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Parkinson's disease and the LRRK2 gene: Patterns of low frequency alleles predict risk

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Abstract

It is well known that the *p.G2019S* mutation in *LRRK2* is associated with Parkinson's disease. However, this mutation is found for only a small fraction of cases. In order to improve prediction and demonstrate the relevance of the *LRRK2* gene, variation in *LRRK2* was closely investigated. Sequencing data on exons (few mutations) and flanking regions was available for 275 sporadic cases having onset at ages 60 or older and 277 neurologically health control subjects having a similar age-sex composition, members of an NINDS cohort hosted by the Coriell Institute. A total of 84 SNPs had minor alleles found for at least 5 subjects. These SNPs were represented by 49 relatively independent variables represented by SNP genotype or diplotype (for SNPs in high linkage disequilibrium). The data was used to construct a single statistical model defining high and low risk. The data analytic approach (GoM) identified three patterns (*I*, *II*, *III*): *I* - high risk and a specific set of minor alleles distributed throughout the gene; *II* - low risk and major alleles; *III* - high risk and diverse infrequent minor alleles. The sizes of these model-based groups were 120.04, 242.77 and 187.19, approximating the sizes of the case and control groups. Cases often matched *I* or *III* (100%: 46, 4, 137; 50%+ resemblance: 91, 4, 178) Controls often matched *II* (100%: 0, 178, 0; 50%+ resemblance: 27, 250, 0). In summary, gene-wide signatures found for *LRRK2* may discriminate between high and low risk persons.

Biography

Elizabeth H Corder, PhD is an epidemiologist and statistician (UNC-Chapel Hill) who endeavors to describe the genetic backgrounds for common age-related conditions such as Alzheimer's disease, breast cancer and heart attack where no single gene variant can predict risk for individuals. She cofounded Matrix Genomics, Inc. in 2005.