Introduction: Cytoplasmic dynein 1 is a cytoskeletal motor transporting various cargos in cells and playing specific roles such as empowering neurotrophic signaling important for neuronal survival. *DYNC1H1* (MIM#600112) gene encodes a heavy chain 1 of the cytoplasmic dynein. Heterozygous mutations of this gene are linked to neuromuscular (MIM#158600, MIM#614228) and neurodevelopmental disorders (MIM#614563). Here we describe a study performed to investigate the pathogenicity of a novel intron variant in *DYNC1H1*.

Materials and Methods: A male, 14 years of age, was referred for genetic assessment for intellectual disability and abnormality of cerebral cortex. WES was applied to analyse DNA of the proband and both parents. The DNA of healthy brother was analysed by Sanger sequencing. To determine the effect of identified splice site variant on mRNA structure, total blood mRNA of the proband was isolated, template cDNA was synthesized, and Sanger sequencing was performed.

Results: Analysis of DNA samples revealed heterozygous donor splice site variant NC_000014.9(NM_001376.5):c.6405+1G>C in *DYNC1H1* gene as *de novo* in the proband's DNA. *In silico*, this altered donor site probably affects mRNA splicing. PCR of proband's cDNA resulted in two different fragments. Sanger sequencing revealed retaining intron 31 in one of them, presumably leading to a frameshift and premature stop codon truncating motor region of the protein (NP_001367.2:p.(Ile2136LeufsTer20)).

Conclusions: The molecular analysis of the donor splice site variant NC_000014.9(NM_001376.5):c.6405+1G>C in *DYNC1H1* revealed disrupted mRNA splicing which leads to truncated and probably dysfunctional protein causing neurodevelopmental phenotype of the proband.

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P08.024.B Development delay in paediatric patient with deletion on chromosome 15q26.2

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Introduction: Subtelomeric chromosomal regions are gene rich. Approximately 2.5% of the patients with mental retardation with or without association of dysmorphic features have deletions in these segments.

Materials and Methods: We performed a aCGH analysis in paediatric patient using the CytoScan_750k Array platform (Affymetrix) which comprises 550 k non-polymorphic and 200 k SNP markers by the Chromosome Analysis Suite (ChAS) Software (v4.0).

Results: We present a 4-year old girl with following dysmorphic signs - downward corners of the mouth and large oral opening, saddle nose with wide nasal root, retracted eye bulbs, triangular pointed eyebrows, asymmetrical placement of the eyelid, smaller opening of the lid, asthenic pointed forehead, short philtrum, small chin and sparse hair. She had development delay with fine rough motoric skills without significant hypotonia and signs of hyperactivity with poor vocabulary. Height and weight were under 3th percentile. Karyotype analysis was normal as well as FISH analysis for 4p- deletion performed by suspicions for Wolf-Hirschorn syndrome. aCGH analysis showed pathological deletion of 5,025 kb segment on 15q26.2 (14 OMIM genes) and additional duplication of 4,179 kb segment on the 1p36.33 chromosome (57 OMIM genes) according to ClinVar and OMIM database. The genes IGFR1, MEF2A, CHSY1, and TM2D3 in the deleted region could be delineated according to patient phenotype.

Conclusions: The deletion on 15q26.2 may lead to the description of clinically recognizable syndrome associated with development delay. Further examinations should be performed for including other genes in the pathological condition.

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P08.025.C Solve-RD: the ITHACA perspective

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CERTIFICATE OF ATTENDANCE

This is to certify that

Violeta Anastasovska

ESHG

has participated in the

European Human Genetics Virtual Conference 2021

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