used anti-glycemic drugs did not affect PD risk, indicating that the observed protective effects of sulfonylureas are likely to be specific to their

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TABLE 1 *The effect of anti-glycemic drug class tagging SNPs on risk of PD*

Compound class	Gene/ variant	SNP	Chr.	Position	Effect allele	Other allele	Exposure (glucose) β	Exposure (glucose) SE	Outcome (PD) β	Outcome (PD) SE	R^2	F-statistic
Sulfonylureas	*KCNJ11, ABCC8*	rs757110	11	17,418,477	C	A	0.0126	0.0018	0.0290	0.0173	0.0005	32.7
		rs117287142	11	17,401,050	A	G	0.0225	0.0076	0.2312	0.1265		
		rs2074310	11	17,421,886	T	C	0.0129	0.0018	0.0295	0.0174		
		rs3758953	11	17,499,547	A	G	−0.0064	0.0017	−0.0236	0.0233		
		rs4148630	11	17,435,966	G	A	−0.0084	0.002	−0.0245	0.0221		
Thiazolidinediones	*PPARG*	rs138779828	3	12,414,770	G	A	−0.0186	0.0059	0.0389	0.0795	0.0001	12.3
		rs2067819	3	12,359,049	G	A	0.0079	0.0021	−0.0009	0.023		
Insulin analogues	*INSR*	rs2894553	19	7,182,145	C	T	0.0102	0.0029	−0.0284	0.0311	0.0001	10.8
		rs74569625	19	7,252,613	G	A	−0.0105	0.0036	−0.0136	0.0594		
GLP-1 analogues	*GLP1R*	rs1004280	6	39,025,882	A	G	0.0076	0.002	0.002	0.0227	0.0001	16.0
		rs10305423	6	39,017,062	C	T	0.0244	0.0051	−0.0408	0.0579		
		rs880067	6	39,016,357	C	T	−0.0063	0.002	0.0202	0.0206		

Abbreviations: SNP, single nucleotide polymorphism; PD, Parkinson's disease; β, effect estimate of the tagging SNP (linear for the exposure [glucose], and the natural logarithm of the odds ratio for the outcome [Parkinson's disease]), Chr., chromosome; SE, standard error of the effect estimate.

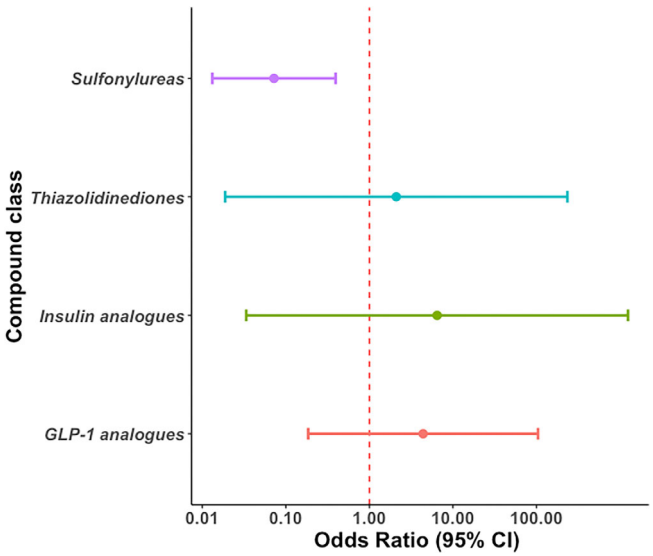

FIG. 1. Genetic variants in anti-glycemic drug targets and risk of Parkinson's disease. Forest plot depicting the odds ratios and their associated 95% confidence intervals for each class of anti-glycemic drugs with regard to the risk of developing Parkinson's disease. The dotted vertical red line marks the null effect. The odds ratios are depicted on a logarithmic scale. [Color figure can be viewed at wileyonlinelibrary.com]

mechanism of action and not because of improved insulin sensitivity per se. Indeed, large-scale epidemiological studies have not identified a consistent link between use of anti-glycemic agents and PD risk,[3] supporting the notion that the peripherally mediated anti-glycemic effects of sulfonylureas, which have a poor blood–brain barrier penetrance, are unlikely to be responsible for their protective effects. In contrast, the association between variants in genes coding for sulfonylurea targets, which are abundantly expressed on nigrostriatal dopaminergic neurons, and PD risk suggests that sulfonylureas could have neuroprotective effects in the central nervous system, possibly by blockage of K_{ATP}-channels and/or by inflammasome inhibition.[1,7] Our findings suggest that brain-penetrant sulfonylurea-derivatives could be promising targets for both prevention and disease modification in PD.[7]

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Data Availability Statement

The GWAS summary data are available through the website of the International Parkinson's Disease Genomics Consortium: https://pdgenetics.org/resources

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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