Linkage to a new locus on chromosome 6 in an Iranian pedigree diagnosed with early onset Parkinson's disease (EOPD)

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Abstract

Statement of the problem: Parkinson's disease-(PD) is a common neurodegenerative disorder characterized by motor (resting tremor, bradykinesia, and rigidity) and nonmotor features. The incidence of PD increases with age. Five principal genes have been identified for this condition, naming: *SNCA*, *LRRK2*, *PRKN*, *PINK1*, and *DJ-1*. Mutations in these genes account for the disease in a few percent of patients, suggesting other PD-causing genes remain to be identified.

The purpose: To identify the potential genes responsible for PD in a highly consanguineous Iranian family, showing no deleterious mutation in any of the previously identified genes. Age-at-onset of symptoms was in the second decade of life, and the inheritance was autosomal recessive.

Methodology: Genotyping was performed in unaffected parents, two unaffected and two affected siblings. Exome sequencing was done on two affected and two unaffected siblings. Homozygous regions common to all affected and absent in non-affected were sought. Preliminary filtering of sequence variations was done to identify all (nonsynonymous, stopgain, stoploss, deletion, and insertion) homozygous changes present in both affected that were absent in unaffected siblings in homozygous state and were positioned within the locus identified by homozygosity mapping. Subsequently, variations with a reported MAF<0.01 in public databases were removed to finally find the disease-causing variations.

Findings: The disease status in the family was linked to a large homozygous region (15Mb) on chromosome-6, containing 130 genes. The filtering criteria used for WES revealed seven variations that had been located in the homozygous region. One of these variants segregated with the disease status in the family and was not detected in 500 Iranian healthy controls. Our ongoing functional studies on the candidate gene suggest a promotion in apoptosis upon overexpression of this gene in Hela cells. **Conclusion and significance:** Our finding can provide insight into the etiology of dopaminergic neuronal death in the midbrain as the principal hallmark of Parkinson's disease.

Recent Publications

1. Delamarre, A., & Meissner, W. G. (2017). Epidemiology, environmental risk factors and genetics of Parkinson's disease. *La Presse Médicale*, *46*(2), 175-181.
2. Pfeiffer, R. F. (2016). Non-motor symptoms in Parkinson's disease. *Parkinsonism & related disorders*, *22*, S119-S122.
3. Puschmann, A. (2017). New Genes Causing Hereditary Parkinson's Disease or Parkinsonism. *Current Neurology and Neuroscience Reports*, *17*(9), 66.
4. Jansen, I. E., Ye, H., Heetveld, S., Lechler, M. C., Michels, H., Seinstra, R. I & Gibbs, J. R. (2017). Discovery and functional prioritization of Parkinson's disease candidate genes from large-scale whole exome sequencing. *Genome biology*, *18*(1), 22.
5. Goswami, P., Joshi, N., & Singh, S. (2017). Neurodegenerative signaling factors and mechanisms in Parkinson's pathology. *Toxicology in Vitro*.



Biography

Afagh Alavi has completed her M.Sc. and Ph.D. studies at the University of Tehran. She is currently an assistant professor in the University of Social Welfare and Rehabilitation Sciences in Iran. Her research field is the genetic of neuromuscular disorders. She has published more than 17 papers in reputed journals.

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