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Expanding the reproductive organ phenotype of *CHD7*-spectrum disorder

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Abstract

CHD7 disorder is a multiple congenital anomaly syndrome with a highly variable phenotypic spectrum, and includes CHARGE syndrome. Internal and external genital phenotypes frequently seen in *CHD7* disorder include cryptorchidism and micropenis in males, and vaginal hypoplasia in females, both thought to be secondary to hypogonadotropic hypogonadism. Here, we report 14 deeply phenotyped individuals with known *CHD7* variants (9 pathogenic/likely pathogenic and 5 VOUS) and a range of reproductive and endocrine phenotypes. Reproductive organ anomalies were observed in 8 of 14 individuals and were more commonly noted in males (7/7), most of whom presented with micropenis and/or cryptorchidism. Kallmann syndrome was commonly observed among adolescents and adults with *CHD7* variants. Remarkably, one 46,XY individual presented with ambiguous genitalia, cryptorchidism with Müllerian structures including uterus, vagina and fallopian tubes, and one 46,XX female patient presented with absent vagina, uterus and

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AUTHOR CONTRIBUTIONS

Tomoki T. Nomakuchi and Louise C. Pyle conceived the report, collected the cases, and wrote the manuscript. Blythe Stewart collected the cases and reviewed the manuscript. Kai Jiao reviewed and edited the manuscript. Melinda Danowitz, Jacqueline Leonard, Kosuke Izumi, Ian Krantz, Thomas F. Kolon, David Langdon, Cara Skraban, Jason Van Batavia, Elaine Zackai, Rebecca Linn, Caitlin Alexander, Mark Zaontz, and Maria G. Vogiatzi contributed cases, reviewed and edited the manuscript.

ovaries. These cases expand the genital and reproductive phenotype of *CHD7* disorder to include two individuals with genital/gonadal atypia (ambiguous genitalia), and one with Müllerian aplasia.

Keywords

CHARGE; CHD7; DSD; Kallmann syndrome

1 | INTRODUCTION

Heterozygous pathogenic variants in *CHD7* causes a wide spectrum of phenotype including CHARGE syndrome (OMIM #214800). CHARGE syndrome is an autosomal dominant multiple congenital anomaly syndrome that presents with variable constellations of the classic features of eye Coloboma, Heart defects, choanal Atresia, growth Retardation, Genitourinary anomalies, and Ear malformations, among other congenital anomalies and neurobehavioral problems (Bedeschi et al., 2020; Pagon et al., 1981). CHD7 is a chromodomain helicase-DNA binding protein that plays a role in chromatin remodeling, and heterozygous pathogenic *CHD7* variants are identified in most individuals clinically diagnosed with CHARGE syndrome (Janssen et al., 2012). As an ATP-dependent nucleosome remodeling factor, CHD7 utilizes the energy released from ATP hydrolysis to regulate the position and density of nucleosomes at target loci (Basson & van Ravenswaaij-Arts, 2015). A recent study showed that in addition to its nucleosome remodeling activity, CHD7 can directly recruit histone methyltransferase activity to its targets (Yan et al., 2020). CHARGE syndrome presents with a variable phenotypic spectrum, with no clear genotype–phenotype correlation (Jongmans et al., 2006). With increasing availability of molecular testing, individuals with pathogenic *CHD7* variants who do not meet the clinical criteria, and those with less typical presentations are recognized; the terms "*CHD7*-related disorders" or "*CHD7*-disorder" have been adopted more recently to better account for this spectrum (Hale et al., 2016; van Ravenswaaij-Arts et al., 2022).

Genital anomalies are commonly seen in individuals with pathogenic/likely pathogenic variants, or variants of unknown significance (VOUS) in *CHD7* (henceforth referred to as "*CHD7* variants"). Typical findings include micropenis and cryptorchidism in males, and vaginal hypoplasia in females (Blake & Prasad, 2006). Underdevelopment of genitals seen in *CHD7* disorder are likely secondary to congenital hypogonadotropic hypogonadism (HH; Pinto et al., 2005). Moreover, *CHD7* variants have been identified in patients with HH with or without features of CHARGE syndrome (Balasubramanian et al., 2014; Xu et al., 2018). Some of these individuals are more specifically diagnosed with Kallmann syndrome, defined by the combination of HH with anosmia (Pinto et al., 2005).

