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CDK13-Related Disorder: Novel Insights From A Series of 27 Cases and Recommendations for Clinical Management

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Received: 18 November 2024 | **Revised:** 15 January 2025 | **Accepted:** 31 January 2025

Funding: This work was supported by Italian Ministry of Health (PNRR-MR1-2022-12376811) and Ministry of Research (FOE_2020).

Keywords: *CDK13* | *CDK13*-related disorder | CHDFIDD | cyclin-dependent kinase | syndromic intellectual disability

ABSTRACT

In 2016, Sifrim and colleagues described the first group of patients carrying heterozygous pathogenic variants in *CDK13* and sharing major clinical features mainly consisting of congenital heart defects, intellectual disability and peculiar facial features (Congenital Heart Defects, Dysmorphic Facial Features, and Intellectual Developmental Disorder; CHDFIDD, OMIM # 617360). This condition is generally referred to as *CDK13*-related disorder, and since then other reports have provided further clinical and molecular information. Here we describe a group of 27 previously unreported patients to more accurately profile the clinical spectrum associated with *CDK13* variants, disclosing novel associated findings, such as complex craniosynostosis and variable skeletal features (e.g., cranio-cervical anomalies). We also focused on the ocular phenotype that appears to include bilateral congenital glaucoma, posterior embriotoxon, buphthalmos and Duane anomaly. Finally, we observed two cases of mother-to-daughter transmission. Our work clarifies some novel features of CHDFIDD, defines the differential diagnosis of this disorder, and provides recommendations for its clinical management.

1 | Introduction

The cyclin-dependent kinase (CDK) family is a group of serine/threonine protein kinases involved in different cellular processes, such as transcription, regulation of the cell cycle and differentiation [1]. Among the 21 members described to date, some have causally been linked to specific clinical conditions, mostly characterized by syndromic intellectual disability (ID) [2], malformations of the central nervous system [3], microcephaly [4, 5], and cancer [6].

CDK13 is a ubiquitously expressed gene encoding a protein with a still poorly characterized function. It is reported to form a complex with cyclin K and phosphorylate specific serine

For affiliations refer to page 154.

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residues at the C-terminus of RNA polymerase II, regulating transcription and growth signaling pathways [7, 8]. In 2016, Sifrim et al. [9] described seven individuals with syndromic cardiac malformations, who harbored de novo missense variants in *CDK13*. Since then, several pathogenic heterozygous variants in this gene have been reported, in association with a syndrome characterized by neurodevelopmental issues, cardiac malformations and other recurrent phenotypic features. Initially this condition was described with the acronym CHDFIDD (congenital heart defects, dysmorphic facial features, and intellectual developmental disorder; OMIM #617360), but currently it is generally referred to as *CDK13*-related disorder, due to a variable phenotypic spectrum that is still under definition. Among the main features, mild to moderate ID is almost universally present, involving both motor and speech abilities. Feeding difficulties in infancy are also common. Structural brain abnormalities are usually nonspecific and include aplasia/hypoplasia of the corpus callosum or asymmetric lateral ventricles. Of note, despite the original definition, cardiac malformations have been reported in less than half of the cases and are represented mostly by atrial or ventricular septal defects, while more severe anomalies, such as tetralogy of Fallot and Ebstein anomaly, have been described very rarely. The disorder is also characterized by a facial gestalt consisting of short and upslanted palpebral fissures, low-set and posteriorly rotated ears with minor morphological anomalies, large nasal root, and small mouth with thin upper lip vermillion. Hearing impairment and ocular anomalies are also common.

In this study we describe a cohort of 27 previously unreported individuals with heterozygous pathogenic/likely pathogenic variants in *CDK13*. We analyze their clinical features and compare them with a thorough review of the phenotype of previously reported patients. We report bilateral congenital glaucoma, premature closure of the cranial sutures and variable skeletal defects as novel features. We also document two cases of mother-to-son transmission, and a set of monozygotic twins sharing a mild presentation limited to neurodevelopmental issues. Our findings help in defining the wide clinical spectrum of the *CDK13*-related condition, outlining its differential diagnosis and providing suggestions to improve the clinical management of affected individuals.

