Scientists find gene behind a highly prevalent facial anomaly

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Whitehead Institute scientists have identified a genetic cause of a facial disorder known as hemifacial microsomia (HFM). The researchers find that duplication of the gene OTX2 induces HFM, the second-most common facial anomaly after cleft lip and palate.

HFM affects approximately one in 3,500 births. While some cases appear to run in families, no gene had been found to be causative. That is until Whitehead Fellow Yaniv Erlich and his lab set out to do just that. Their work is described in this week's issue of the journal *PLOS ONE*.

Patients with HFM tend to have asymmetrical faces, —typically with one side of the upper and lower jaws smaller than the opposite side—a smaller or malformed ear on the affected side, and, in some cases, neurological or developmental abnormalities.

Thought to be brought on by circulation difficulties during embryonic development, HFM is also thought to be sporadic—meaning that it occurs spontaneously rather than through inheritance. However, one family in northern Israel has more than its share of the anomaly.

To identify the origin of this family's disorder, Erlich and lab technician Dina Zielinski began studying the genomes of a five-year-old female member of the family, along with those of her mother, grandmother, and male cousin, who all exhibited traits of HFM. Later, the genetic information from the grandmother's Russian cousin, who resides in the Philadelphia area, was recruited to the study.

"What's unique here is that this is the largest family with this disorder described in the literature," says Erlich. "Most of the time, you see one person affected, or perhaps two people—a parent and a child. Such a large family increases the power of the genetic study and clearly signals that there is a genetic component to a disease."

To find the cause of this family's HFM, Zielinski began by searching for a point mutation, but the five of the study participants held no such mutation in common. Next she looked for sections of the genome that are duplicated. All had an extra copy of one 1.3 megabase pair section of chromosome 14. Duplications this large are frequently detrimental.

Within this large piece of DNA, Zielinski identified eight candidate genes that could cause the type of HFM running in this family. She then used two algorithms to compare the molecular signatures of these eight genes to other genes known to be responsible for various facial malformations with features similar to HFM. After this analysis, the gene OTX2 that codes for a transcription factor rose above the seven other candidates.

These results are supported by what is known of OTX2's function. Previous data indicates that the gene codes for a protein that is expressed in the heads and pharyngeal arches of mouse embryos in developmental stages corresponding to the periods when HFM abnormalities are thought to arise in humans.

Although this is a tantalizing hint as to OTX2's activity during development, Zielinski cautions that little is known about its overall role, in part because it serves as a transcription factor that regulates other genes.

"OTX2's activity is very complicated," says Zielinski, who is first author of the *PLOS ONE* paper. "Development is dependent on tight control of these transcription factors that turn other genes on and off. The feedback between OTX2 and other transcription factors is complex but we know that OTX2 plays a critical role in craniofacial patterning."

Intriguingly, another, darker role of OTX2 was highlighted during the course of the study. The little girl who was this research's main focus was

diagnosed with medulloblastoma, a highly malignant tumor originating at the base of the brain in or near the cerebellum. OTX2 is a known oncogene for her subclass of medulloblastoma, confirming that her OTX2 expression is out of line.

"OTX2 is one of the most common genes that is amplified in medulloblastoma," says Erlich. "So first you have this gene that is involved in facial development, and then the same gene is involved in some cases of medulloblastoma. It suggests a very interesting link between the two."

Despite the dim prognosis normally associated with this cancer, the girl has gone through treatment and is currently in remission.

Although an extra copy of OTX2 causes HFM in this family, it is not the only faulty gene responsible for this disorder. Zielinski looked at seven other familial cases of HFM and none had duplication of OTX2, opening up the possibility that there could be several other errant genes involved in familial HFM.

More information: "OTX2 duplication is implicated in hemifacial microsomia" *PLOS ONE*, May 9, 2014.

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