Less typical genital anomalies have been previously described in individuals diagnosed with CHARGE syndrome (Ragan et al., 1999; Reynaert et al., 2016). Here, we report two patients with *CHD7* variants with significant reproductive organ anomalies. We reviewed 12 additional individuals seen in our clinic between 2010 and 2021 with confirmed *CHD7* variants, with or without classic CHARGE phenotype, as well as Kallmann syndrome and/or reproductive organ anomalies.

2 | METHODS

We initially ascertained two cases of *CHD7* disorder with atypical genitourinary phenotype through inpatient Clinical Genetics consult referrals (Cases 1 and 2, described in detail in the following text). To further systematically assess the prevalence and variability of genital and reproductive endocrine anomalies associated with *CHD7* variants, we reviewed our internal cohort of individuals with *CHD7* variants. This was a retrospective chart review of the clinical course, imaging, and laboratory findings for individuals seen in the Individualized Medical Genetic Clinic between 2010 and 2021, a genetics clinic that includes multisystemic deep phenotyping. This work was approved by the Children's Hospital of Philadelphia (CHOP) Institutional Review Board (IRB) #21-019274.

3 | RESULTS

We identified a total of 14 individuals with *CHD7* variants and a suspected CHD7-disorder (Table 1). Reproductive organ phenotypes seen in this group were genital hypoplasia and/or cryptorchidism in five males and one with nonbinary ("ambiguous") genitalia (Case 1 below). One female was identified with Müllerian aplasia (Case 2 below). We identified three individuals with a diagnosis of Kallmann syndrome, including one female without any feature of CHARGE syndrome (Case 13). This individual was identified with a VOUS (p.R1189H) during evaluation for isolated Kallmann syndrome. Of note, all six individuals above pubertal age (12–24) exhibited signs of HH. We additionally identified a male with history of cryptorchidism but no features of CHARGE syndrome, who was found to have a likely pathogenic *CHD7* splicing variant (c.7608 + 5G>A) during evaluation for HH (Case 10).

3.1 | Case 1

A 37 and 4/7 weeks gestation newborn infant was noted to have non-binary/ambiguous genitalia, and admitted to the NICU for evaluation and management. Pregnancy was unremarkable. Delivery and resuscitation were routine, and growth parameters were within normal limits. Physical exam was notable for a clitorophallic structure with a perineal opening at the base. The labioscrotal folds were mildly rugated without palpable gonads. Ultrasound of the pelvis revealed a fluid-filled vagina with vertical septum, uterus, and bilateral gonadal tissues reported as ovaries. No additional dysmorphic features were identified.

Adrenal ultrasound was performed given the concern for congenital adrenal hyperplasia and demonstrated mild thickening of left adrenal limb without diffuse enlargement. Additional imaging did not identify structural renal or cardiac anomalies. Serum electrolytes, morning cortisol, 17-α-hydroxyprogesterone, and 17-hydroxyprognenolone were normal. Gender assignment was deferred, and the infant was discharged at day of life 7.

Genetic testing included a 46,XY karyotype with normal chromosomal microarray. Trio whole exome sequencing identified a de novo variant c.8440G > C (p.Gly2814Arg) in *CHD7*, classified as a variant of unknown significance, given the lack of association with phenotype (isolated non-dimorphic genitalia). This variant is seen at 1.22×10^{-5} minor

allele frequency in gnomAD, and in silico analysis predicted probably damaging (Polyphen) and deleterious (SIFT) effects, with an intermediate REVEL score of 0.471. No other reportable variants were identified.

At 4 months, the infant underwent cystoscopy/vaginoscopy, hysteroscopy and diagnostic laparoscopy with gonadal biopsy. The procedure confirmed the presence of a genitourinary sinus connecting to both the vagina and bladder, as well as uterus and fallopian tubes. Bilateral abdominal gonads were noted on laparoscopy, and they were grossly and histologically consistent with testicles with normal tubules, germ and Leydig cells. Serum testosterone concentrations at 4 months of age (i.e., during the last part of mini-puberty) was 55 ng/dL, indicating normal Leydig cell function. Anti-Müllerian hormone at 6 days of life was 34.19 ng/mL, which is low for a male (normal 78.11–606.46 ng/mL) and elevated for a female (normal <6.73 ng/mL), indicating reduced AMH release from the Sertoli cells (Yates et al., 2019). A male gender assignment was elected by the family. The infant underwent bilateral orchiopexy at 7 months, and multi-stage hypospadias surgical repair between 16 and 25 months. His course was complicated by right scrotal abscess, necessitating right orchiectomy at the time of second-stage hypospadias repair at 25 months. At the most recent evaluation at 3 years of age, his development was overall appropriate for age, except for mild speech delay requiring speech therapy.

