CASE REPORT

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Deciphering congenital heart defects, facial dysmorphism and intellectual developmental disorder (CHDFIDD) associated with constitutional CDK13 pathogenic variants – case report and literature review

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Abstract

There are 21 human cyclin-dependent kinases which are involved in regulation of the cell cycle, transcription, RNA splicing, apoptosis and neurogenesis. Five of them: CDK4, CDK5, CDK6, CDK10 and CDK13 are associated with human phenotypes. To date, only 62 patients have been presented with mutated CDK13 gene. Those patients had developmental delay, dysmorphic facial features, feeding difficulties, different structural heart and brain defects. 36 of them had missense mutation affecting the protein kinase domain of CDK13. Our patient is the first person reported so far with a frameshift mutation which introduce premature stop codon in the first exon of the CDK13 gene. She has symptoms characteristic for congenital heart defects, facial dysmorphism and intellectual developmental disorder (CHDFIDD).

Key words

congenital heart defects, case report, cyclin-dependent kinase 13, facial dysmorphism and intellectual developmental disorder, CDK13 gene

INTRODUCTION

Cyclin-dependent kinases in humans are involved in the regulation of the cell cycle, transcription, RNA splicing, apoptosis and neurogenesis [1]. There are 21 human cyclin-dependent kinases and 29 cyclins. To date, constitutional mutations in five cyclin-dependent kinases (CDK4, CDK5, CDK6, CDK10 and CDK13) have been associated with human phenotypes [2]. The *CDK13* gene is also called CDC2L, CDC2L5, CHED, and is located on the short arm of chromosome 7 (7p14.1). *CDK13* is one of serine threonine kinases and is ubiquitously expressed with highest expression in the cerebellum, tibial nerve, endocervix, uterus, fallopian tubes and ovaries [2]. In the cell, it is involved in the regulation of: growth, response to external stimuli, cell size and lipid localization [3]. *CDK13* also plays an important role in neuronal development by axonal elongation [4].

In 2016, the first evidence linking CDK13 to human disease was reported by A. Sifrim et al. [5] who sequenced exomes of 610 probands with syndromic and non-syndromic congenital heart defects. Seven patients with different *de novo* missence *CDK13* mutations had heart defects, delay in developmental milestones, and dysmorphic features; six of them also had motor delay, intellectual disability and clinodactyly. Since the first report, 62 patients with similar pathogenic variants in *CDK13* [5, 6] have been presented in literature and the syndrome was named: Congenital heart defects, facial dysmorphism and intellectual developmental disorder (CHDFIDD) [5].

The case is presented of a patient with CHDFIDD and *de novo* heterozygous pathogenic variant p.Ala162GlyfsTer108 in one allele of *CDK13* gene. At present, this is the only patient reported with a frameshift mutation which introduces premature stop codon in the first exon of the *CDK13* gene.

CASE REPORT

The patient was a girl, born together with her healthy twin sister at 32 weeks of gestation by caesarian section, as the second child of healthy, non-consanguineous parents. The patient's birth weight was 1825g, length- 43 cm, OFC-29 cm. Soon after birth, she was intubated and resuscitated. In the fifth day of life, she was transferred to the intensive care unit because of clinical deterioration and ascites. Laparotomy was performed due to necrosis of intestinal loops, and during surgery she was diagnosed with an underdeveloped ascending colon – microcolon. She was fed by parenteral feeding until the age of five years. Cranial ultrasound after birth did not

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show any abnormalities. Echocardiography from that period revealed: patent ductus arteriosus (PDA), patent foramen ovale (PFO), I/II° tricuspid regurgitation.

At the age of nine, the girl was admitted to the Genetic Clinic at the Medical University in Lublin, Poland. Among her main health problems were short stature, dysmorphic features,and intellectual disability. During medical interview, her mother said that the psychomotor development of the patient was delayed: she started sitting without support at the age of 12 months, she was standing at 17 months and started walking at 18 months. She started speaking first words at the age of 18 months. Since the age of one, she has been under the care of a psychologist and a logopedist. First evaluation by psychologist at the age of five revealed that the patient had mild intellectual disability. At the age of nine she attended the third grade of primary school and had an individual learning programme. Her mother said that she was a very calm child and had memory problems during lessons at school.