2 | Materials and Methods

2.1 | Study Cohort

Individuals were enrolled through a multicenter international collaboration in the frame of ERN-ITHACA and GeneMatcher networking. Data were centralized (AUSL-IRCCS di Reggio Emilia) and retrospectively reviewed. Inclusion criteria were the presence of a pathogenic or likely pathogenic *CDK13* variant and availability of clinical information. Clinical data were collected through the referring physicians using a customized clinical table covering pregnancy and birth, developmental and cognitive milestones, physical examination, diagnostic imaging, metabolic assessment and genetic testing (Table S1). Written informed consent was obtained from each participant (or from parents or legal guardians). The study was approved by the AVEN Ethics Committee (protocol n.110184, 08/09/2023).

2.2 | Genetic Analysis

Information on genetic analyses was provided by the referring physicians, and consisted in the results of single gene, gene panel, or whole exome/genome sequencing (WES/WGS), or *CDK13* Sanger sequencing for segregation analyses. Further genetic tests, performed on a case-by-case basis, also included conventional karyotype, chromosomal microarray analysis, gene panel sequencing and additional hypothesis-driven testing (Table S1). *CDK13* variants were centrally reviewed, annotated (NM_003718.5, GRCh38), and classified according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) recommendations [10] and subsequent updates [11]. Databases gnomAD v4.1.0 and HGMD professional 2024.2 were also used in the assessment (accessed July 2024).

2.3 | Review of the Literature

A MEDLINE (PubMed) search was performed using the keyword 'CDK13', limited to articles available in English. The last search was carried out in March 2024. Relevant references in the acquired articles, which were not found in the MEDLINE search, were further investigated. We excluded all studies with insufficient information, possible biases or inconsistent conclusions. We retrieved 15 publications describing a total of 110 individuals with *CDK13*-related disorder, and extracted information about their clinical characteristics (Table S2). Individuals reported in the ClinVar or DECIPHER databases were not included because the clinical information was incomplete.

3 | Results

We report 27 novel individuals with a molecularly confirmed diagnosis of *CDK13*-related disorder, 10 females and 17 males. Median age was 14.7 years (range 5 months—48 years) and median age at diagnosis was 10.1 years (birth—47 years). Nineteen different pathogenic/likely pathogenic variants (including 10 not reported before) were identified in CDK13: 11 missense substitutions affecting residues located within the protein kinase domain, and eight variants likely leading to premature termination of translation (PT) consisting of four small delins resulting in a frameshift, three nonsense variants and one splice-site change (Figure 1). A de novo occurrence was confirmed in 21 individuals. The prevalence of the main clinical features is summarized in Table 1. For a detailed overview, see Table S1. Data from 110 patients previously published in the literature are summarized in Table S2 and variants are schematically represented in Figure S1.

4 | Discussion

Here we describe the clinical, genetic and diagnostic imaging findings in a large cohort of individuals with *CDK13*-related disorder. Alongside information from the literature, these data contribute to a more accurate characterization of the clinical spectrum associated with *CDK13* variants, and allow us to propose an update for the clinical approach to this multisystemic condition (Table 2).

