Mutation in receptors of the corpus callosum causes developmental issues in children

A mutation in the receptor DCC, needed for guidance of axons of the corpus callosum during development, is found to cause isolated agenesis. This provides information that can be used for prenatal detection of agenesis and the risk factor of an abnormal neurodevelopmental outcome.

Jordan Hill

The complete or partial absence of the corpus callosum is called agenesis and affects about 1 in 4,000 newborns and 3-5% of children with intellectual disabilities. Many genetic mutations can cause agenesis and intellectual disabilities, but the genetics of isolated agenesis is not fully understood. In a paper recently published in Nature Genetics, Ashley Marsh and her team investigated the formation of the corpus callosum and the effect that a mutation on a specific receptor plays on isolated agenesis. Marsh concluded that a mutation on the ligand-receptor DCC caused isolated agenesis in humans. This observation has implications for prenatal diagnosis and parental counseling.

The corpus callosum plays an important role in the communication between the left and right hemispheres of the brain. It is crucial to processing motor, sensory, and high-level cognitive signals. When the corpus callosum has been damaged or is missing, the communication becomes interrupted and can cause epileptic seizures, vision impairments, hearing impairments, difficulty reading facial expressions, difficulty understand abstract concepts, and more. When this occurs in the fetus or growing child, agenesis can cause developmental and behavioral delays and intellectual disorders. There are several ligands in the corpus callosum. The primary ligand that this recent study focused on was Netrin. Netrin is a class of proteins that are responsible for guiding axons as they grow to their proper locations. The receptor DCC is a netrin receptor that is important for guiding callosal axons at the midline.

46 individuals from 9 different families volunteered to have blood samples taken. They also consented to diffusion MRI and tractography, which allowed the research team to confirm agenesis. Once the data was collected the research team was able to run a linkage analysis and whole-exome sequence. This provided the team with the ability to create a family tree and mark who were carriers and who suffered from agenesis and who suffered from congenital mirror movements. They also took the blood samples to amplify and sequence the DCC coding region of everyone's DNA.

Previously, mutations in DCC were known to cause congenital mirror movement, but with this study it was also found that mutations in DCC cause isolated agenesis in humans. They were not able to determine the exact factors behind the mutation because this most likely includes hormonal context during development, the type and location of DCC mutation, and the genetic background of the individual. Heterozygous mutation of the Netrin receptor DCC resulted in isolated ACC but only had a very mild outward effect and the cognitive outcome was favorable. The exact opposite occurred with syndromic agenesis, or when agenesis was passed from parent to child.

This study was fascinating as they looked at the genetic aspect of agenesis of the corpus callosum. They were able to find a significant difference between agenesis being passed down and agenesis being isolated to the one individual. The work that was performed could easily be used to screen fetuses, much like how they do prescreen of other genetic disorders. This is important for preparing parents who may not be used to caring for a child with developmental delays. This work is also important for understanding the next step in how these specific genes play a role in the development of a fetus.

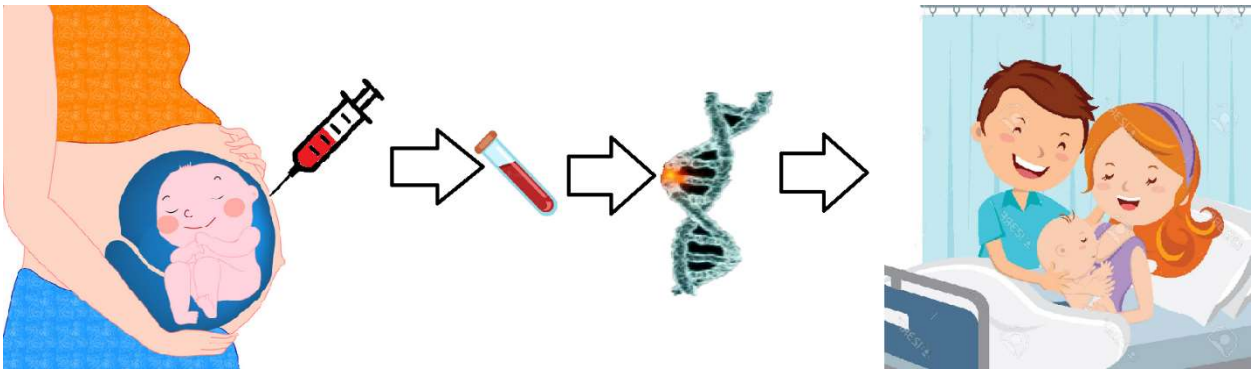

Figure 1: This study can lead to prenatal screening of mutated genes. This allows parents of newborns to be happy because they will have a better understanding of what to expect from their newborn and how to best help them.

Reference

1. Marsh, A., Heron, D., Edwards, T. *et al.* Mutations in *DCC* cause isolated agenesis of the corpus callosum with incomplete penetrance. *Nat Genet* 49, 511–514 (2017). https://doi.org/10.1038/ng.3794