A chromosome analysis revealed normal female karyotype: 46, XX. Array-CGH testing also did not show any abnormality; patient's result – arr (1–22,X)x2. The patient was finally diagnosed by Whole Exome Sequencing. Peripheral blood samples were collected from the patient and from her parents which revealed a *de novo* heterozygous potentially pathogenic variant p.Ala162GlyfsTer108 in one allele of the *CDK13* gene. This is a frame-shift mutation which introduces premature stop codon in the first exon of the *CDK13* gene. The presence of variant detected by next generation sequencing was confirmed by Sanger sequencing.

During the last visit in the Genetic Clinic at the age of 15 years and six months, the patient was 145 cm tall (below the 3rd percentile) and weighed 45 kg. She attended the eighth grade of a special school. She was undergoing growth hormone treatment because of *somatotropic pituitary insufficiency, although t*he MRI of the pituitary gland did not show any abnormalities. The patient remained in constant contact with a nephrologist because of hyperoxaluria. An abdominal ultrasound showed bilateral, duplex of the pelvicalyceal collecting systems, and in the left kidney a 12 mm deposit in the lower cup. The patient remained on a low-sodium and low-calcium diet. She visited a neurologist who performed an EEG which showed a non-paroxysmal series of slow waves 5–7 Hz without sharp elements in left frontal pre-temporal area.

After psychological examination, she was diagnosed with a mild intellectual disability: problems with memorizing, illegible handwriting, problems with manual activities, and tripped while walking. The patient also remained in constant contact with a Nutrition Clinic because of short bowel syndrome. Figures 1 and 2 present the patient at the ages of nine and 15.

DISCUSSION AND CONCLUSIONS

Cyclin-dependent kinase 13 (CDK13), also called cell division cycle 2-like protein kinase 5 (CDC2L5) or cholinesterase-related cell division controller (CHED) [7],

