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RESEARCH

Expansion of phenotypic and genotypic data in autism spectrum disorders due to variants in the *CHD8* gene

Mariia A. Parfenenko[1] · Ilya S. Dantsev[1] · Sergei V. Bochenkov[1] · Rabiat G. Kuramagomedova[1] · Natalia V. Vinogradova[1] · Mariia P. Afanaseva[1] · Olga S. Groznova[1] · Victoria Iu. Voinova[1]

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Abstract
Autism spectrum disorders are a group of the most common disorders of neuropsychiatric development, characterized by difficulties in social interaction and adherence to stereotypic behavioral patterns. This group of conditions frequently co-occurs with intellectual disability, epilepsy, attention-deficit hyperactivity disorder, connective tissue disorders and others. Among the most common molecular-genetic causes of autism spectrum disorders are pathogenic variants in the *CHD8* gene. *CHD8* codes for chromodomain-helicase-DNA-binding protein 8 - a chromatin remodeler that regulates cellular proliferation and brain development in embryogenesis. 6 children and 1 adult (mother of 1 of the children) and were found to have clinically significant variants in *CHD8* on whole genome sequencing (3 children and 1 adult had likely pathogenic variants, 3 children– variants of unknown significance). Their phenotype consisted of autism spectrum disorders, developmental delay, ataxia, overgrowth and other signs typically observed in patients with pathogenic variants in *CHD8*, as well as common comorbidities of autism spectrum disorders, such as attention-deficit hyperactivity disorder and connective tissue disorders. Additionally, 4 patients had hepatomegaly and 2– hyperbilirubinemia (1 had both) - clinical features have not been previously associated with pathogenic variants in *CHD8*. 2 patients also presented with cardiovascular abnormalities, primarily arrythmias and, in 1 case, cardiomyopathy– also uncharacteristic of patients with pathogenic variants in *CHD8*. Further research is required to determine the mechanisms underlying the abovementioned clinical features, which are likely carried out through complex interactions between CHD8 and other regulatory proteins.

Keywords Autism spectrum disorders · Autism comorbidities · Chromodomain-helicase-DNA-binding protein 8 · Whole genome sequencing · Gastrointestinal tract disorders

Introduction

Autism spectrum disorders (ASDs) are a heterogeneous group of neurodevelopmental disorders characterized by adherence to rigid and stereotypic behaviors and cognitive patterns, as well as difficulties in social interaction. The rates of ASDs diagnoses in children are increasing every decade, with 1/100 children being diagnosed worldwide [1]. ASDs frequently co-occur with other neuropsychiatric disorders, such as intellectual disability, epilepsy, attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, bipolar disorders and others, as well as somatic conditions, such gastrointestinal tract disorders, allergies, connective tissue disorders and others [2–5]. Clinical diagnosis of ASDs is achieved with the help of diagnostic tests, as well as clinical evaluation/interview, with early clinical diagnosis and subsequent early intervention being associated with a better prognosis [6–8]. Meanwhile, genetic testing may be used to determine the molecular cause of an ASD. For example, clinically significant variants are found in approximately 22% of patients with an ASD undergoing whole exome sequencing, and up to 68% of patients undergoing trio-whole genome sequencing with subsequent reanalysis [9, 10].

✉ Mariia A. Parfenenko
masha.parfenenko@student.msu.ru

[1] Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation, Moscow, Russia

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ASDs were first described in 1925 by the soviet pediatric psychiatrist G.E. Sukhareva, in several children with impaired social skills and high intelligence [11].

The *CHD8* gene (OMIM: 610528) codes for the chromodomain-helicase-DNA-binding protein 8, a chromatin remodeler that belongs to the CHD (chromodomain helicase DNA binding) subfamily of ATP-dependent chromatin-remodeling factors. CHD8 has two isoforms– $CHD8_L$– which contains two chromodomains - a helicase/ATPase domain and a DNA binding domain, and $CHD8_S$– which contains only the amino-terminal chromodomain. Both isoforms are expressed throughout nearly all tissues, with varying $CHD8_L$/$CHD8_S$ ratios. CHD8 is known to directly interact with β-catenin, and, through negative regulation of the Wnt-β-catenin signaling pathway, affect neurogenesis–neuron proliferation, myelinization and synaptogenesis [12]. CHD8 also acts as a signaling molecule, participating in transcriptional regulation and epigenetic remodelling.

Mice with *CHD8* haploinsufficiency were observed to have a widened node of Ranvier, decreased expression of myelin-related genes, thinner myelin sheaths of axons in the corpus callosum, and increased overall brain size compared to wild-type mice, with the mice themselves presenting with motor delay, pronounced hypoactivity, and anomalous responses to social stimuli [13, 14]. Meanwhile, biallelic dysfunction of *CHD8* in mice leads to embryonic death, due to the fact that CHD8, specifically $CHD8_S$, is known to inhibit apoptosis via recruiting histone H1 to the promoters of p53 target genes, so the absence of the $CHD8_S$ isoforms leads to unwanted apoptosis during early embryogenesis [15].

