SRD5A3-CDG (Cantagrel et al Cell, 2010, Morava et al, Brain, 2010)

There are different CDG syndromes. SRD5A3-CDG is a CDG that has been discovered only recently. It is a very rare disease.

**Clinical features** SRD5A3-CDG is often called a cerebello-ocular syndrome. This means the disorder mainly presents with neurological and ophthalmological abnormalities. Often, the first symptoms can already be seen at young age. A reduced muscle tone and eye problems, for example, can already occur in the first six months of life.

Impaired sight and nystagmus are the eye problems most frequently observed in SRD5A3-CDG. Nystagmus is a symptom involving quick and rhythmic involuntary movements of the eyes. Furthermore, in many patients, the eyes lie deep in their sockets and there is a wider distance between both eyes than normal. These features are often combined with an abnormal position of the ears. Eye problems that are less frequently observed are congenital cataract, increased eyeball pressure (glaucoma) and coloboma. With coloboma there is a missing part in one of the structures of the eye. The most common type of coloboma occurs in the iris, but colobomas may also appear in the eyelid, the lens, the optical nerve, the choroid or the retina in SRD5A3-CDG patients. In addition to the ophthalmological symptoms, psychomotor retardation is characteristic in this disorder. The severity of the developmental problems, however, varies between individuals. Additionally, patients often suffer from cerebellar abnormalities, leading to ataxia, a neurological symptom involving problems in balance and movement coordination. Coagulation disorders, leading to either an increased blood clot formation or an increased bleeding tendency, often occur in SRD5A3-CDG. A presentation with a combination of the symptoms mentioned above leads to a strong clinical suspicion of SRD5A3-CDG. The suspicion is even higher when an abnormal cornification of the skin, (medically called “ichthyosis”), is found. Ichthyosis is characterized by an increased thickness of the skin, leading to the formation of dry plaques or scales. The skin is very dry and flaky. Next to these frequently seen symptoms, patients may present with problems that are less typical for SRD5A3-CDG, including heart abnormalities, spasticity and stereotypic movements. Symptoms that may occur frequently in other types of CDG, like renal abnormalities, gut problems and skeletal disorders, are hardly seen in this disorder.
**Cause** SRD5A3-CDG is caused by a mutation in the SRD5A3 gene. This gene codes for the enzyme 5α-reductase type 3. The mutation causes this enzyme to be deficient. The enzyme is responsible for the formation of polyprenol from dolichol (a reaction in lipid metabolism, required for the binding and carrying of glycans in the early steps of the glycosylation pathway). This is an essential, early step in protein glycosylation. A deficiency in this enzyme causes a defect early in the glycosylation pathway.

**Diagnostics** Glycosylation can be tested with screening tests (such as TIEF) that can be performed on blood samples. Other metabolic surveys (LLO analysis in skin tissue), liver function tests, or coagulation tests may be applied as well. The definite diagnosis of SRD5A3-CDG is established by a genetic blood test.

**Genetics** Every cell in the human body contains genetic material in the form of DNA, in which lay many genes coding for certain traits. Every gene has two copies; one inherited from mother, one from father. The inheritance pattern of SRD5A3 CDG is autosomal recessive. This means you will only get the disease, if you do have two 'faulty' copies of the involved gene. If you have only one changed copy of the gene, you don’t have the disease; you are a carrier. If both parents have one changed gene (and thus are healthy carriers) they have a 25% percent chance to have a child that inherits two changed copies and has the disease. So, it is possible that your sick child has healthy brothers and sisters. They did at least inherit one ‘normal’ gene from one of their parents. The chance that a new baby also has the disease is 25%. When both parents have one changed gene (and are, therefore, healthy carriers), there is a chance that a child inherits the changed gene from both parents. The child will then have two mutated genes en it will get the disease. The chance for a child to inherit two mutated genes and get the disease is 25%. It is possible for an affected child to have healthy siblings. They have inherited a healthy gene from at least one of their parents.

**Treatment** Currently, as for most CDG syndromes, no treatment is available for SRD5A3-CDG. Problems can, however, be detected at an early stage to provide proper counseling. Furthermore, several symptoms can be treated. Some of the eye problems can be corrected (mostly operatively) and coagulation disorders can be treated with medication. Additionally, children experiencing learning problems can be assisted through special guidance and support.