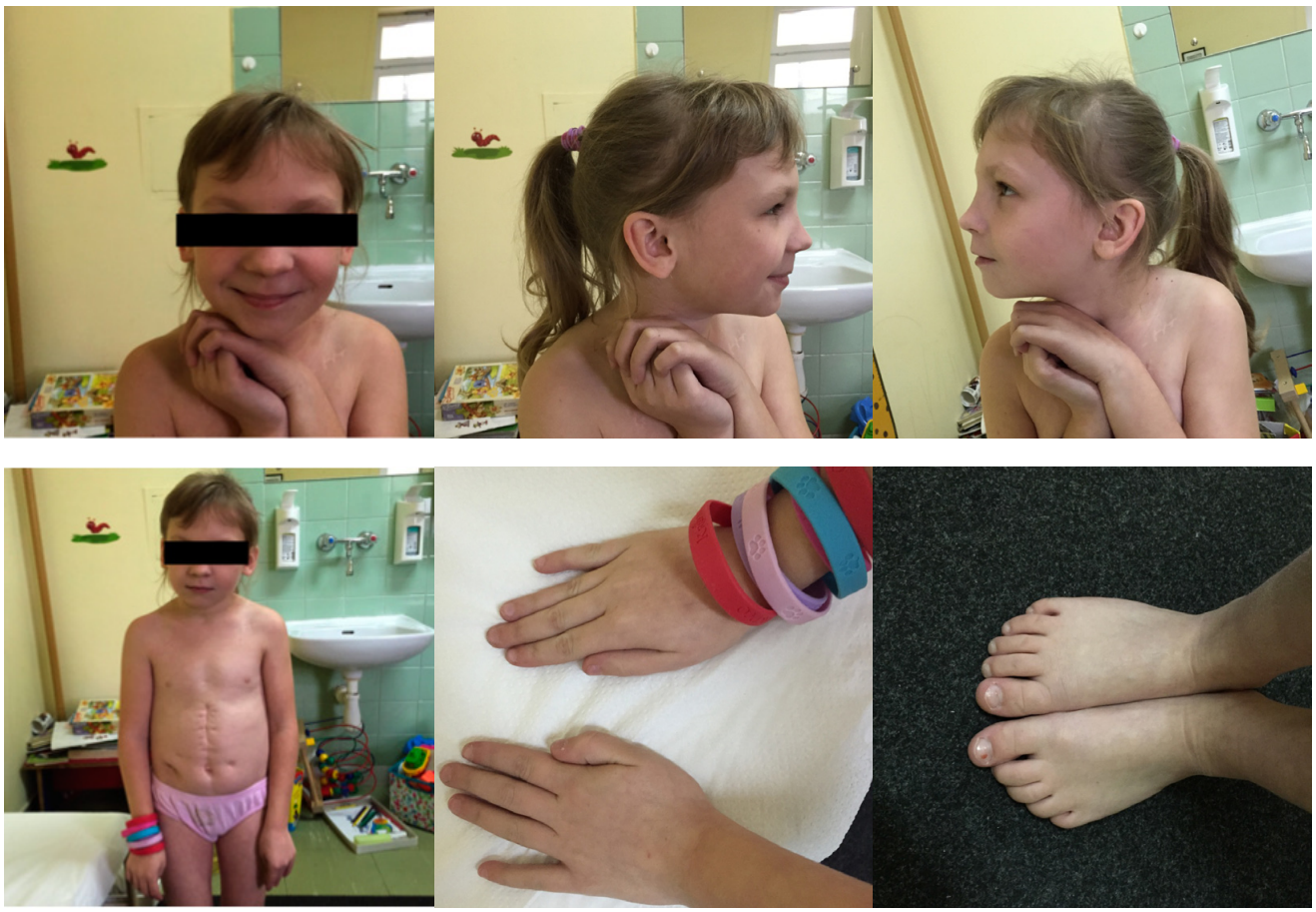

Figure 1. The patient at the age of 9. Note the broad nasal bridge with full tip, small mouth, and abdominal scars after laparotomy due to necrosis of intestinal loops on the fifth day of life