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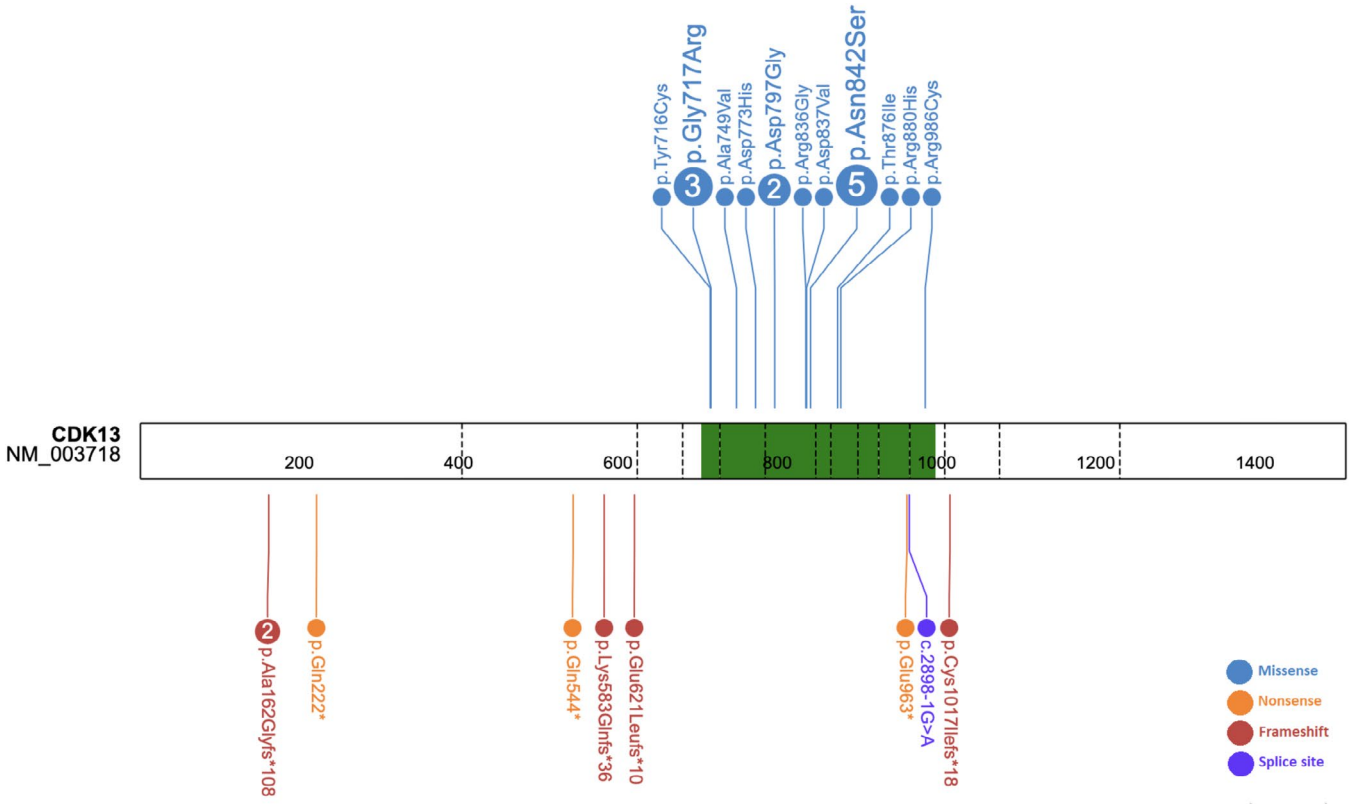

FIGURE 1 | Schematic representation of the variants in CDK13 reported in the present cohort. The green area identifies the kinase domain (residues 705–998). The different variant classes are indicated by red dots (frameshift variants), orange dots (nonsense variants), blue dots (missense variants) and violet dots (splicing variants). Numbers inside the dot correspond to the number of participants carrying the same variant (single cases, if not specified). The cartoon was created using ProteinPaint. [Colour figure can be viewed at wileyonlinelibrary.com]

Global developmental delay (DD) and/or ID, ranging from mild to severe, are one of the main concerns in the present cohort (22 out of 23 evaluated cases, 95.7%), in agreement with the literature (100/107 cases, 93.5%). In most cases, language is markedly compromised, and the dominant aspect is childhood apraxia of speech, as previously reported [12]; augmentative communication is expected to facilitate the interaction between individuals and their family members or caregivers. Autistic features and attention deficit hyperactivity disorder (ADHD) were also frequent. Notably, while *CDK13* variants largely underlie a syndromic condition, cognitive and behavioral problems were identified as isoloated or predominant symptoms in a subset of affected individuals. Participants #13 and #14, a pair of identical twins, exhibited severe ID associated with autism, restricted interests, repetitive behavior, absent language and psychomotor distress, without other major abnormalities. Similarly, participant #1 showed mild ID, attention deficit, sleep disturbances, hyperphagia and mild dysmorphic features.

Congenital heart defects (CHD) were observed in 42.2% (43/102) of individuals in the literature and in 56% (14/25) of the present cohort. In the present study, the most common anomalies consisted in atrial septal defects (30.4%) and valve anomalies (26.1%), alone or in combination, while more severe defects were absent. However, previous literature [12, 13] describes a few cases that could require an early intervention (surgical or pharmaceutical) or a periodical follow-up to avoid serious long-term impairment. Given the overall prevalence of cardiac anomalies in *CDK13*-related disease (44.9%), we recommend including *CDK13* testing in the differential diagnosis of 22q11.2 deletion syndrome and RASopathies, and for apparently isolated CHD identified in newborns and during prenatal examinations. Echocardiography should be performed at least at the time of diagnosis.

Prenatally, CHD in *CDK13*-related disorder has been associated with cystic hygroma, hydrops and hydrothorax [14]. In our cohort, prenatal manifestations included cardiac hyperechogenicity, right pyelectasis and retrognathia (participant #19), intrauterine growth restriction (#7, #15), polyhydramnios and hydrops (#24), hydronephrosis and ventriculomegaly (#26). In some cases, severe neonatal findings led to WES/WGS and molecular diagnosis soon after birth (participants #3, #6 and #24).

