Genome-wide association study of Parkinson's disease using MAX3 test

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One of the priority task of medical genetics is to discover the genetic basis of the etiology and pathogenesis of Parkinson's disease (PD). In this work, we search for known disease markers among patients with confirmed diagnosis of PD and control group. We also conduct a genome-wide association study (GWAS) to identify further common variants that contribute to disease.

A sample of 50 patients with diagnosed PD and 10 control individuals was acquired for the study. As a control group, we took examined elderly individuals with no signs of PD and for whom the development of this pathology in the future is considered as unlikely.

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Data acquisition

The list of germline single nucleotide polymorphisms (SNPs) was obtained with Genomenal NGSWizard software. Among all SNPs we selected around 3000 SNPs appeared in PD-associated genes. PD-associated genes were taken from OMIM, ClinVar and MDSGene databases. Selected SNPs were also analyzed with ClinVar and dbSNP databases. We observed two pathogenic SNPs: one appeared in LRRK2 gene and was found in two patients, another appeared in GLUD2 gene and was found in three patients. Thus, the pathogenic genetic variants for Parkinson's disease were found for 5 out of 50 patients.

Genome-wide association studies

For further data analyses, we performed a GWAS. We used the MAX3 test to check the hypothesis of an association between Parkinson's disease and biallelic single nucleotide polymorphisms. As a result, we obtained 83 SNPs in which the p-value is less than 1e-9, while all 10 people from the control group and at least 43 people with Parkinson's disease are present in the sample.

Data analysis

A fraction of mutations is located on chromosome 17 in the locus where gene KCNJ12 is located. According to published data, the change of KCNJ12 protein could be involved in PD pathogenesis. In this regard, we additionally analyzed all SNPs from this locus. 264 mutations we observed, but not a single of them was reported in ClinVar database. Most of them were previously analyzed by some projects like 1000genomes, Topmed, GnomAD, ExAC and PAGE. This helped us to determine global alternative allele frequencies for SNPs. Based on this data we isolated suspicious SNPs with high p-values and low global alternative allele frequencies. We state that this combination of signs may indicate pathogenic and associated with PD SNPs. Eventually we identify 3 SNPs with p-value lower than 7e-6 and global alternative allele frequency low than 9%.

Since the sample size was small, we plan to make meta-analysis with results of another GWASes of PD in the future.

POS in chr17	REF	ALT	dbSNP	Type	gMAF(AAF)	p-value
21415448	G	T	rs74880280	Missense	0.09	7.56579e-06
21415939	C	T	rs73313923	Missense	0.0004	0
21416211	C	T	rs77987694	Missense	0.00	0

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