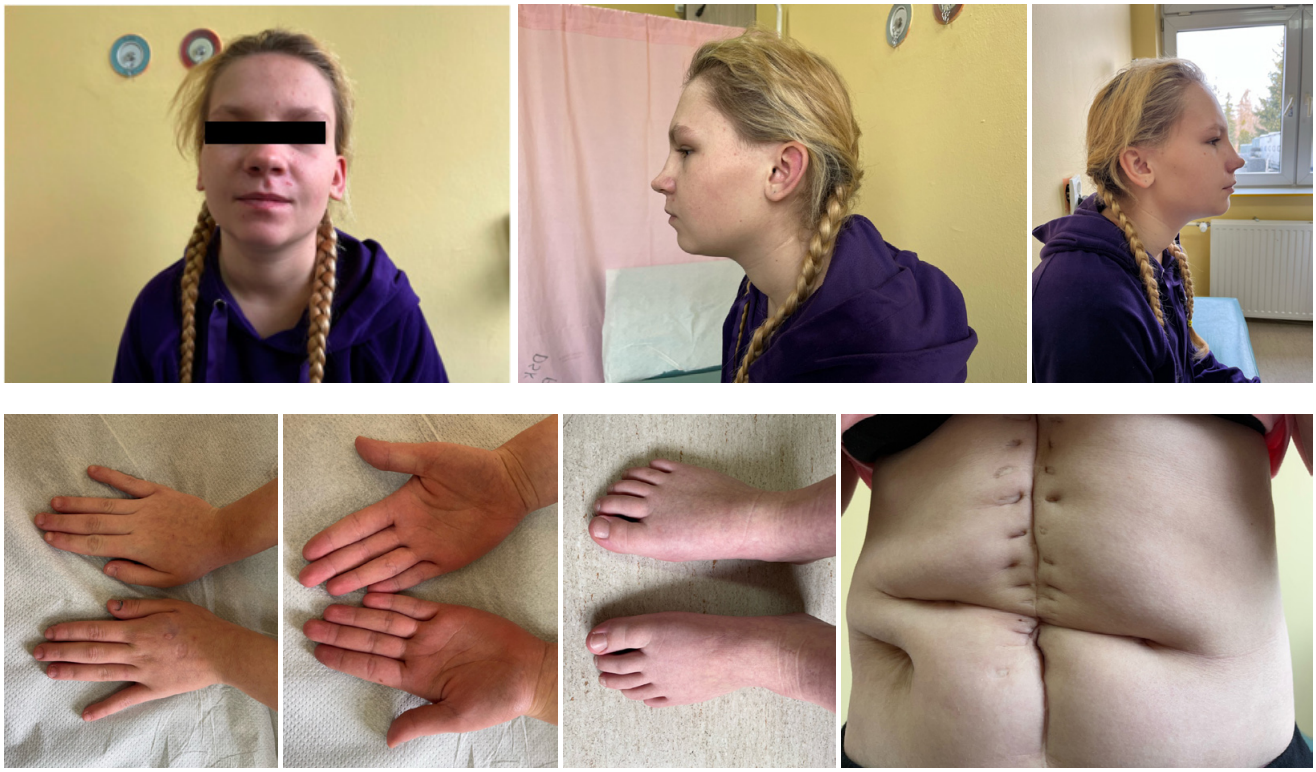

Figure 2. The patient at the age of 15. Note the broad nasal bridge with full tip, hypertelorism and scars after laparotomy

regulates transcription by phosphorylating serine residues in the largest subunit of RNA polymerase II (RNAPII) [3]. Greifenberg et al. [3] showed that cells depleted of *CDK13* diminished the expression of 250 genes mostly involved in transmembrane receptor protein kinase signalling, enzyme-linked receptor protein signaling pathway, regulation of cell growth, lipid localization, regulation of response to external stimuli, regulation of cell size, and cell projection organizations. The same cells depleted of *CDK13* increased the expression of 242 genes mostly involved in inorganic anion transport, cellular amino acid, serotonin and biogenic amine biosynthesis, chloride transport, and central nervous system neuronal development. The role of the CDK13 in the cells is so important, in that mutations in the gene are the cause of characteristic phenotype. To date, 62 patients have been presented in literature with mutations in the *CDK13* gene [5, 6], 36 of whom had missense mutation affecting the protein kinase domain of *CDK13,* and 18 had a pathogenic variant affecting amino acid residue 842 (p.Asn842Ser) [2]. Eighteen patients presented by Rouxel et al. [6] had missense variants in *CDK13,* classified as pathogenic, or likely pathogenic, according to the American College of Medical Genetics and Genomics.

The authors also performed Genome-wide DNA methylation analysis. Among the most common symptoms noticed in those patients were: low stature, dysmorphic facial features (wide nasal root, epicanthal folds, upslanting palpebral fissures, curly hair), developmental delay, attention deficit hyperactivity disorder and autism spectrum disorder, sensorineural hearing loss, epilepsy, congenital heart malformations, strabismus, gastroesophageal reflux disease, haemangiomas of different localizations, recurrent otitis media. Yakubov et al. [8] presented a patient with p.Asn842Ser mutation in *CDK13* and abnormal facial features, psychomotor developmental delay and pseudohypoaldosteronism.

