Seven genes for X-linked intellectual disability

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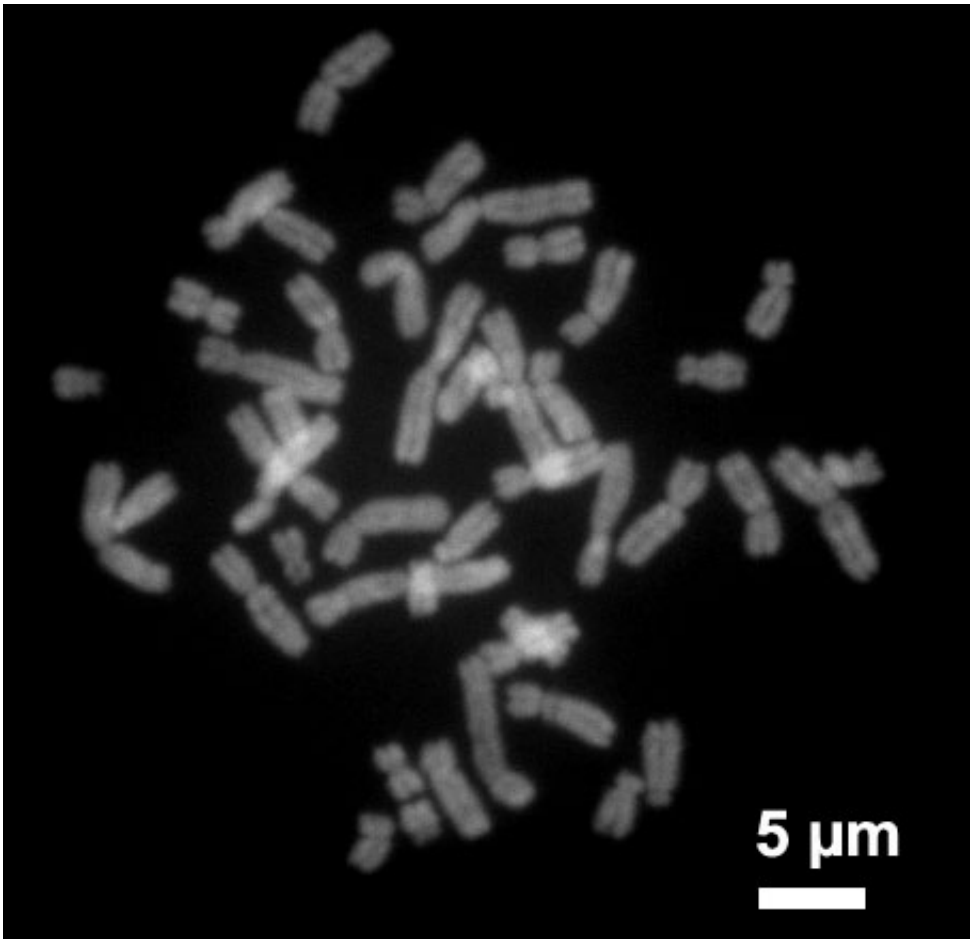

Human chromosomes during metaphase. Credit: Steffen Dietzel/Wikipedia

X-linked intellectual disability is a disorder that predominantly affects men and can have highly variable clinical manifestations. Scientists at

the Max Planck Institute for Molecular Genetics in Berlin have found seven new genes that can cause this genetic disease: Mutations of these genes on the X chromosome lead to various forms of intellectual disability. In their work, the researchers used a method of genetic analysis that significantly simplifies the search for rare genetic defects.

X-linked intellectual disability is caused by defective genes on the X chromosome. As males only have one X chromosome and the disease is passed on in a recessive manner, the disorder mainly occurs in boys. Women are affected only if both their X chromosomes carry the defective genes. Women with one healthy and one mutated X chromosome are usually healthy but have a 50% chance of passing the mutated X chromosome on to their offspring.

Because of the high variability of the clinical picture, the search for the responsible genetic defect was, until a few years ago, very tedious. Some families have been waiting for over 15 years for the cause of their relative's disorder to be clarified. An international research team headed by Max Planck researcher Vera Kalscheuer has now analysed 405 families, in which cases of X-linked intellectual disability occur. The researchers have discovered changes in a number of genes that were already known to be related to the disorder. In addition, they discovered that X-linked intellectual disability can also be caused by mutations in seven other genes that, until now, were not associated with the disorder.

For some years now, scientists have been aided in their research of genetic diseases by high-throughput sequencing. This technology allows to sequence a large number of DNA segments simultaneously and to more easily identify genetic defects. Using this method, the scientists investigated all DNA regions of the X chromosome containing protein-relevant information. "In addition to known disease-related genes, we have discovered seven novel genes as the cause of X-linked intellectual disability and analysed what signaling pathways in the cells each protein

is involved in," says Kalscheuer. According to the researchers, the clinical presentation and severity of the disorder depend on the responsible gene and the nature of the mutation. For example, if the mutation is located in a region that is important for brain development and protein function, the result is likely to be a more severe disease progression.

With the help of systematic re-sequencing of all X-linked genes, the responsible genetic defect can be identified in around 60 percent of families with X-linked intellectual disability. This requires that a condition known as fragile-X syndrome, caused by an expansion of a trinucleotide repeat, has been ruled out. However, this cannot be done with the method used here.

According to the scientists, the proteins associated with the newly discovered genes may also be involved in epilepsy, autism and schizophrenia. In future, the researchers aim to investigate the functions of the responsible proteins more closely in order to improve our understanding of what causes these and similar disorders.

More information: Hu H, et al. X-exome sequencing of 405 unresolved families identifies seven novel intellectual disability genes , *Molecular Psychiatry* (2015). DOI: 10.1038/mp.2014.193

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