New genetic analysis improves diagnosis of intellectual disability

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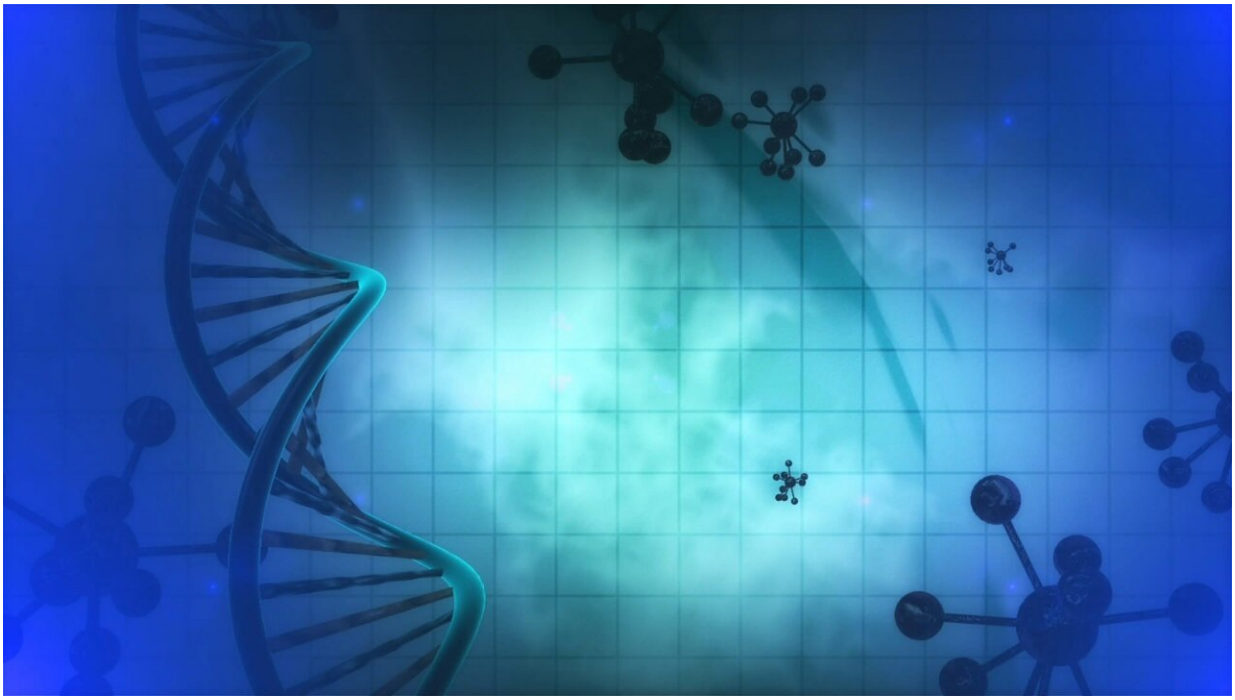

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Whole-genome sequencing can be used to diagnose intellectual disability more accurately than other methods of genetic analysis, researchers at Karolinska Institutet report in the scientific journal *Genome Medicine*. Whole-genome sequencing using analytical tools developed by the researchers will now be introduced for first-line clinical diagnosis at Karolinska University Laboratory in Sweden.

"Recent technical leaps in genetic diagnostics have revealed many new genetic aberrations that cause intellectual disability," says Anna Lindstrand, associate professor at the Department of Molecular Medicine and Surgery, Karolinska Institutet, and clinical genetics specialist at Karolinska University Hospital. "Given that there are currently over 800 different diagnoses described in the literature, making a diagnosis can be a time-consuming process."

An estimated 1.5 percent of the Swedish population have some sort of intellectual disability, caused in most cases by genetic aberrations, anything from small point mutations (one or a few base pairs) in individual genes or a few base-pair repetitions, to larger structural chromosome mutations comprising one or more genes.

Most individuals with an intellectual disability are offered a clinical examination using so-called gene dose array and DNA analysis for Fragile X syndrome. These genetic tests produce a molecular causal diagnosis in about 12 percent of cases, from which further analytical tests are subsequently ordered ranging from individual genes to the entire genome (whole-genome sequencing).

In the present study, the researchers developed their own analytical tool, which, in combination with whole-genome sequencing, discovers point mutations, structural chromosome aberrations and repetitions (expansions).

Conducting parallel gene dose array tests and whole-genome sequencing for 100 individuals the researchers were able to show that more than twice as many patients (27 percent) could obtain a causal diagnosis with their own whole-genome analysis compared with the array technique.

"In just a short space of time, whole-genome sequencing has become inexpensive enough to be used as an all-round test for finding different

genetic mutations," says Dr. Lindstrand. "The cost of sequencing a person's entire genome is now just marginally higher than other genetic analyses currently employed to find genetic mutations."

Karolinska University Laboratory in Stockholm, Sweden, will now be one of the first clinical laboratories in the world to introduce whole-genome sequencing as a first-line clinical diagnostic tool for intellectual disability.

More information: Anna Lindstrand et al, From cytogenetics to cytogenomics: whole-genome sequencing as a first-line test comprehensively captures the diverse spectrum of disease-causing genetic variation underlying intellectual disability, *Genome Medicine* (2019). DOI: 10.1186/s13073-019-0675-1

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