EP09.014 Clinical exome sequencing for diagnosis of patients with intellectual disability, autism and psychomotor delay

Helena Paszeková[1], Kristýna Hanuláková[1], Tomáš Píš[1], Věra Hořínová[2,3], Zděnka Vlčková[1], Renáta Michalovská[1]

[1] GHC Genetics s.r.o., V Holešovičkách 1156/29, Prague 182 00, Czech republic

[2] Nemocnice Jihlava, Vrchlického 4630/59, Jihlava 586 01, Czech republic, [3] Reprofit International s.r.o. Hlinky 48/122, 603 00 Brno

GHC GENETICS

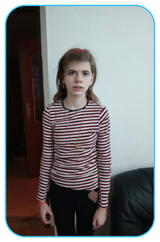
Objectives: Intellectual disability (ID) and autism spectrum disorder (ASD) share common clinical features and that can lead to confusion in the diagnosis. Intellectual disability occurs in approximately 2% to 3% of the general population. Mild intellectual disability affects seventy-five to ninety per cent of those affected. Between 30% and 50% of cases are non-syndromic or idiopathic. About a quarter of cases are caused by a genetic disorder, and about 5% of cases are inherited. The aim of this study was to use clinical exome sequencing to identify the underlying genetic cause of rare and severe cases of ID, ASD and psychomotor delay.
Method: SOPHiA Clinical Exome Solution v3 (SOPHiA GENETICSTM), NextSeq500/550 sequencer (Illumina, Inc)

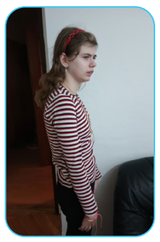
Case 1
Medical history: A 14-year-old girl from the second pregnancy, uncomplicated delivery and normal development up to the age of 2.5 years began to show developmental regression and presumed ASD. Small, pronounced thoracic kyphosis, low-set ears, synophrys, indicated clinodactyly, cafe-au-lait spots on neck and chest. Suspected atypical Rett syndrome with ASD. She can answer simple questions, but is not oriented in time and place. She has impaired language development – repeats phrases from fairy tales, can tell when she is hungry, but does not speak in continuous sentences. Normal female karyotype, negative array CGH.

Results: A suspected intragenic rearrangement was found in the patient - a deletion probably affecting exons 10-15 in the PHIP gene. The variant was found using CNV analysis. Not reported in ClinVar. Mutations in the PHIP gene are associated with the autosomal dominant Chung-Jansen syndrome. The variant was not found in the patient's mother, and according to the literature, most mutations in the *PHIP* gene arise *de novo*.

Chung-Jansen syndrome (CHUJANS) is characterized by global developmental delay, intellectual disability or learning disabilities, behavioral abnormalities (autistic features, ADHD, anxiety, aggression, impulsive behaviour, mood swings), dysmorphic features (high forehead, synophrys, long philtrum, thin lips) and obesity. The severity of the phenotype and other features are variable e.g. hypotonia, fatigability, narrow lips, lower set ears, clinodactyly, strabismus, joint hypermobility, cafe-au-lait spots, hypermetropia and nystagmus.

Gene	Variant	Phenotype	Phenotype MIM number	Inheritance
PHIP NM_017934	CNV *de novo* exon 10-15 deletion NC_000006.11(NM_017934.7):g.(?_79015012)_(79019304_?)del	Chung-Jansen syndrome	617991	AD





Case 2
edical history: A 8-year-old girl from the first pregnancy, uncomplicated delivery and normal development. Psychomotor development age-appropriate up to 2 years, then slowing down. Normal MR, hearing, brain imaging. Normal female karyotype, negative array CGH.

Clinical genetic examination:
2 y.o. eutrophic, developmentally equivalent to 1 y.o., does not walk, hypertelorism, slight strabismus, plagiocephaly
3.5 y.o. speaks monosyllabic words, bradycephaly, flattened head, low hairline, cafe-au-lat spot on the back, exanthema on the lips
6 y.o. 115cm/24kg, speaks but dyslalia, psychomotor development disability, especially fine motor skills, attention deficit disorder, synophrys, smaller mouth

Results: Heterozygous *de novo* deletion c.552_553delTA (p.Asp184GlufsTer14) of the *WAC* gene causing frameshift and premature termination. Not reported in ClinVar. Mutations in the *WAC* gene are associated with autosomal dominant DeSanto-Shinawi syndrome.

DeSanto-Shinawi syndrome (DESSH) is characterized by varying degrees of developmental delay and intellectual disability (especially speech delay), as well as reduced muscle tone (hypotonia), behavioral abnormalities (autistic features, ADHD, aggressive outbursts, anxiety), some facial differences (synophrys, broad forehead, lowered nasal bridge with bulbous nasal tip, deep-set eyes), gastrointestinal and ocular abnormalities.