Brain anomalies (Figure 2) were detected in 9 out of 20 individuals with available MRI (45%), in line with the prevalence reported in the literature (31/75; 41.3%). Most of these features are nonspecific and include abnormal cerebral ventricle morphology (6 cases), corpus callosum anomalies (7 cases), and single cases of asymmetric cerebral and cerebellar hemispheres (participant #11), Chiari 1 malformation associated with dorsolumbar syringomyelia (#11), polymicrogyria covering a wide area in the frontal and parietal lobe of the right hemisphere (#6). Although several of these features can be considered benign, their increased frequency in syndromic individuals warrants caution, as some of them may lead to complications. We believe that periodic neuropsychiatric evaluation is important in children with

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TABLE 1 | Main phenotypic features of the present cohort and comparison with the data collected from the literature.

Features	Our series (27)	%	Literature (110)	%	Total (137)
Neurological					
DD and/or ID	22/23	95.7%	100/107	93.5%	93.8%
ID	20/23	87.0%	N/A	N/A	N/A
DD	22/24	91.7%	N/A	N/A	N/A
Autism spectrum disorder	8/20	40.0%	24/88	27.3%	29.6%
ADHD	3/16	18.8%	16/66	24.2%	23.2%
Behavioral anomalies	12/20	60.0%	45/80	56.3%	57.0%
Epilepsy	2/27	7.4%	11/93	11.8%	10.8%
Craniofacal features					
Arched eyebrows	11/25	44.0%	15/42	35.7%	38.8%
Upslanting palpebral fissures	7/24	29.2%	23/43	53.5%	44.8%
Deeply set eyes	7/25	28.0%	11/33	33.3%	31.0%
Hypertelorism	13/26	50.0%	58/94	61.7%	59.2%
Epicanthus	16/26	61.5%	35/83	42.2%	46.8%
Wide nasal root	19/24	79.2%	72/103	69.9%	71.7%
Short columella	9/24	37.5%	22/42	52.4%	47.0%
Thin upper lip	12/24	50.0%	45/92	48.9%	49.1%
Ear anomalies	21/25	84.0%	49/80	61.3%	66.7%
Hemangioma	2/27	7.4%	19/82	23.2%	19.3%
Ophthalmological					
Myopia	3/21	14.3%	7/53	13.2%	13.5%
Strabismus	8/25	32.0%	29/70	41.4%	38.9%
Audiological					
Hearing loss	3/26	11.5%	9/81	11.1%	11.2%
CHD					
Valve anomalies	6/23	26.1%	7/96	7.3%	10.9%
Atrial defects	7/23	30.4%	29/105	27.6%	28.1%
Ventricular defects	5/22	22.7%	6/92	6.3%	9.4%
Pulmonary artery stenosis	2/22	9.1%	12/99	12.1%	11.6%
At least 1 cardiac anomaly	14/25	56.0%	43/102	42.2%	44.9%
Renal/Urogenital					
Cryptorchidism	5/16	31.3%	14/31	45.2%	40.4%
At least 1 renal/urogenital anomaly	7/23	30.4%	30/66	45.5%	41.6%
Gastrointestinal					
GERD	3/20	15.0%	11/63	17.5%	16.9%
Constipation	5/21	23.8%	21/72	29.2%	28.0%
Feeding difficulties	10/23	43.5%	67/95	70.5%	65.3%

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TABLE 1 | (Continued)

Features	Our series (27)	%	Literature (110)	%	Total (137)
Growth					
Growth delay	7/27	25.9%	N/A	N/A	N/A
Obesity/overweight	6/26	23.1%	N/A	N/A	N/A
Skeletal					
Scoliosis	5/22	22.7%	5/68	7.4%	11.1%
Joint mobility anomalies	9/23	39.1%	15/80	18.8%	23.3%
Craniosynostosis	3/22	13.6%	11/74	14.9%	14.6%
MRI					
MRI brain findings	9/20	45.0%	31/75	41.3%	42.1%

Abbreviations: ADHD, attention deficit hyperactivity disorder; CHD, congenital heart disease; DD, developmental delay; GERD, gastroesophageal reflux disease; ID, intellectual disability; MRI, magnetic resonance imaging; N/A, not available.

