97 A NOVEL MISSENSE MUTATION IN *SGSH* GENE CAUSING SANFILLIPO TYPE 3A MUCOPOLYSACCHARIDOSIS

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The Sanfilippo syndrome, or mucopolysaccharidosis III, is an autosomal recessive lysosomal storage disease due to impaired degradation of heparan sulphate. A type IIIA (MPS3A; MIM #252900) is caused by homozygous or compound heterozygous mutations in the *SGSH* gene (MIM #605270) encoding N-sulfoglucosamine sulfohydrolase. MPS IIIA is characterised by progressive central nervous system degeneration manifested as severe intellectual disability (ID)/developmental delay, delayed speech development, autism spectrum disorder and other behavioural problems, epilepsy, and sleep disturbances. Other symptoms include joint stiffness, contractures, scoliosis, hip dysplasia, hearing loss, recurrent respiratory tract and sinopulmonary infections and diarrhoea. Most patients have the onset of clinical symptoms at a mean age of 2.5 years. Clinical features and disease severity vary considerably and the disease course may be rapid or slowly progressive.

We report on a seven-year-old boy of a healthy nonconsanguineous family, with clinical features of MPS-III syndrome: macrocephaly, coarse face, thick hair, ID, delayed language and speech development, hyperactivity/attention deficit disorder, elbow stiffness/contractures, mild thoracolumbar scoliosis, lumbar lordosis, mild sensorineural hearing loss, frequent upper-respiratory and ear infections, recurrent loose stools, and abundant excretion of heparan sulphate in the urine.

Clinical exome sequencing including GNS, HGSNAT, NAGLU, *SGSH* genes was performed in family members using Illumina TruSight One Kit. In the *SGSH* gene, two missense mutations were identified: c.734G>A (p.Arg245His), inherited from the mother, already described and associated with the classic severe phenotype, and a novel, likely pathogenic variant c.1382T>C

(p.Leu461Pro) inherited from the father. This sequence change replaces leucine with proline at codon 461 of the protein. Although the function of the domain in which this variant is located is still insufficiently known and the variants in this area are mostly of unknown clinical significance, likely pathogenic computational verdict is based on 10 pathogenic in silico predictions and the classical clinical presentation of this patient.

The novel missense mutation reported here, further contributes to the knowledge of the molecular basis of MPSIIIA. As gene therapy is on the horizon, early diagnosis and genotyping are of particular importance for timely targeted treatment.

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98 CLINICAL EXOME SEQUENCING IN THE DIAGNOSIS OF AUTISM SPECTRUM DISORDER

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The autism spectrum disorder (ASD) is a complex neurodevelopmental disorder whose etiology is still poorly understood and attributed to genetic and environmental factors. The next-generation sequencing (NGS) enables simultaneous detection of pathogenic variants in hundreds of genes involved in the pathogenesis of various diseases. The goal of this study was to determine the role of clinical exome testing in the diagnostics of ASD.

For purpose of this study, we analyzed 32 ASD patients that were diagnosed and treated at the Department of Medical Genetics and Reproductive Health in Children's Hospital Zagreb. After detailed psychiatric evaluation and diagnosis of ASD, all patients underwent a clinical geneticist's evaluation and clinical exome testing. Chromosomal disorders and fragile X syndrome have been previously excluded in all patients. Clinical exome sequencing has been performed using Illumina TruSight One Kit.

Clinical exome analysis revealed pathogenic variants in 8 out of 32 analysed patients (25%). Pathogenic variants were found in genes: CAMTA1 (transcription factor), DEAF1 (transcription factor expressed in the brain), BCORL1 (transcriptional corepressor), EP300 (chromatin remodeling transcription factor), DICER1 (posttranscriptional microRNAs modulator), MED13 (regulation of DNA-binding transcription and RNA polymerase II factor activation), CHD7 (chromo domain helicase DNA-binding protein 7) and in *SGSH* gene (N-sulfoglucosamine sulfohydrolase). Benign variants and variants of unknown significance were present in 9 out of 32 patients (28.1%). Secondary findings, unrelated to primary indication were noted in 5 out of 32 patients (15.6%). The remaining patients had normal clinical exome testing results (31.3%).

Clinical exome sequencing disclosed genetic background in 25% of ASD patients, identifying pathogenic gene variants that are involved in fundamental cell processes, protein expression and enzyme activity in the brain. Despite the high diagnostic yield, the etiology of ASD remains still unknown in the majority of patients. Additional investigations, including whole-exome sequencing, epigenetic testing and environmental risk factor analysis are necessary to better define a complex genetic architecture and environmental risks in ASD.

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