CHD8 is among the most frequently involved genes when it comes to ASDs in humans [16]. Despite that fact, there is still limited research regarding the clinical presentation of ASDs associated with pathogenic variants in *CHD8*. In addition to ASD/autistic traits, patients with variants in *CHD8* also present with prenatal onset macrocephaly, facial dysmorphisms such as hypertelorism, supraorbital ridge and downslanting palpebral fissures, overgrowth, intellectual disability, seizures and sleep disorders [17]. The accumulation and systemic analysis of clinical data from patients with clinically significant variants in *CHD8* would further expand the known phenotype of this form of ASD and aid in formulating the prognosis for individual patients. Additionally, accumulation of data regarding genetic variants in *CHD8* would facilitate the interpretation of newly found variants in that gene and assist in elucidating its function in neurogenesis, as well as its role in the development of ASDs. The aim of the present study was to describe several patients with clinically significant variants in *CHD8* and varying phenotypic features, meanwhile observing and analyzing the potential underlying mechanisms of several new, previously unreported clinical features.

Patients and methods

Our cohort consists of 6 children and 1 adult (mother of one of the children) with variants in *CHD8*. All patients originally applied to Charity Fund for medical and social genetic aid projects «Life Genome» to receive whole genome sequencing (WGS) and has a primary clinical diagnosis of an ASD/neurodevelopmental disorder with autistic features. Their phenotypes were assessed by clinicians based on physical examinations, as well as findings from laboratory and instrumental methods. The clinical data was primarily analyzed retrospectively.

WGS (PE150), which was used to discover the variants in *CHD8*, was carried out using high-throughput sequencing platforms DNBSEQ-T7 (MGI) and DNBSEQ-G400 (MGI) (MGI, China) using PCR-free protocol and 30x reading depth. Preparation of DNA libraries was carried out using a PCR-free protocol and enzymatic fragmentation. A standard pipeline was used for the bioinformatic analysis. The variants were assessed according to the pathogenicity criteria of the American College of Medical Genetics [18]. All patients (or their parents/legal guardians) gave informed consent to the molecular genetic testing and clinical evaluation.

Results

3 children had variants classified as variants of unknown significance (VUS) and 3 children and 1 adult had likely pathogenic variants (Table 1).

The children, 2 girls and 4 boys, were aged 2 to 13 years old (mean age = 8.3). Their phenotypes, specifically the presence/absence of clinical features typically observed in patients with pathogenic variants in *CHD8*, as well as common comorbidities of ASDs, are described in Table 2. All patients (except for P3 and his mother (MoP3)) had no family history of neurodevelopmental disorders.

Apart from the clinical features described in literature in patients with variants in *CHD8* and common comorbidities of ASDs, some of the patients from our cohort also presented with clinical features that were worth noting. The following features were observed in patients with likely pathogenic variants in *CHD8*, as well as VUS.

4 patients (P1, P2, P3 and P5) were found to have hepatomegaly and 2 (P2 and P4)– to have hyperbilirubinemia. The patients that had hyperbilirubinemia didn't have any clinically significant variants in the *UGT1A1* gene (OMIM: 191740) that is associated with familial hyperbilirubinemia

Table 1 Variants in *CHD8* found in 6 children and 1 adult. The patients were assigned a number, with the "P" in front of it standing for "patient" and "MoP" - "mother of patient"

Patient	Variant	Pathogenicity	Previously reported in literature	Frequency in gnomAD database (%)	Presence in unaffected relatives
P1	ENST0000064664 7 0.2: c.4105 4109del ENSP00000495240.1: p.Asp1369ProfsTer12	Likely pathogenic variant	Not reported	0	No data
P2	ENSP00000495240.2:c.6349G > T ENST00000646647. 1:p.Glu2117Ter	Likely pathogenic variant	Not reported	0	Parents refused testing
P3	ENST0000064664 7 0.2: c.7112dup ENSP00000495240. l: p.Asn2371LvsfsTer2	Likely pathogenic variant	Previously reported	0	Not present
MoP3	ENST0000064664 7 0.2: c.7112dup ENSP00000495240. l: p.Asn2371LvsfsTer2	Likely pathogenic variant	Previously reported	0	Not present
P4	ENST00000646647 0.2: c.1716 + 4908A>C	Variant of unknown clinical significance	Not reported	0	No data
P5	ENST0000064664 7 0.2: c.6437A>C ENSP00000495240. l: p.Gln2146Pro	Variant of unknown clinical significance	Not reported	0	No data
P6	chr14:21394141 C > T c.5654G > A p.Arg1885Gln	Variant of unknown clinical significance	Not reported	0.00001216	Parents refused testing

Table 2 Phenotype of 6 children and 1 adult with variants in *CHD8*. The highlighted clinical features were chosen from clinical descriptions of patients with variants in *CHD8* in literature, with the addition of common comorbidities of ASDs. The features for each patient are marked with present "+", absent "-" or "ND"– no data. (*the patient had an IQ score of 81, which is considered "low average" according to the current Wechsler classification; **primarily presented as valve abnormalities.)

