

Disturbed proprioception by PIEZO2 causes a novel muscular atrophy disease

Muscular atrophy is the wasting of muscle mass leading to muscle weakness. Muscular atrophy occurs during immobilization, for example after a bone fracture, but may also have a genetic origin. Genes are blueprints of any organism and contain information of how muscles are built or how the brain can send orders for muscle contraction via nerve cells. Sequence errors in genes, called mutations, result in faulty construction plans leading to malfunctions. There is a great number of patients with inherited muscular atrophy, in which the disease-causing gene is unknown. The research group of Professor Brunhilde Wirth at the Institute of Human Genetics at the University Hospital of Cologne and the Center for Molecular Medicine Cologne (CMMC) has succeeded to identify mutations in a gene called *PIEZO2* that cause a new type of muscular atrophy. The scientists now published their results in the renowned magazine *The American Journal of Human Genetics*.

Close your eyes, lift and extend your arms, and blindly bring your index fingers to match in front of you. To end up with the fingers close to each other is easy, but complex processes happen unconsciously in the background to make things working. Even though there is no visual information about the exact position of arms and fingers, we still have a good clue where the arms actually are – a sense called proprioception. It is the feeling of body part positioning in space. The sensing of whether a muscle is contracted or not, even though we cannot see, teaches us where our body parts are. A properly working *PIEZO2* is needed for exactly this. The *PIEZO2* gene is a blueprint for a protein that senses stretch in muscles and in the skin – a so-called mechanoreceptor, because it senses mechanical force.

Markus Storbeck, postdoctor in Wirth's lab, has analyzed sequence data of more than 20,000 genes of muscular atrophy patients and has identified so-called homozygous frameshift mutations in the *PIEZO2* gene. This means that a short piece of sequence is either missing or inserted so that the language of the *PIEZO2* construction plan is distorted and cannot be read anymore. Accordingly, cells cannot produce *PIEZO2* proteins and lack this important mechanoreceptor leading to disease. Even though this is an inherited disease, parents of patients are not affected by it, but both carry a single mutated gene copy (heterozygous). Patients have two affected genes copies (homozygous), one is passed on from the mother, and the other is passed on from the father. Geneticists call this an autosomal recessive mode of inheritance.

The medical doctor and PhD student Andrea Delle Vedove has conducted experiments on cultivated cells taken from the patients' skin. By his work he demonstrated that the identified mutations in *PIEZO2* make it impossible for the cell to read the sequence. Cells consider the blueprints to be waste and thus, construction plans are destroyed by the cell. Consequently, there is no *PIEZO2* protein in patients' cells and cells lack the ability to sense mechanical forces like stretch or pressure.

The disease caused by *PIEZO2* mutations is congenital, which means it is present at birth and muscular defects already arise during embryonic development. Healthy unborn babies move in the uterus – a prerequisite for muscle development and growth by “workout”. The scientists around Professor Wirth believe that proprioception, as it is mediated by *PIEZO2*, is needed to govern this early muscle development. Muscles that fail to sense stretch are too short at birth leading to deformities, like scoliosis and joint rigidity. Some of them may be surgically corrected, but there is no treatment available for the motoric deficits in the patients. As for all genetic diseases, the identification of the disease-causing gene and a deeper understanding of the mechanism that leads to disease is necessary to develop strategies for treatment. The first steps on this way have just been made.

Original publication:

Delle Vedove A.*, Storbeck M.*, Heller R., Hölker I., Hebbar M., Shukla A., Magnusson O., Cirak S., Girisha K.M., O’Driscoll M., Loeys B. and Wirth B. **Homozygous *PIEZO2* frameshift mutations cause non-progressive muscular atrophy with arthrogryposis, perinatal respiratory distress, scoliosis and sensory neuropathy.**

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