3.2 | Case 2

A 12-year-old female with CHARGE syndrome was admitted for a repeat mandibular distraction procedure. She had multiple known congenital anomalies associated with CHARGE syndrome (Table 1). Prior to anesthesia, Urology was consulted due to difficult Foley catheter placement. External exam by Urology was notable for absent vaginal opening. Pelvic ultrasound revealed absent uterus and ovaries.

She was born at 37 weeks gestation to a then 39-year-old mother. Pregnancy was complicated by polyhydramnios and prenatal diagnosis of congenial pulmonary valve stenosis. She was admitted to the cardiac intensive care unit following delivery, where additional congenital anomalies were noted including Pierre-Robin sequence with Veau II cleft of the hard and soft palate, small bilateral choreoretinal coloboma, and dysmorphic features including hypoplastic and asymmetric ears, and flat and broad nasal bridge. Renal-bladder ultrasound revealed bilateral grade 4 vesicoureteral reflux with bilateral hydronephrosis. *CHD7* sequencing revealed a pathogenic variant in *CHD7* (c.2504_2508del; p.Y835fs*14).

The infant underwent valvuloplasty, followed by a 3-month NICU admission complicated by necrotizing enterocolitis, *C. difficile* infection and MRSA pneumonia. She required tracheostomy placement at 1 month. She underwent palatoplasty and mandibular distraction at age 1, and was decannulated at 3 years old, although she continued to require BiPAP while asleep for severe obstructive sleep apnea. She additionally underwent bilateral ureteral reimplantation at 2 years of age, due to recurrent urinary tract infections despite antibiotic prophylaxis.

She sat independently between 18 and 24 months and walked at 3 years. She utilized approximately 40 signs to communicate at age 3 and continued to communicate primarily via signs or gestures with use of 2-word phrases at age 12. Although she passed her newborn hearing screen, audiology evaluation later revealed moderate to severe bilateral mixed hearing loss.

She was evaluated for short stature at age 2. Normal thyroid hormones and morning cortisol were noted at the time; additional endocrinologic studies were deferred until expected pubertal age. Her height and weight remained below first percentile for age, and her *Z*-scores at age 11 were 3.87 for height and 3.08 for weight.

Upon the discovery of absent uterus and ovaries on ultrasound, she underwent additional endocrinologic and genetic evaluation. Endocrinologic evaluation revealed no external signs of thelarche or adrenarche; labs revealed pre-pubertal gonadotropic hormones, with undetectable estradiol, consistent with HH. Thyroid studies, cortisol, and ACTH were within normal range. IGF-1 was below normal, with *Z*-score of −2.1 for age and Tanner stage. Pelvic MRI confirmed the absence of vagina, uterus, and ovaries. Brain MRI revealed normal morphology of the pituitary gland. Trio whole exome sequencing was performed and confirmed the known de novo pathogenic *CHD7* variant, without additional reportable variants.

4 | DISCUSSION

Although genitourinary abnormalities are a classic feature of CHARGE syndrome, detailed description of internal and external genital phenotype and the spectrum of abnormalities thereof are not commonly reported. External genital hypoplasia is most often attributed to HH. Reports refer broadly to “GU features,” without deeply delineating or defining the genital phenotypes, and pelvic imaging is not always completed or available. Sex organ anatomy is not routinely ascertained in individuals with CHARGE syndrome as was the situation in Case 2, therefore the prevalence and spectrum of significant internal or external genital anomalies are unknown. In a series of 32 patients, Ragan et al. identified 22 cases of CHARGE syndrome with genitourinary anomalies, including one boy with penile agenesis, one female with Mayer–Rokitansky–Küster–Hauser syndrome and one female with agenesis of uterus and ovaries (Ragan et al., 1999). Detailed clinical information including the presence and severity of endocrine abnormalities are not available, and since the cases were reported prior to the discovery of *CHD7* as the causative gene, genotypes are likewise not available. This is the first report, to our knowledge, of nonbinary (ambiguous) genitalia together with confirmed *CHD7* variant (case #1). Reynaert et al. additionally reported an 18-year-old girl with CHARGE syndrome, HH, who was found to have absent uterus and ovaries during evaluation for primary amenorrhea (Reynaert et al., 2016). This individual had a novel frameshift deletion in *CHD7* exon 15. This makes case #2 the second, to our knowledge, of a 46,XX individual with Müllerian agenesis.