Clinical feature/ Patient	P1	P2	P3	MoP3	P4	P5	P6
Age	12	3	12	38	9	13	2
Sex	Male	Male	Male	Female	Female	Male	Female
Variant pathogenicity	Likely pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic	Variant of unknown clinical significance	Variant of unknown clinical significance	Variant of unknown clinical significance
ASD/ autistic traits	+	+	+	+	+	+	+
Intellectual disability	-*	-	-	-	-	+	+
Developmental delay	+	+	+	-	+	+	+
Seizures	+	-	+	-	-	+	-
Sleep disorders	-	+	+	+	+	-	-
Hypotonia	+	-	+	+	+	+	-
Ataxia	+	+	+	+	+	+	+
Structural brain abnormalities visible on the MRI	-	-	+	+	-	-	-
Regression of skills	-	+	-	-	+	+	+
Disorders of the gastro-intestinal tract	-	-	+	+	+	-	+
Constipation	-	-	+	-	+	-	-
Macrocephaly	+	+	+	+	+	-	-
Overgrowth	+	+	+	+	+	+	-
Joint hypermobility as well as other signs of a connective tissue disorder	+	+**	+	-	+	+	+
Allergy	+	-	+	+	+	-	-
Attention-deficit hyperactivity disorder	+	+	-	+	+	+	-
Depression	-	ND	+	+	+	-	-
Anxiety	-	ND	+	+	+	+	+
Obsessive-compulsive disorder	-	ND	+	-	ND	ND	ND

and Gilbert syndrome. Both of those features, as far as we know, have not been previously reported in patients with pathogenic variants in *CHD8*.

2 patients presented with cardiovascular disorders that were uncharacteristic of patients with pathogenic variants in *CHD8* and were worth expanding upon.

P2– presented with a combination of structural and functional cardiac abnormalities. An ECG in lying position showed a sinus bradyarrhythmia, with a heart rate of 94 – 69 bpm., deviation of the cardiac electrical axis to the right (angle alpha 110 degrees). PR 130 ms (N 100–120 ms), QRS 80 ms (N 55–80 ms), QTc 343–387 ms (N 370–430 ms) (QT was corrected using the Bazett formula), an incomplete right bundle branch block. The following signs of a repolarization disorder were observed: a flattened T wave in the III derivation and a negative T wave in the V1-V2 derivations. An ECG in standing position showed a sinus arrhythmia with heart rate 103 – 86 bpm, deviation of the cardiac electrical axis to the right (angle alpha 119 degrees). PQ 130 ms, QRS 80 ms, QTc 359–394 ms, and an incomplete right bundle branch block. The following signs of a repolarization disorder were observed: a flattened T wave in the III and aVF derivations and a negative T wave in the V1-V2 derivations. An echocardiogram showed dysfunction of chords of the mitral valve with minimal regurgitation. Prolapse and structural anomalies of the tricuspid valve with tricuspid regurgitation 1-1.5. Dilatation of the pulmonary artery trunk (3.92/7.3Z) and its branches (left branch (2.5Z), right branch (4.6Z)). Pulmonary regurgitation 1-1.5 +, at least 2 flows, dilatation of the fibrous ring (2.45Z). Slight expansion of the right ventricle due to inflow, as well as dilatation of both atria. Other findings include left ventricle excessive trabecularity with the ratio of trabecular to compact zones at the level of the middle and apical lateral and lower segments is 1:2 – 1:3 with areas of compact layer thinning up to 2–3 mm, as well as local contractility impairment of the left ventricular myocardium (dyskinesia of the basal anterior septal segment). Diastolic dysfunction of the right ventricle, type I. Estimated pressure in the pulmonary artery PG = 30.7 mm Hg.

P3, at the time of the clinical evaluation, had mild sinus arrythmia and an incomplete right bundle branch block, as well as arterial hypertension. It should be noted that in infancy, he was diagnosed with Wolff-Parkinson-White syndrome and underwent radiofrequency ablation at the age of 2 years.

