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# Novel NSDHL mutation as a rare cause of fetal cortical malformation – First prenatal description of CK syndrome

Brinckwirth, Beatrix1, Hotz, Alrun2, Gläser, Dieter3, Alter, Svenja2, Kopp, Julia2, Tzschach, Andreas2, Richter, Tanja3, Geipel, Annegret4, Fischer, Judith2, Komlosi, Katalin2

Institute of Human Genetics, University of Freiburg, Germany and Practice for Ultrasound & Prenatal Medicine, Freiburg, Germany, Freiburg, Germany

## Objective

Introduction: Pathogenic variants in genes related to the migration and differentiation of cortical neurons can result in malformation of cortical development. Even with trio based whole exome sequencing (trio-based WES) which is successfully implemented in prenatal diagnostics the underlying cause of brain malformation and intellectual disability often remains unknown or inconclusive. A large proportion of identified genetic variants by WES remain of uncertain significance (VUS) and further functional analyses of the gene products are often not performed prenatally.

## Methods

Clinical report: 31 year old G1 P0, Colitis ulcerosa, local Cortisol, 1. TS and cffDNA for Trisomy 21 normal, male fetus. Ultrasound 19/40: mild ventriculomegaly suspicion of abnormal insula and cavum septi pellucidi. As the assessment of brain development is more precise >20 weeks control scan at 22/40: suspicion of lissencephaly type 1 with abnormal gyration and absent corpus callosum, no other organ involvement => Amniocentesis. Control scan 25/40: progressive cerebral maldevelopment. After multidisciplinary counseling the pregnancy was terminated 27/40 at parent's request.

## Results

Methods & Results: 1. Cytogenetic analysis: normal male karyotype, 2. Chromosome microarray analysis: no pathogenic microdeletion or -duplication. 3. trio-based WES: Fetus: novel hemizygous intronic sequence variant c.686$^{+5}$G>A in the NSDHL gene, Mother: heterozygous carrier of the same variant. Segregation analysis in the maternal family suggested de novo mutation in the mother and X chromosome inactivation showed a normal pattern. 4. mRNA analysis of fetal cord blood: "aberrant splicing" = evidence of skipping of exon 6 of the NSDHL gene in at least 50% of the transcripts. Further clinical characterization is now planned in the mother with functional mRNA analysis and MR brain scan.

## Conclusion

Conclusion: The NSDHL gene (MIM *300275) is located at Xq28 on the X chromosome and encodes an enzyme involved in the later steps of cholesterol biosynthesis. The enzyme is highly expressed in the brain where it is relevant for migration and differentiation of cortical neurons. Pathogenic variants in the NSDHL gene cause loss of function or malfunctioning of the NSDHL protein resulting in CHILD syndrome (MIM #308050, X-linked, dominant, lethal in males) and CK syndrome (MIM #300831, allelic, X-linked, recessive, only males are affected) both associated with malformation of the brain. So far, less than 20 patients with CK syndrome from three families with 3 different pathogenic variants have been reported and no prenatal phenotype has yet been described. In our case the functional analysis shows defective processing of the gene with defective gene product in the fetus in at least 50% of the transcripts. This finding supports the pathogenicity of our novel NSDHL variant and makes the diagnosis of CK syndrome the most probable cause of cortical malformation. Previous cases showed a preferential transmission of the mutation to offspring of up to 80% and therefore the risk of recurrence in future male pregnancies is high. Our case describes for the first time the prenatal ultrasound findings of CK syndrome and adds to the phenotypic spectrum of NSDHL disorders. It underlines the importance of subsequent functional analysis of an identified VUS in prenatal genetic diagnosis to enable proper genetic counseling for family planning including reproductive options like PID to hereby reduce or avoid the physical and psychological burden of recurrent severe disease.