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Sequencing a single genome yields cause of inherited bone disorder

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Combining new, whole-genome sequencing technology with classic genetic approaches to understanding inherited diseases, Duke University Medical Center geneticists and colleagues at Johns Hopkins have discovered two gene mutations that cause metachondromatosis, a rare, heritable disorder that leads to bony growths, typically on hands and feet.

They did it by sequencing the entire genome of just one individual.

Traditionally, rare inherited diseases (sometimes called "Mendelian" diseases, referring to those caused by mutations in a single gene and passed on through classic genetic patterns) have been studied using an approach called "linkage" in which a small number of markers are assessed for co-inheritance with the disease. The approach has been successful in many cases, but it can be very time-consuming and has been unsuccessful in as many as 1,500 studies where the presence of a gene inherited in Mendelian fashion is suspected, but has not been found, according to David Goldstein, PhD, director of the Center for Human Genome Variation at Duke.

Goldstein says a new strategy his team used to find mutations that cause metachondromatosis enables faster identification of Mendelian genes. "But perhaps more important, it may allow us to identify a lot of Mendelian genes that have been difficult to pin down with traditional analyses."

The opportunity to study genetic causes of metachondromatosis arose

when Goldstein was lecturing at Johns Hopkins. Nara Sobreira, a graduate student in human genetics at Hopkins and a lead author of the study, mentioned to Goldstein that she was studying a small family that included six individuals across four generations affected with metachondromatosis.

The research team chose one member of the family and sequenced the entire genome of that person. Next, they used data from partial linkage data from other family members to identify areas in the genome where potentially causative mutations were most likely to be found. The analysis turned up six probable regions, implicating about one percent of the total genome. "This amount of genetic material would be very challenging to sequence using traditional strategies," said Goldstein.

The team used whole genome sequencing to zero in on a tiny string of 11 base pairs deleted from exon four of a gene called PTPN11. They found that all members of the family affected with metachondromatosis carried this mutation. The researchers confirmed PTPN11 alteration as the cause of the disease when they found a different mutation in the same gene in a second family with a history of the disease that also appeared in all of those affected with the disorder. Both mutations were predicted to lead to loss of function, or the inability of the body to make a protein necessary for normal development.

The researchers also sequenced exon 4 of PTPN11 - the location of the causal mutations - in 469 unrelated controls but did not find any mutations in the gene in that group.

Elizabeth Cirulli, a graduate student at Duke, a lead author and a member of Goldstein's team, says this is the first time that nonsense mutations in PTPN11 - errors that disable a protein -- have been described in human disease. "The next step would be to figure out how this mutation directly contributes to the development of

metachondromatosis," she said.

Sobreira said that finding the gene that causes metachondromatosis may also reveal the molecular basis of other diseases, like Maffucci syndrome and Ollier's disease, since individuals with those disorders share similar physical characteristics with those who have metachondromatosis.

Goldstein says the study adds to a small but growing list of examples where whole-genome sequencing approaches have successfully identified rare, high-penetrant risk factors for disease. Penetrance is a measure of how potent a mutation is in causing disease.

"The fact that linkage evidence was able to narrow our search for variants to just a fraction of what it might otherwise have been, cut our research time considerably," Goldstein says. He says that one interesting feature of this study is that the initial linkage evidence was only modest, approaching the sort of linkage evidence sometimes seen in large, multiple families for common diseases. "We are therefore hopeful that this sort of family-based sequencing might have utility in the study of genetic variants involved in more common diseases."

More information: Sobreira NLM, Cirulli ET, Avramopoulos D, Wohler E, Oswald GL, et al. (2010) Whole-Genome Sequencing of a Single Proband Together with Linkage Analysis Identifies a Mendelian Disease Gene. PLoS Genet 6(6): e1000991. doi:10.1371/journal.pgen.1000991

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