HH in CHARGE syndrome are often seen together with abnormal olfactory bulb development, meeting criteria for Kallmann syndrome (Pinto et al., 2005). Although Kallmann syndrome is genetically heterogeneous, a subset of individuals with isolated

Kallmann syndrome may harbor *CHD7* variants, and manifest some of the features of CHARGE syndrome (Jongmans et al., 2009). CHD7 protein is a nucleosome remodeling factor that likely influences expression of genes crucial for developmental processes (Bouazoune & Kingston, 2012). The specific etiology of HH and olfactory bulb abnormality in individuals with *CHD7* variants is not well understood. Evidence from mouse models suggests that normal *CHD7* expression is necessary for proper neural crest cell migration and olfactory axon migration (Schulz et al., 2014). The cells that release gonadotropin-releasing hormone migrates along the olfactory axon during development; therefore, disruption of olfactory axon migration in turn would result in hypogonadotropic hypogonadism (Balasubramanian & Crowley, 2017). Importantly, the hypothalamic–pituitary–gonadal axis can be evaluated by measuring the gonadotropin and sex steroid levels during “mini-puberty” that occurs during the first 3–6 months of life (Lanciotti et al., 2018). Individuals with CHARGE syndrome could therefore be assessed for hypogonadotropic hypogonadism in infancy, which could in turn help clinicians and families plan for evaluation and treatment during expected pubertal period.

Although the Kallmann syndrome phenotype in CHARGE syndrome is well characterized, absent female reproductive organs cannot be attributed to Kallmann syndrome, and could be secondary to a yet uncharacterized role of *CHD7* in reproductive organogenesis. During early embryogenesis, the CHD7 protein regulates the expression of a number of developmentally critical genes including *SOX9* and *TWIST1* (Bajpai et al., 2010). *SOX9* is necessary for early male reproductive organogenesis through its role in anti-Müllerian hormone production (Barrionuevo et al., 2006). The precise role of the CHD7 protein in development and in the pathogenesis of CHARGE remains under investigation, and it is possible that additional downstream factors are involved in female reproductive organ development. In summary, above cases illustrate the phenotypic diversity of individuals with *CHD7* variants with or without CHARGE syndrome, with respect to the genital anomalies. Our observations reinforce the necessity for complete external morphologic phenotyping including the genitalia in *CHD7* disorder, coupled with endocrinologic evaluation around the time of expected puberty.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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TABLE 1

Genotype and phenotypic characteristics of the cases.