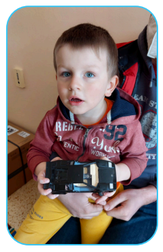
Gene	Variant	Phenotype	Phenotype MIM number	Inheritance
WAC NM_016628	*de novo* c.552_553delTA p.Asp184GlufsTer14	Desanto-Shinawi syndrome	615049	AD

Case 3
Medical history: A 5-year-old boy from the first pregnancy, without complications, normal adaptation. Excessive growth monitored, macrocephaly, 18 kg at 1 year. General developmental delay, autistic features were noted at the age of 3 years. Low hairline, slightly inverted nasal root, pronounced forehead and relative macrocephaly, overall large, eutrophic. He is non-verbal, prone to aggression, has limited comprehension. Normal male karyotype, negative array CGH, negative FRAXA.

Results: Hemizygous missense variant c.1136G>A (p.Arg379His, rs140032597) of the *UPF3B* gene, associated with Intellectual developmental disorder, X-linked syndromic 14. This disorder is inherited as an X recessive trait, which means that the mother is a healthy carrier of the variant. Reported as a variant of uncertain significance/likely benign in ClinVar

Intellectual developmental disorder, X-linked syndromic 14 is characterized by mental retardation (moderate to severe), autistic features, tall stature, high-arched palate, arched nasal root, macrocephaly, long fingers and toes, possible scoliosis, weak muscles.

Gene	Variant	Phenotype	Phenotype MIM number	Inheritance
UPF3B NM_080632	c.1136G>A p.Arg379His rs140032597	Intellectual developmental disorder, X-linked syndromic 14	300676	XLR



Case 4
Medical history: A 11-month-old girl from the second pregnancy, uncomplicated delivery and normal development. Ptosis of the left eyelid since birth, smaller (5,640g/64cm at 8.5 months), bilateral epicanthus, hypertelorism, synophrys, prominent nose, dysplastic protruding ears, high-arched palate. Mother has similar phenotype – small, deformed finger joints, exophtalmus, mild strabismus, low-set protruding ears, crowded teeth, arthritis, especially in the hand bones. Normal female karyotype, negative array CGH.

Results: Heterozygous missense variant c.330-69C>A (rs372031770) in the intronic region of the *SETD5* gene found in the proband and her mother, associated with Intellectual developmental disorder, autosomal dominant 23. Not reported in ClinVar.

Intellectual developmental disorder, autosomal dominant 23 has some phenotypic features that are present in the proband or her mother, such as synophrys, prominent nose, strabismus, crowded teeth. Ptosis may be a part of the highly variable dysmorphic features. The mental defect can range from mild to severe, frequently manifesting with delayed speech and ASD.

Gene	Variant	Phenotype	Phenotype MIM number	Inheritance
SETD5 NM_001080517	c.330-69C>A rs372031770	Intellectual developmental disorder, autosomal dominant 23	615761	AD

Case 5
Medical history: A 1.5-year-old girl from the fourth pregnancy (3 brothers) with valvular stenosis, failure to thrive, psychomotor developmental delay and dysmorphic features (epicanthus, hypertelorism, wide mouth, prominent teeth, low set ears). She understands, speaks in two syllables. Short stature, doesn't eat much. She has curly hair, low hairline, coarse facial features, rough voice. Normal female karyotype, negative array CGH.

Results: Heterozygous missense *de novo* variant c.1415C>T (p.Thr472Met, rs121918457) of the *PTPN11* gene causing autosomal dominant LEOPARD syndrome 1 and Noonan syndrome 1. Reported as a pathogenic variant in ClinVar.

LEOPARD syndrome 1 is characterized by short stature and growth retardation, facial dysmorphism (prognathism, triangular face, biparietal bossing, prominent and low-set ears, hypertelorism, epicanthus, strabismus, broad flat nose, cleft palate), abnormalities of the heart (often pulmonic stenosis), mild mental retardation, sensorineural hearing loss, genital abnormalities. Lengitines or cafe-au-lait spots can develop with age, but may be absent.

Noonan syndrome 1 is characterized by short stature, failure to thrive in infancy, micrognathia, low-set ears, hypertelorism, epicanthus, congenital heart defects, dental malocclusion, genital abnormalities, low posterior hairline, articulation difficulties, mental retardation (25%).

Gene	Variant	Phenotype	Phenotype MIM number	Inheritance
PTPN11 *NM_001330437*	*de novo* c.1415C>T p.Thr472Met Rs121918457	LEOPARD syndrome 1 Leukemia, juvenile myelomonocytic, somatic Metachondromatosis Noonan syndrome 1	151100 607785 156250 163950	AD AD AD

CONCLUSION

In these cases of our patients with undetermined diagnosis and common feature of ID, ASD or psychomotor delay, we could demonstrate the variability of different rare syndromes affecting intellect. The variants detected by clinical exome sequencing can be of different types of sequence alteration, inheritance and expressivity, ranging from CNVs, small deletions, missense mutations, frameshifts, *de novo*, previously undescribed or already described. Analysing the clinical exome for these patients can therefore be challenging and accurate interpretation of the suspected causal variant is required.

The authors declare that they have no conflict of interest. All presented data comply with informed consent, applicable regulations and GDPR.

Help line
+420 800 390 390

Write us
info@ghcgenetics.cz

Ambulance
V Holešovičkách 1156/29, Praha 8