CDK13-related disease, and based on the clinical presentation, appropriate brain/spine imaging may be considered.

Craniofacial findings (Figure 3) mainly consist of deeply set eyes, hypertelorism with epicanthus, highly arched eyebrows (often with a marked median apex), wide nasal bridge, short columella, thin upper lip vermilion and widely spaced teeth. Abnormalities of ear morphology are common and include over-folded superior helix, posterior angulation, low-set ears, cupping ears and abnormal conformation of the lobe. Notably, the association of ear anomalies with CHD, ID and/or central nervous system malformations (e.g., corpus callosum hypoplasia) may mimic other conditions, such as CHARGE syndrome [15] and Mowat-Wilson syndrome [16]. Overall, the craniofacial phenotype is variable and not easily recognizable at clinical evaluation, but we suggest that the particular shape of the eyebrows, with a steep inclination of the apex, may aid the diagnosis in some individuals (Figure 3A,D,F).

Craniosynostosis and abnormal skull morphology are recurrent in our cohort (5/22, 22.7%). Craniosynostosis has been reported previously in 11 individuals, and always described as involving the metopic sutures if details were specified. This association was confirmed in three cases from the present cohort. Participant #11 showed craniosynostosis at birth consisting in fusion of the metopic suture and also partial fusion of the right lambdoid suture (Figure 1). As a result, she retained a subset of craniofacial features (e.g., proptosis) even after surgical correction was performed. Of note, individuals with metopic craniosynostosis usually show facial alterations such as wide nasal bridge and highly arched eyebrows. The frequency of these features among individuals with *CDK13*-related disorder suggests that abnormal skull morphology could be more common than currently described, also considering that diagnostic imaging is not always performed.

Musculoskeletal issues are less common and seldom detailed in the literature. Scoliosis is described in 22.7% (5/22) of cases in our cohort and 7.4% in the literature, where it may be underreported. We also observe joint mobility anomalies in 39.1% (9/23) of the participants, involving elbows, knees and small joints (in particular of the hands) and consisting of either hypermobility (5 cases) or stiffness (5 cases). In seven cases with available imaging, no radiological signs that could explain these mobility anomalies were identified. Vertebral shape abnormality in the seventh cervical vertebra (enlarged C7 transverse process) and a mild craniocervical junction dysmorphism were described in one participant each. This emphasizes the need to be mindful of these anomalies (e.g., by avoiding stress on the cervical region) in order to prevent possible consequences, although none were observed in our cohort.

A careful clinical and physiatric/orthopedic evaluation and periodic follow-up, especially during growth, is advisable. Diagnostic imaging (e.g., spinal x-ray) should be considered on the basis of the clinical evolution or at the time of diagnosis.

We observed a heterogeneous group of eye anomalies in our cohort. Strabismus was reported in 8/25 participants, associated with Duane anomaly in one case; intermittent exotropia was reported in a single case. More severe anomalies were observed in a case with congenital bilateral glaucoma associated with posterior embriotoxon (participant #1), and in a case with cycloplegia and buphthalmos (participant #10). Buphthalmos is defined as an increased size of the eyeball resulting from increased intraocular pressure, and is closely related to glaucoma. Its congenital form, primary infantile glaucoma, is caused by an abnormal outflow of aqueous humor to the anterior chamber of the eye, that can lead to increased internal pressure and possible damage to the optic nerve if untreated. Considering the overall frequency of ocular anomalies (>40%) that may occasionally include severe defects, expanding on the recommendations by Rouxel et al. [17] we suggest a base-line ophthalmological evaluation, comprising tests to exclude abnormal ocular pressure or glaucoma (tonometry, gonioscopy, visual field test, optic nerve assessment).

Hearing loss was present in 3/26 participants (11.5%), similar to the proportion reported in the literature (9/81; 11.1%). One participant showed congenital bilateral mixed hearing loss associated with otospongiosis and hypoplasia of the internal auditory canals and cochlear nerves. We suggest auditory testing at the time of diagnosis, especially if language delay is noticed.

Growth is usually within the normal range. In our cohort only one individual exhibits short stature, while height is at the lower

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TABLE 2 | Suggested clinical management in patients with CDK13-related disorder.