Case #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Age at last evaluation	3 years	12 years	14 months	12 years	6 months	6 years	5 years	3 years	3 years	18 years	18 years	24 years	17 years	16 months
Sex	M	F	M	M	M	F	F	F	F	M	M	F	F	F
Status	Living	Living	Living	Living	Deceased	Living	Living	Living	Living	Living	Living	Living	Living	Living
Variant	C.8440G > A (p.Gly2814Arg)	c.2504_2508del (p.Tyr835fs)	C.2959C > T (p.Arg987Ter)	c.3964del (p.Leu1322fs)	c.7545delG (p.Arg2516fs)	c.7181 T > C (p.Leu2394Pro)	C.6104–2A > G	C.4863G > A (p.Trp1621Ter)	c.5528delG (p.Gly1843fs)	c.7608 + 5G > A	C.4849G > A (p.Gly1617Ser)	C.5734C > G (p.Arg1912Gly)	C.3566G > A (p.Arg1189His)	C.7162A > G (p.Lys2388Glu)
Variant Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	Unknown	Unknown	Unknown	Unknown	Unknown	Paternal
Variant Classification	vous	Pathogenic	Pathogenic	Pathogenic	Likely Pathogenic	Likely Pathogenic	Pathogenic	Pathogenic	Pathogenic	Likely Pathogenic	VOUS	VOUS	VOUS	VOUS
Genetic test	WES	WES	WES	*CHD7* single-gene testing	WES	WES	WES	WES	WES	HH Panel	*CHD7* single-gene testing	HH Panel	HH Panel	WES
Karyotype	46,XY	46,XX	46,XY	46,XY	46,XY	46,XX	46,XX	46,XX	46,XX	46,XY	46,XY	46,XX	N/A	46,XX
Eyes	Normal vision, no dilated ophthalmologic exam	Bilateral colobomas	Bilateral colobomas	Strabismus	Bilateral colobomas, right microphthalmia	Normal dilated ophthalmologic exam	Left coloboma	Bilateral coloboma, right microcornea, esotropia	Right coloboma	Myopia; no dilated ophthalmologic exam	Right conductive hearing loss	Right coloboma, left optic nerve dysplasia with reduced peripheral vision	Normal vision, no dilated ophthalmologic exam	Left coloboma
ENT	Normal audiologic evaluation	Midline CL/P, bilateral SNHL, laryngomalacia	Bilateral CL/P, SNHL, laryngomalacia	Bilateral mixed hearing loss	Glossoptosis	Bilateral SNHL	Right mild conductive hearing loss	Bilateral conductive hearing loss	bilateral SNHL	No audiologic evaluation, normal sense of smell	Submucosal cleft palate, anosmia	Bilateral SNHL, anosmia	Anosmia	Normal routine hearing screen
Respiratory	Normal	Obstructive sleep apnea with overnight BiPAP dependence	OSA with overnight CPAP dependence	Mild intermittent asthma	OSA	Normal	Normal	Asthma, OSA	Pulmonary hypoplasia secondary to congenital diaphragmatic hernia	Asthma	Asthma	Normal	Normal	Tracheomalacia
Cardiac	Normal echocardiogram	PS, ASD	ToF	PS	Single ventricle with unbalanced CAVC, D-TGA, PS, RAA, aberrant L. subclavian artery	RAA, aberrant L. subclavian artery, hypoplastic left pulmonary artery	ASD, PDA	PDA	Normal echocardiogram	Mild tricuspid insufficiency, otherwise normal echocardiogram	Normal echocardiogram	No concerns, echocardiogram not done	PFO	PFO
Endocrine	Low anti-Mullerian hormone level	Short stature, HH	Short stature, normal gonadotropins for age	Short stature, normal growth hormones, prepubertal levels of gonadotropins and testosterone at age 12	HH	Short stature, normal growth hormones	No endocrinologic evaluation	Normal growth hormones, gonadotropins not evaluated	Normal growth hormones, gonadotropins not evaluated	HH	Short stature, Kallmann syndrome	Kallmann syndrome	Kallmann syndrome, osteoporosis	No endocrinologic evaluation

Case #	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Gastrointestinal	Constipation	G-tube dependence	G-tube dependence	G-tube dependence	Nasoduodenal feeding tube dependence	Normal	Nasogastric feed dependence	G-tube dependence	Congenital diaphragmatic hernia, G-tube dependence	Normal	Normal	TEF	Normal	TEF/EA, anterior displacement of anus, omphalocele
Genitourinary	Ambiguous genitalia, perineal hypospadias, bilateral cryptorchidism; presence of uterus, vagina and fallopian tubes without ovarian tissues	Absent vagina, uterus, and ovaries. Bilateral grade 4 vesicoureteral reflux	Micropenis, bilateral cryptorchidism	Micropenis	Micropenis, bilateral cryptorchidism	Normal	Normal	Normal	Normal	Bilateral cryptorchidism	Bilateral cryptorchidism	Normal	Normal	Normal
Neurologic	Speech delay	Right CN VII palsy, global developmental delay	Global developmental delay, seizures, right CN VII palsy	Global developmental delay, Right CN VII palsy	Multi-compartment intracranial hemorrhage, asymmetric crying face	Right CN VII palsy, global developmental delay	Bicoronal craniosynostosis, gross motor delay, migraines	Hypotonia, gross motor delay	Global developmental delay	ADHD; normal MRI of the brain and pituitary	Bilateral CN VII palsy	Migraines	Absent olfactory bulb, migraines	Normal
Orthopedic	Normal	Congenital C1-occiput and C6–7 fusion, scoliosis	Normal	Congenitally fused C1-occiput	Normal	Normal	Normal	Normal	Normal	Normal	Muscular torticollis	Scoliosis	Normal	Normal

Abbreviations: ASD, atrial septal defect; CAVC, common atrioventricular canal; CL/P, cleft lip/palate; EA, esophageal atresia; HH, hypogonadotropic hypogonadism; OSA, obstructive sleep apnea; PFO, patent foramen ovale; PS, pulmonic stenosis; RAA, right aortic arch; SNHL, sensorineural hearing loss; TEF, tracheoesophageal fistula; TGA, transposition of great arteries; ToF, tetralogy of Fallot; WES, whole exome sequencing.