Medical Xpress

How genetic mutations affect development more complex than previously thought

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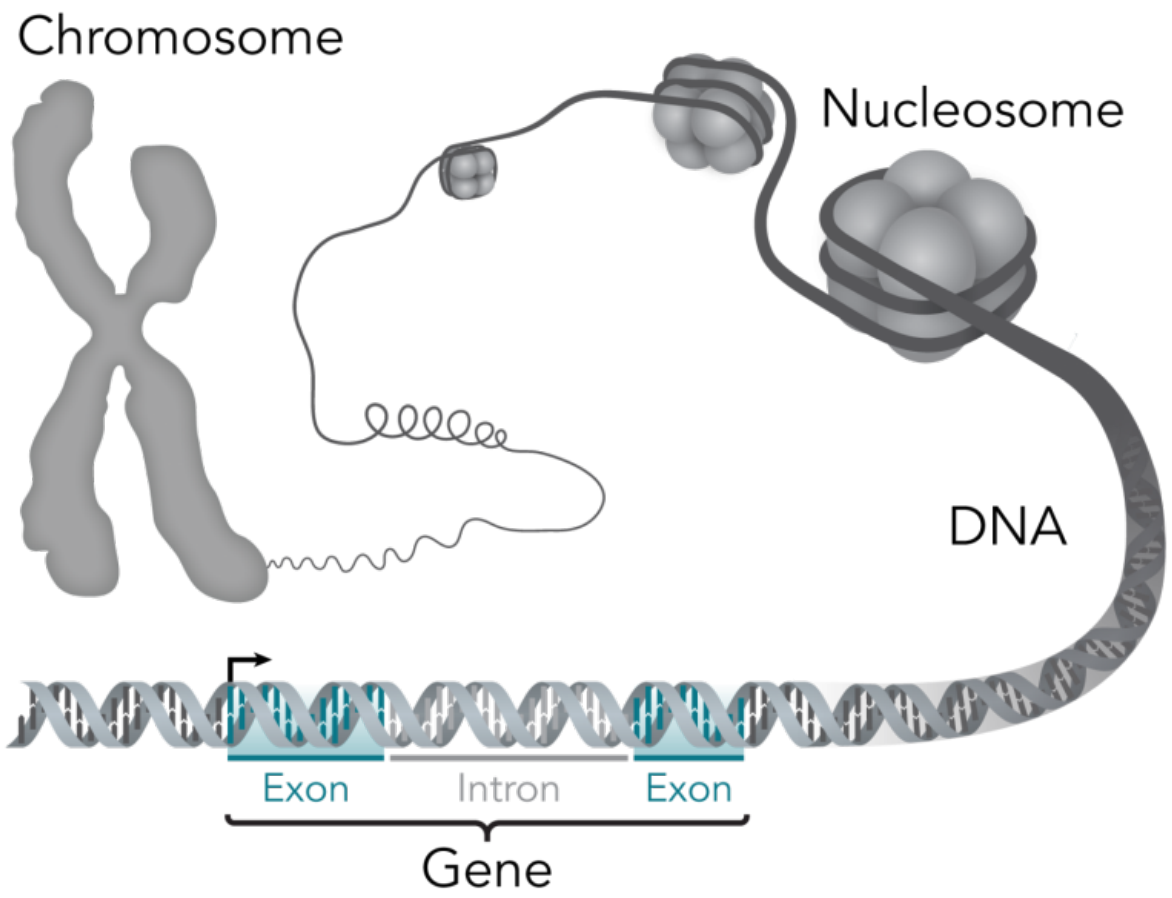

This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

A large-scale study, published in Wellcome Open Research and which passed peer review today, has shown that inactivating the same gene in mouse embryos that are virtually genetically identical can result in a wide range of different physical features or abnormalities. This suggests that the relationship between gene mutation and consequence is more complex than previously suspected.

The researchers, from the Deciphering the Mechanisms of Development Disorders (DMDD) consortium that is coordinated at the Francis Crick Institute, looked at 220 mouse embryos each missing one of 42 different genes. By scanning the entire embryo in minute detail, the researchers picked up on even the smallest differences in features – right down to the level of whether the structure of individual nerves, muscles and small blood vessels were abnormal.

The genes studied by DMDD are known as 'embryonic lethal', because they are so crucial to development that an embryo missing any one of them can't survive to birth. Studying these genes can help us understand how embryos develop, why some miscarry, and why some mutations can lead to abnormalities at birth.

Clinicians commonly find that people with the same genetic disease can show different symptoms or be affected with differing severity. In part this is likely to be due to the fact that we all differ in our precise genetic makeup. However, this study in mice shows that even when individuals have virtually identical genomes, the same mutation can lead to a variety of different outcomes amongst affected embryos.

This is a striking result, coming as it does from such a large study in

which embryos have been studied in unprecedented detail. It shows us that even with an apparently simple and well-defined mutation, the precise outcome can be both complex and variable. We have a lot to learn about the roles of these lethal genes in embryonic development to understand why this happens.

"This is a surprising result, and more research into gene function is needed in order to make sense of the finding," says Dr Tim Mohun, who led the study at Deciphering the Mechanisms of Developmental Disorders (DMDD).

"The fundamental processes driving how we develop have been conserved through evolution. This makes studying animal models enormously helpful in increasing our understanding of why some babies develop birth defects. This study throws new light on what we thought was a fairly straightforward relationship between what's coded in our genes and how we develop. Researchers need to appreciate this added layer of complexity, as well as endeavouring to unpick the intricate processes of genetic control at play," says Dr Andrew Chisholm, Head of Cellular and Developmental Sciences at Wellcome, which funds the DMDD.

"This study highlights the power of genetic analyses in mice and provides an unprecedented resource of data to inform clinical genetic studies in humans," says Dr David Adams, Group Leader at the Wellcome Trust Sanger Institute, who collaborated with the study.

More information: Robert Wilson et al. Highly variable penetrance of abnormal phenotypes in embryonic lethal knockout mice, *Wellcome Open Research* (2016). DOI: 10.12688/wellcomeopenres.9899.1