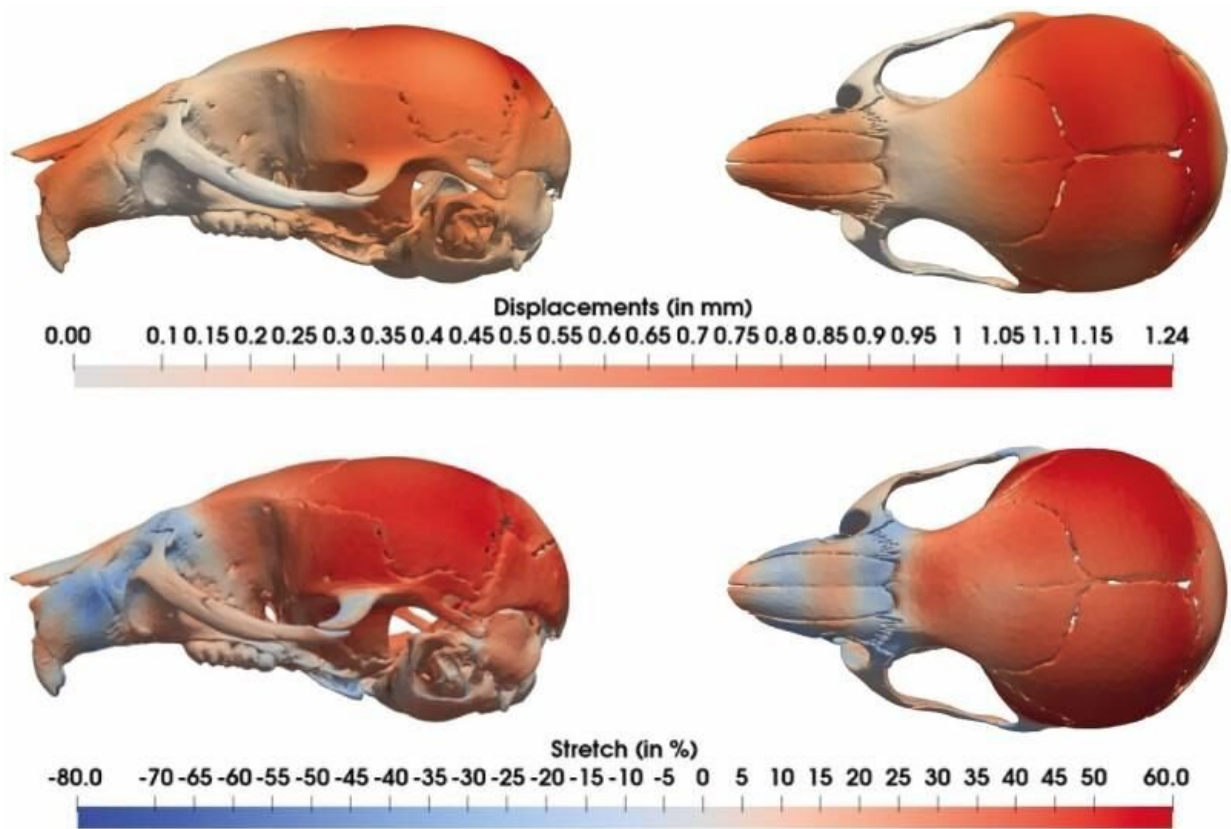


Researchers show genetic basis of facial changes in Down syndrome

April 26 2023



Heatmaps showing skull expansion (red) and facial bone reduction (blue) generated using a computer model to show the differences between Down syndrome and normal skulls (seen from the side and above). These changes are very similar to those in humans with Down syndrome. Credit: Development

Researchers at the Francis Crick Institute, King's College London and University College London have shed light on the genetics behind changes in the structure and shape of the face and head in a mouse model of Down syndrome.

Described in a paper published today in *Development*, the researchers found that having a third copy of the gene *Dyrk1a* and at least three other [genes](#) were responsible for these changes taking place in development—called craniofacial dysmorphology—which involve shortened back-to-front length and widened diameter of the head.

Affecting 1 in 800 [live births](#), Down [syndrome](#) is known as a "gene dosage disorder"—meaning that it involves changes in the number of copies of a gene. People with Down syndrome have three copies of chromosome 21 instead of two. Having three copies of certain genes on this chromosome causes aspects typical of Down syndrome, but it's not yet known which genes are responsible.

Using [genetic engineering](#), teams led by Victor Tybulewicz of the Francis Crick Institute and Elizabeth Fisher of University College London created mouse strains with duplications of three regions on mouse chromosome 16, which mimics having a third chromosome 21. The mice show lots of traits associated with Down syndrome, including changes in the shape of the face and skull.

Previous research has linked a gene called *Dyrk1a* to aspects of Down syndrome, so the researchers wanted to test how it impacted craniofacial dysmorphology.

Now working with Jeremy Green's group at King's College London, they showed that mice with an extra copy of *Dyrk1a* had a reduced number of cells in the bones at the front of the skull and in the face. Also, cartilaginous joints at the base of the skull called synchondroses were

abnormally fused together. These effects were partly reversed when the third copy of Dyrk1a was removed, showing that three copies of Dyrk1a are necessary to cause these changes in the skull.

The researchers believe that having a third copy of Dyrk1a hinders the growth of neural crest cells that are needed to form the bones at the front of the skull.

In addition to Dyrk1a, the research showed that three other genes also contribute to the changes in the skull, but more research is needed to confirm their identity.

Victor Tybulewicz, Group Leader of the Down syndrome Laboratory at the Crick, who worked with first author Yushi Redhead, said, "There's currently limited treatments for the aspects of Down syndrome which have a negative impact on people's health, like congenital heart conditions and [cognitive impairment](#), so it's essential we work out which genes are important.

"Understanding the genetics involved in the development of the head and face gives us clues to other aspects of Down syndrome like heart conditions. Because Dyrk1a is so key for craniofacial dysmorphology, it's highly likely that it's involved in other changes in Down syndrome, too."

Researchers at King's College London used shape-measuring tools to map the changing skull shape of the mice. These showed changes in [skull](#) shape that were remarkably similar to those seen in people with Down syndrome.

Jeremy Green, Professor of Developmental Biology at King's College London, said, "With the help of great collaborators at the University of Calgary in Canada and a medical imaging software group here at King's,

we were able to apply both quite traditional and some very novel methods for comparing complex anatomical shapes. These were sensitive enough to pick up differences even at fetal stages. This helped us pin down not only the locations of genes that cause Down syndrome but also get clues as to how those genes cause the differences that they do."

This research forms part of an ongoing project to understand the genetics of Down syndrome. The researchers will next aim to identify the genes involved in heart defects and in cognitive impairment, bringing us a step closer to understanding how to develop targeted treatments for aspects of Down syndrome which impact health.

More information: Yushi Redhead et al, Craniofacial dysmorphology in Down syndrome is caused by increased dosage of Dyrk1a and at least three other genes, *Development* (2023). [DOI: 10.1242/dev.201077](https://doi.org/10.1242/dev.201077)

Provided by The Francis Crick Institute

Citation: Researchers show genetic basis of facial changes in Down syndrome (2023, April 26) retrieved 8 May 2024 from <https://medicalxpress.com/news/2023-04-genetic-basis-facial-syndrome.html>

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