# Discover the Genetic Cause for Intellectual disability

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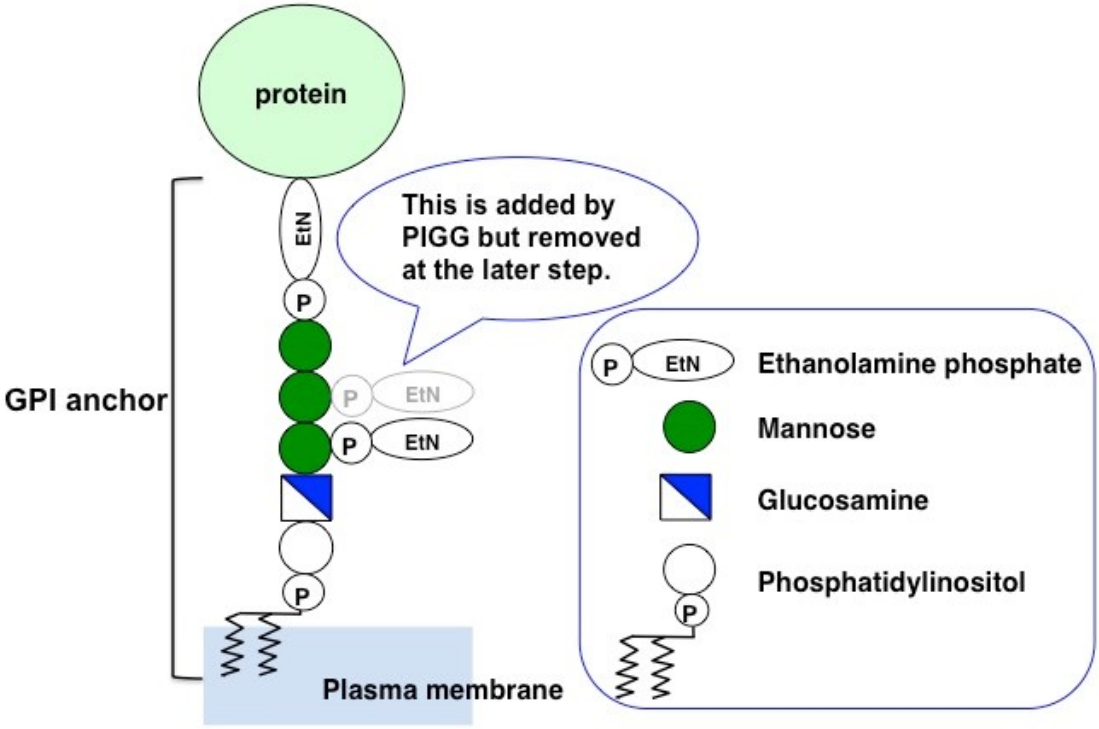


Structure of the GPI anchored proteins: Precursor proteins and GPI are synthesized separately in the ER and the protein is attached to the completed GPI anchor and further modified and transported to the plasma membrane.

A research group led by Osaka University and collaborative institutions discovered that disorders in the same gene PIGG are the cause for intellectual disability with seizures and hypotonia. PIGG is one of the enzymes active in the GPI anchor glycolipid synthesis and the current study revealed its significance in the development of the cerebral nervous system.

Associate professor Yoshiko Murakami and her research team at the Research Institute for Microbial Diseases, Osaka University, together with other research groups from the University of Geneva (Switzerland), the University of Leeds (UK), Yamagata University and Yokohama City University based their discovery on an analysis of five patients from three families, who showed severe delays in psycho-motoric development and epilepsy and revealed the significance of PIGG in the development of the cerebral nervous system.

Among the diseases that cause intellectual disorders with seizures and hypotonia, many causes of disorders remain unknown. Since variations in the PIGG gene have been discovered as one cause, it is now possible to diagnose PIGG deficiency for disorders for which diagnosis was not possible so far. With these research results the researchers hope to provide medical personnel and family members of patients with the opportunity to become aware of inherited GPI deficiencies and undergo examinations.

The Research results was published in electronic version in the *American Journal of Human Genetics* on March 17 2016.

In 2006, Murakami's research group, together with a British research group with whom they conducted a joint research project, reported on the first inherited GPI deficiency (IGD), the PIGM deficiency. Based on the analysis using next-generation sequencers, the research was successively reported on since 2010 with IGD receiving attention as a

new genetic disorder causing developmental delays and epilepsy.

GPI anchors are glycolipids that anchor protein at a cell's surface. They are synthesized through various enzymatic steps and added to protein. Even after having been added, they undergo various modifications and are transported to the cell's surface. Protein groups of this shape are called GPI-anchored proteins with more than 150 different types known to exist with humans. 27 genes are involved in the biosynthesis and modification of GPI anchors. If these genes mutate and no GPI anchors are synthesized in all body cells, these 150 important proteins will turn defective, meaning that life would not be possible.

So far, IGD has been reported with mutations of 13 genes among the 27. These are not cases of complete deficiency but partial deficiencies caused by function deterioration through mutation. Here symptoms arise due to decrease in various GPI anchored proteins that are transported to the surface of nerve cells as a result of mutation. This report presents the discovery of a PIGG deficiency as the IGD of the 14th gene. Unlike the other 13 genes, the GPI anchored proteins were transported as usual to the cell surface in cultured cells with normal structure, which is why the importance of PIGG's existence remained unclear. However, the current research discovered that mutations of PIGG are the cause of severe cranial nerve problems and that PIGG plays an extremely important role in the actual development of the cerebral nervous system. This is expected to serve as a hint in advancing the analysis of its functions.

**More information:** Periklis Makrythanasis et al. Pathogenic Variants in PIGG Cause Intellectual Disability with Seizures and Hypotonia, *The American Journal of Human Genetics* (2016). DOI: 10.1016/j.ajhg.2016.02.007

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