System	Evaluation	Follow-up	Comment
Neurological	• Child neurological and psychiatric evaluation at the time of diagnosis and/or during the first years of life to monitor development • Plan specific support to stimulate the weakest areas • Consider introducing augmentative communication as main/alternative communication channel • School support or Special Education could be required	• Every 3–6 months during the first 2 years of life, afterwards at least annually	• Consider brain and/or spine MRI based on the clinical presentation
	• Baseline EEG	• Based on the EEG and clinical evolution (e.g., onset of seizures)	
Ophthalmological	• Complete ophthalmological evaluation comprising tests for glaucoma (tonometry, gonioscopy, visual field test, optic nerve assessment)	• Annually or based on the clinical presentation	
Audiological	• Baseline auditory evaluation	• Once a year or every 2 years based on the clinical and instrumental evaluations	
Cardiac	• Cardiological evaluation with ECG and Ecocardiography at birth or at the time of diagnosis	• At intervals determined by the congenital anomalies that may be present.	• Refer to a heart surgeon if necessary
Renal/urogenital	• Abdominal ultrasound scan at birth or at the time of diagnosis	• At intervals determined by clinical problems	
Musculoskeletal	• Periodic monitoring of the spine and of joint mobility • Spinal X-ray for scoliosis and any vertebral anomalies; dynamic cervical spine X-ray	• Physiatric/orthopedic evaluation if any anomalies are noted or suspected (scoliosis, stiff joints)	
Skull	• Careful evaluation for signs secondary to craniosynostosis (such as metopic ridge or facial asymmetry)		• Consider CT scan of the skull • Refer to a neurosurgeon
Gastrointestinal/feeding	• For those with feeding difficulties: Refer to a child nutritionist/pediatric gastroenterologist for evaluation of swallowing, feeding and nutritional status • Pediatric gastroenterological evaluation in case of constipation	• Monthly/every 3 months in the first months of life, then at least once a year during childhood	
Growth	• Monitor growth parameters, considering that height could be at lower limit • If overweight, monitor eating habits • Pediatric endocrinological evaluation based on clinical findings	• At time of diagnosis, monthly in the first 6 months of life, every 3–6 months in the first 3 years of life, then yearly	• Refer to child nutritionist/psychologist if eating disorders are suspected
Skin	• Skin examination • Dermatological evaluation of atypical nevi	• Periodic skin examination (at least annually)	

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TABLE 2 | (Continued)

System	Evaluation	Follow-up	Comment
Hematological tests	• Routine blood chemistry (blood count, renal and liver function, glucose), APTT, PT-INR, immunological tests (IgG, IgA, IgM, and lymphocyte subpopulations), a thyroid function tests (thyroxine FT4, TSH levels), thyroid autoantibodies (TPOAb, TGAb), antitransglutaminase antibodies, IGF1, IGFBP3	• At time of diagnosis, then once a year or every 2 years based on clinical problems	
Genetics	• Clinical genetic evaluation	• Once a year/every 2 years with updating of recommendations based on the evolution of scientific knowledge and literature	

