The Variability of Genetic Disease

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It is never boring to be a physician because patients are so different. Each patient has a story to tell, and few have disorders that match textbook descriptions. By the same token, we need to be careful when predicting the future for our patients, and finding the appropriate therapy is not always straightforward. In the case of genetic diseases, this variability can be extraordinary.

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often a matter of trial and error as much as science and protocol. Why are diseases so variable? A study by Girirajan et al. in the Journal provides some new insights.

There are three obvious candidates for determining disease manifestation, or phenotype, as geneticists call it. First, the environment has a major role. Disease will not be expressed in persons with lactose or gluten intolerance if they are not exposed to lactose or gluten. Only a small proportion of persons who are homozygous for the common hemochromatosis mutation have overt disease, and the disease is less prevalent in women than in men, perhaps because of menstrual-blood loss, which limits iron accumulation.

A second factor is chance. Mutations causing disease are sometimes transmitted by completely healthy parents. Breast cancer does not develop in all female carriers of a BRCA1 mutation, and holoprosencephaly occurs in only a minority of those with a mutation in the human sonic hedgehog gene (SHH), reflecting stochastic events as much as environmental or genetic factors that offer protection from or increase the risk of disease.

And thus, the third factor underlying phenotypic variability of inherited disease is genetic background. Modifier genes (genes that modify the clinical outcome of a genetic mutation) have been traditionally difficult to study, and most successes have come from the study of specific candidate genes that reside in the same biologic pathway or module as the disease gene itself.

But this picture is about to change. It is now possible to cheaply and quickly sequence the exomes (the parts of genes that encode amino acids) of all 22,000 human genes. Microarray-based comparative genomic hybridization (array CGH) provides tools that allow the systematic interrogation of the entire genome at high resolution to identify rare events that may act as modifiers of a pathogenic gene mutation or of a chromosomal copy-number variation (a deletion or duplication of a chromosomal segment that results in the number of copies of that segment, including the genes contained therein, being less than or exceeding two). Such techniques can pick up modifiers that would previously have remained undetected.

Following an earlier study, Girirajan et al. used array CGH to detect small chromosomal imbalances that affected up to 90 genes in children with intellectual disability. About 15 to 30% of these children would be expected to have a copy-number variant detectable by means of array CGH but not by karyotyping. The authors then looked for second-site modifier events. They focused on rare cases in which children carried two independent, large copy-number variants. This situation occurs in less than 1% of the unaffected population but was detected in 8.6% of children with a learning disability. Most striking was the enrichment for additional events in children with copy-number variants that also were found in control samples. The obvious implication is that this class of copy-number variants is not sufficient to cause intellectual disability by itself but will do so when there is the added burden of a second chromosomal imbalance.

The data presented by Girirajan et al. argue for a simple, additive model of chromosomal imbalance, in which the number of affected genes correlates with the severity of the clinical manifestations. Intriguingly, male sex emerged as an independent risk factor for developmental delay. Not only were boys overrepresented among cases with developmental delay and second-site copy-number variants, but presumably unaffected women were more likely to transmit such second chromosomal imbalances to their offspring. This is entirely compatible with a model that assumes that since males have only a single X chromosome, they are generally more vulnerable to genetic insults than females, who have two X chromosomes.

The robust study and careful analyses of Girirajan et al. show us one scenario that explains why persons with the same chromosomal abnormality may have very different clinical outcomes: some of them may simply have a second genetic event that makes matters worse for them. Such complexity is now being made more visible for genetic disease. We can look forward to further improvements in our understanding of the variation in genetic disease, which will in turn permit physicians to better inform their patients about the cause of their condition, its prognosis, and the therapy that is most likely to benefit them.

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