Table 1. Comparison of the features of the case report patient, and the characteristic features of patients with CHDFIDD, presented by Hamilton et al. [9]

Characteristic features of patients with CHDFIDD mentioned by Hamilton et al. [9]	Patient's features
Developmental delay	+
Intellectual disability	+
Feeding difficulties	+
Seizures	-
Structural cardiac abnormalities	-
Structural brain abnormalities	-
Joint hypermobility	+
Clinodactyly	-
Craniofacial dysmorphism:	
– short, upslanting palpebral fissures	-
– hypertelorism	+
– telecanthus	
– epicanthal folds	-
– wide nasal bridge	+
– narrow mouth	+
– small mouth	-
– thin upper lip vermilion	-
– low-set posteriorly rotated ears	-
Other	– underdeveloped ascending colon – microcolon – *somatotropic pituitary insufficiency* – bilateral, duplex of pelvicalyceal collecting systems – hyperoxaluria

Exploration of the genotype-phenotype by Hamilton and Suri [2] suggested that missense mutations affecting amino acid residue in position 842 were associated with structural malformations, while patients with haploinsufficiency of *CDK13* had milder phenotypes.

The patient in the presented case report had a frameshift mutation – p.Ala162GlyfsTer108 in one allele of the *CDK13* gene, had common characteristic features such as developmental delay, feeding difficulties, dysmorphic facial features, intellectual disability, as well as symptoms not mentioned inthe literature. The phenotype of the patients presented in literature is heterogenous. Hamilton et al. [9] listed a whole raft of health problems and pathological features of patients with mutated *CDK13,* among them, motor and speech delay, intellectual disability, feeding difficulties, different structural heart defects (ASD, VSD, abnormality of pulmonary valve or arteries, tetralogy of Fallot, Ebstein's anomaly, bicuspid aortic valve with aortic stenosis, and LV non-compaction), different structural brain defects (hypoplastic or absent corpus callosum, periventricular leukomalacia or gliosis, Chiari malformation), as well as various dysmorphic facial features (hypertelorism, blepharophimosis, flat midface, broad nasal bridge with full tip and alar flare, small mouth with thin upper vermillion, low set or posteriorly rotated ears). Table 1 shows a comparison of the features of the present patient and the characteristic features of the patients with CHDFIDD presented by Hamilton et al. [9].

The patient in the presented case report did not have any significant heart or brain abnormality. She had feeding difficulties due to underdeveloped ascending colon, and additionally had symptoms not described in patients presented in literature to date: *somatotropic pituitary insufficiency,* bilateral, duplex of pelvicalyceal collecting systems, and hyperoxaluria. Uehara et al. [10] presented three patients with constitutional mutations inthe *CDK13* gene without congenital heart defects. All patients had intellectual disability and distinctive facial features with up-slanting palpebral fissures, hypertelorism, short and broad columella with a wide nasal bridge. Bostwick et al. [11] reported 16 patients with mutation in the *CDK13* gene, all of whom had developmental delay and dysmorphic features; key findings: hypertelorism, telecanthus, epicanthal folds, small mouth, thin upper lip, wide nasal bridge with a full tip. The patient in the case report also similar dysmorphic facial features. Moreover, six out of 16 patients reported by Bostwick et al. [11] had a diagnosis of autism spectrum disorder, four had variable character of seizures, 15 had feeding difficulties and five had significant constipation. Auditory problems were frequent. In five out of 11 patients who underwent MRI, a structural brain abnormality was identified, most frequently thin or hypoplastic corpus callosum. Structural heart defects were reported in nine patients, mostly atrial septal defect. The patient in the presented case report did not have any structural heart or brain abnormality. Uehara et al. [10] reported that two out of three patients had wide-spaced and peg-shaped teeth, abnormalities that did not occur in the case report patient.

CONCLUSIONS

Further research is needed to explain why patients with pathogenic variants in *CDK13* exhibit such heterogenous symptoms. There is also a need to study the influence of environmental factors on the development of unfavorable mutations. The authors therefore propose preliminary recommendations for this group: a workup for patients suspected of having the mutated *CDK13* gene should include a diligent physical examination, MRI of the brain, echocardiography, and consultations with a neurologist, cardiologist, dietitian, and geneticist.

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