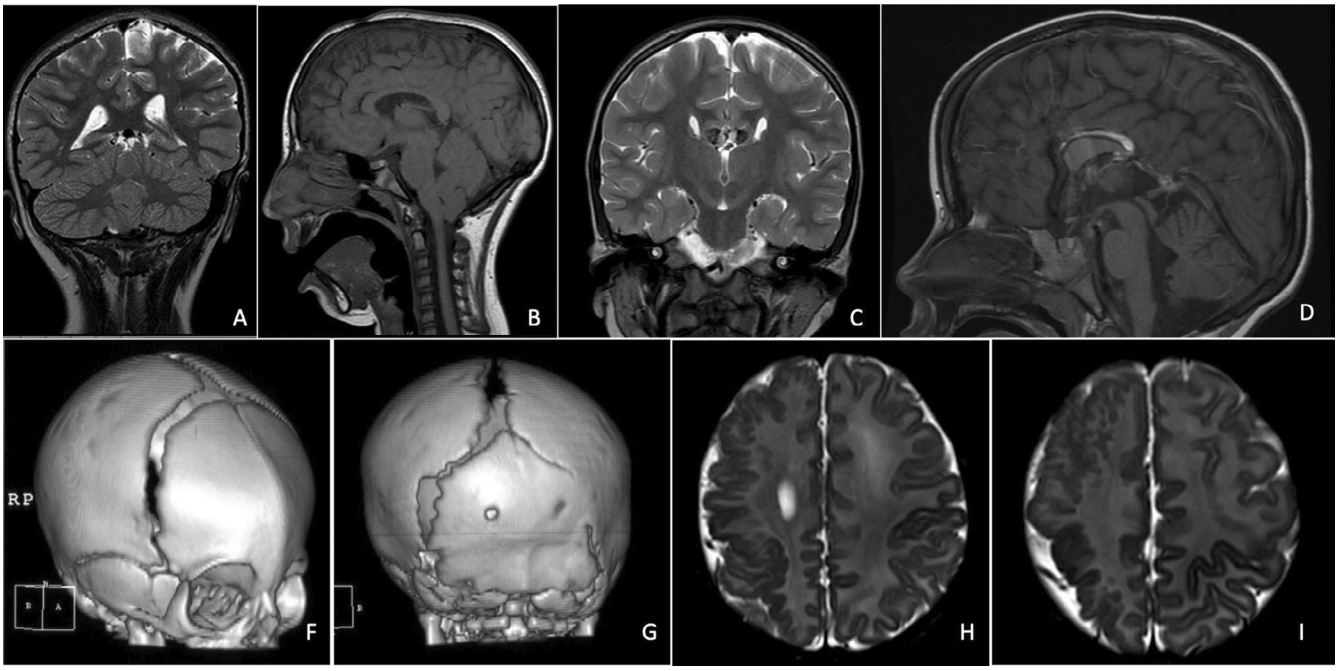

FIGURE 2 | Selected radiological features. (A, B) Brain MRI from participant #11 performed at 5 years of age shows asymmetric cerebral and cerebellar hemispheres (A) and Arnold-Chiari malformation (B). (C, D) Brain MRI from participant #4 shows partial agenesis of the corpus callosum associated with lipoma (performed at 5 years of age). (F, G) Computed tomography scan of the skull performed at 1 month and 6 days of age shows precocious fusion of the metopic (F) and right lambdoid (G) sutures in participant #11. (H, I) Brain MRI from participant #6 (10 days old) shows a wide area of polymicrogyria, mostly in the anterior region of the right side.

limit of normal (3rd-5th percentile) in 6/27 participants (22.2%). Head circumference is highly variable, with a minority of individuals showing either microcephaly (3/26) or macrocephaly (8/26). Feeding difficulties are common (43.5% in our cohort and 70.5% in the literature), suggesting the need to monitor nutrition closely, especially in the first years of life. Weight is variable and may be affected by feeding difficulties and behavioral anomalies such as hyperphagia leading to obesity, as seen in four participants. Hyperphagia has been described previously in four unrelated individuals [18].

A minor group of participants exhibited urogenital anomalies consisting of cryptorchidism (5/16, associated with hydronephrosis in one case), bilateral inguinal hernia (2/16) and hypospadias (2/16). While these anomalies do not seem common, we suggest performing a careful physical examination and possibly abdominal ultrasound to exclude their occurrence.

Recently, a case of leukemia has been described in a 9-year-old boy with *CDK13*-related disorder [19]. *CDK13* has been reported as a tumor-suppressor gene, promoting RNA surveillance and degradation of short, prematurely terminated transcripts [20]. Somatic missense mutations, often clustering in the kinase domain and overlapping with the germline variants involved in *CDK13*-related neurodevelopmental disorder, frequently occur in a variety of cancer types, including about 4% of cutaneous

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FIGURE 3 | Main phenotypic features in our cohort. A–F, Facial phenotype: Wide nasal root associated with large nasal tip, epicanthal folds, arched eyebrows showing a marked median apex with a steep inclination (A, D, F), thin upper lip (A, F), everted lower lip (C, D, E). G–L, Ear anomalies: Hypoplastic and horizontal helix (G, I, K), overfolded helix (G, H, I, L), hypoplastic lobe (G, I, L), uplifted lobe (J), hypertrofic tragus (L). A, G: Subject #11; B, H: Subject #6; C, I: Subject #24; D, J: Subject #25; E, K: Subject #1; F, L: Subject #18. [Colour figure can be viewed at wileyonlinelibrary.com]

melanomas. Experiments in zebrafish and human melanoma cells suggest a role in melanoma progression, but *CDK13* mutations in tumor cells occur alongside driver mutations in known oncogenes (*BRAF*, *NRAS*) and there is no strong evidence of an effect on the baseline risk of oncogenesis. In our cohort no pediatric malignancies were reported, but the possibility of an increased susceptibility to cancer cannot be ruled out completely because of the young median age. Notably, at the age of 17 years, participant #18 (under follow-up at our center) underwent removal of a dysplastic nevus, a known melanoma risk factor, prompting us to recommend annual dermatological evaluation. Based on these observations, we advise clinicians to consider noninvasive precautionary actions such as periodic blood testing and skin examination in individuals with *CDK13*-related condition.