Discussion

Disorders of the cardiovascular system have not yet been directly linked to pathogenic variants in *CHD8* in humans. Myocardial hypertrophy has been reported in mice with *CHD8* haploinsufficiency. It is hypothesized that abnormal CHD8 may lead to cardiac abnormalities through its disordered interaction with the CHD7 protein [19]. Pathogenic variants in the *CHD7* gene (OMIM: 608892) are known to cause Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness, Extremity abnormalities (CHARGE) syndrome (OMIM: 214800)– a rare condition that is characterized by, among other clinical features, cardiac abnormalities, such as conotruncal defects, atrioventricular and atrial septal defects, tetralogy of Fallot and other heart defects [20]. Perhaps, disordered interaction between CHD8 and CHD7 in embryogenesis could have led to development of a CHARGE syndrome-like cardiophenotype in P2. It is interesting to note that patient P2 had no extracardial clinical features that could be associated with the typical clinical presentation of CHARGE syndrome, since he did not have pathogenic variants in *CHD7*, therefore the overall structure and function of CHD7, outside of its interaction with CHD8, remains unaltered.

Another potential explanation for the association of cardiovascular disorders and *CHD8* haploinsufficiency relies on the literature evidence that CHD8 functions as an A-Kinase Anchoring Protein (AKAP)– modulators of protein kinase A signaling. Several clones of *CHD8* cDNA derived from the human heart could potentially act as AKAP [21]. Abnormal AKAP complexes functioning is known to lead to such cardiac disorders as cardiac hypertrophy, contractility dysfunction and arrhythmias [22, 23]. It could be hypothesized that CHD8's abnormal functioning as an AKAP may be the underlying mechanism for heart rhythm abnormalities observed in patients P2 and P3.

The presence of cardiovascular disorders in 2 of the patients, as well as the difference between the abovementioned features could be, at least in part, explained by the fact that CHD8 is known to have several isoforms. The location of each patient's variant within the gene will have varying effects on each isoform structure and function, as well as their numerous interactions within related molecular pathways.

An issue related to variant assessment must be highlighted as well. Since 5 out of 6 variants discovered in the patients were previously unreported, literature data that could assist in a more accurate assessment of their pathogenicity was largely unavailable, which made some of the highest evidence weight pathogenicity criteria of the American College of Medical Genetics, such as PS1 (same amino acid change

as an established pathogenic variant) and PS4 (prevalence in affecteds statistically increased over controls)– unapplicable. Therefore, the variants currently classified as "likely pathogenic" and "VUS" may, with fairly high confidence, be reclassified more accurately as the genotypic data of patients with ASDs and clinically significant variants in *CHD8* is accumulated and analyzed and high throughput sequencing becomes more available to patients with ASDs and their families.

Conclusion

Among the 6 children and 1 adult with genetic variants in *CHD8*, 3 had variants of unknown clinical significance and 4– likely pathogenic variants. All of them had ASDs or autistic traits. Most or all of them presented with developmental delay, history of skill regression, ataxia, hypotonia, macrocephaly and overgrowth– clinical features that are well known to be associated with pathogenic variants in *CHD8*. Additionally, most presented with common comorbidities of ASDs, such as connective tissue disorders, ADHD and allergies.

4 patients had hepatomegaly and 2– hyperbilirubinemia (1 of the patients had both). Those clinical features have not been previously associated with pathogenic variants in *CHD8*. With additional clinical evidence, these signs could be considered an expansion of the known phenotype.

Overall, the traits that have been previously associated with CHD8 haploinsufficiency, the new abovementioned clinical features we've observed, as well as the common comorbidities of ASDs were roughly equally prevalent among patients with likely pathogenic variants and VUS. The only exception to this was macrocephaly, which was present in all patients with likely pathogenic variants, but only in 1 of the 3 patients with VUS.

2 patients presented with cardiovascular abnormalities, in particular Wolff-Parkinson-White syndrome, which required surgical treatment at the age of 2 years old (in 1 patient), and cardiomyopathy with local systolic myocardial dysfunction, myocardial remodeling and structural heart abnormalities (in 1 patient). Such clinical features are uncharacteristic of patients with pathogenic variants in *CHD8*, and, while there are several hypotheses regarding the underlying molecular mechanisms of those abnormalities, further research is required to determine the specific role of *CHD8* in cardiac development and function.

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Author contributions I.D., S.B., R.G., N.V., and M.A. worked with patients, collected and processed clinical data. M.P., O.G., and V.V. reviewed relevant literature, analyzed the clinical and genomic data and wrote the manuscript text. M.P. was selected as the corresponding author. All authors reviewed the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate All results described in the article have been obtained during standard diagnostic procedures provided to patients in our clinic.

Consent to participate All patients (patients' parents) gave written consent for use of their (their children's) clinical and genomic data for research and publication.

Competing interests The authors declare no competing interests.

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