Whole-exome sequencing

It is a genomic technique for sequencing all of the protein-coding genes in a genome (known as the exome). It consists of two steps: the first step is to select only the subset of DNA that encodes proteins. These regions are known as exons – humans have about 180,000 exons, constituting about 1% of the human genome, or approximately 30 million base pairs. The second step is to sequence the exonic DNA using any high-throughput DNA sequencing technology.

The goal of this approach is to identify genetic variants that alter protein sequences, and to do this at a much lower cost than whole-genome sequencing. Since these variants can be responsible for both Mendelian and common polygenic diseases, such as Alzheimer's disease, whole exome sequencing has been applied both in academic research and as a clinical diagnostic.

A strategy based on targeted gene panel sequencing identifies possibly pathogenic variants in fewer than 20% of cases in the early-onset and familial form of dystonia. By using Whole Exome Sequencing (WES), Wirth et al. aimed to identify the missing genetic causes in dystonic patients without a diagnosis despite gene panel sequencing.

WES was applied to DNA samples from 32 patients with early-onset or familial dystonia investigated by sequencing of a 127 movement disorders-associated gene panel. Dystonia was described according to the familial history, body distribution, evolution pattern, age of onset, associated symptoms and associated movement disorders. Rate of diagnoses was evaluated for each clinical feature.

They identified causative variants for 11 patients from 9 families in CTNNB1, SUCLG1, NUS1, CNTNAP1, KCNB1, RELN, GNAO1, HIBCH, ADCK3 genes, yielding an overall diagnostic rate of 34.4%. Diagnostic yield was higher in complex dystonia compared to non-complex dystonia (66.7%-5.9%; $p < 0.002$), especially in patients showing intellectual disability compared to the patients without intellectual disability (87.5%-16.7%; $p < 0.002$).

This approach suggests WES as an efficient tool to improve the diagnostic yield after gene panel sequencing in dystonia. Larger study are warranted to confirm a potential genetic overlap between neurodevelopmental diseases and dystonia [1].

1)
Wirth T, Tranchant C, Drouot N, Keren B, Mignot C, Cif L, Lefaucheur R, Lion-François L, Méneret A, Gras D, Roze E, Laroche C, Burbaud P, Bannier S, Lagha-Boukbiza O, Spitz MA, Laugel V, Bereau M, Ollivier E, Nitschke P, Doummar D, Rudolf G, Anheim M, Chelly J. Increased diagnostic yield in complex dystonia through exome sequencing. Parkinsonism Relat Disord. 2020 Apr 20;74:50-56. doi: 10.1016/j.parkreldis.2020.04.003. [Epub ahead of print] PubMed PMID: 32334381.