Focusing on the molecular aspects, the majority of *CDK13* variants described in the literature are missense and affect residues located in the protein kinase domain (amino acids 705–998). A few nonsense, frameshift and splice site variants have been reported as well. It was hypothesized that the greater the decrease in total kinase activity, the more severe the phenotype is [21], but no clear genotype–phenotype correlation has been established yet. Asparagine at position 842, the critical residue of the active site within CDK13 kinase domain, is a possible hot-spot since it is recurrently mutated among affected individuals (5 in our cohort, 52 in previous reports). Other variants located within the kinase domain are usually associated with multisystemic involvement. Interestingly, considering both the present and previously published cohorts, all individuals with craniosynostosis had missense variants in the protein kinase domain. On the other hand, in the present series, individuals with PT variants exhibit a predominantly neurological phenotype without CHD or other significant malformations, similar to other cases already described in the literature (see cases 39 in [12], 14 and 15 in [18], C2 in [17], p.Tyr351fs and p.Gln544* in [22]). For participants #1 and #2 (son and mother), sharing variant p.Ala162Glyfs*108, the main concerns were hyperphagia and overweight/obesity, with a slight neurological involvement in the son and reportedly normal development in the mother. Notably, the two inherited variants identified in the present cohort were both PT: p.Ala162Glyfs*108, mentioned above, and p.Gln222*, inherited from an apparently healthy mother. This leads us to speculate that PT variants may have a milder effect on CDK13 function and on the clinical phenotype, and therefore are more likely to be transmitted. To date, the only other documented case of inheritance regards a missense variant, p.Gly717Arg, but it is also reported as associated with a mild phenotype, mainly neurological [23]. Inherited variants should be carefully evaluated, even if no specific concerns are reported in the parents. This variability may also explain the recurrence of some variants in the gnomAD database, especially when considering PT variants. Two participants in our cohort (#18, #23) with a missense variant also exhibited ID associated with behavioral issues only. Further studies are necessary to elucidate the possible correlation between the different molecular mechanisms and their clinical consequences.

5 | Conclusions

Our work describes the phenotypic spectrum of *CDK13*-related disorder, calling attention to some underreported features. Among these, we contribute to the definition of musculoskeletal features, such as joint contractures and craniosynostosis, and of clinically silent central nervous system anomalies, comprising syringomyelia and corpus callosum dysmorphisms. In the syndromic context, even mild alterations or anatomical variants may require additional care, and although follow-up is based mainly on the symptomatology, a correct genetic diagnosis may

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help anticipate the patients' needs. Therefore, based on our data and on the literature, we developed a series of suggestions for the clinical approach to this condition (Table 2), expanding upon the previous indications by Bostwick et al. [13].

In families with affected children, genetic counselling should consider that in rare cases the *CDK13* variant might segregate in a mildly or subclinically affected parent. No cases of suspected germline mosaicisms have been reported yet; based on this observation, recurrence risk in de novo cases is comparable to that of the general population (about 1%).

Further analysis on the functional or transcriptional effects of *CDK13* variants, in the context of clinically detailed cohorts such as the one described here, will be required to better elucidate the genotype–phenotype correlations of this condition.

Author Contributions

Conceptualization: G.C., L.G. Methodology: G.C., M.C.B., S.G.C., and L.G. Investigation: A.M., A.T., M.N., E.P., F.C.R., V.C., C.M., F.A.P., I.B., M.P., P.G., D.F., C.F., and M.T. Data collection and analysis: G.C., M.C.B., S.G.C. Data curation: G.C., M.C.B., S.G.C., and L.G. Writing – original draft preparation: G.C., M.C.B., and S.G.C. Writing – review and editing: L.G. Supervision: L.G. All authors discussed, read and approved the manuscript.

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Acknowledgments

This work has been generated within the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA) [EU Framework Partnership Agreement ID: 3HP-HP-FPA ERN-01-2016/739516]. The authors also wish to thank the patient's family members for their cooperation in providing the medical data and photographs necessary for this publication, as well as Luca Valcavi. The authors are grateful for the contribution made by the Fondazione Cassa di Risparmio Manodori of Reggio Emilia.

Consent

Informed consent to publish clinical data and photographs was obtained from the parents/legal guardian of the participants involved in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14726.

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