Prenatal ultrasonographic features associated with ARSL and X-linked chondrodysplasia punctata 1 (CDPX1) literature review and case series

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Prenatal Ultrasonographic Features Associated With *ARSL* and X-Linked Chondrodysplasia Punctata 1 (CDPX1): Literature Review and Case Series

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ABSTRACT

Background: Chondrodysplasia punctata 1 (CDPX1) is an X-linked recessive disorder of cartilage and bone development characterized by stippling on the cartilage and bone, flattened nasal bridge, and brachydactyly, or short fingers. CDPX1 has been associated with variants in the ARSL gene and is known to manifest prenatally, however, there has been no systematic literature review on this evidence.

Aims: Here, we reviewed the current literature on prenatal manifestations of CDPX1, and additionally introduce previously unpublished cases.

Materials & Methods: A systematic review of the literature was performed. Additionally, a GeneMatcher submission was created and a call for cases was presented at the Fetal Sequencing Consortium meetings to find previously unpublished cases.

Results: For the 22 fetuses reported here, we found that 55% had nasal hypoplasia, 41% had bony stippling or calcifications, 32% had polyhydramnios, 5% had oligohydramnios, 23% had shortened long bones, 23% had spinal canal stenosis, 18% had ventriculomegaly, 9% had brachydactyly/brachytelephalangy, 9% had clubbed feet, 9% had premature rupture of membranes, and 9% had intraventricular hemorrhage detected through sonography or radiography. We also found 17 unique variants in ARSL for these 22 fetuses.

Discussion: A previously unpublished association of ARSL variants with intrauterine fetal death or stillbirth has been noted in this study. It is also possible that intracranial hemorrhage is an underrecognized feature associated with CDPX1 variation. However, there have been challenges in applying ACMG criteria to ARSL, a gene without an associated Variant Curation Expert Panel.

For a complete list of the Australian Genomic Autopsy Study Team Members, see the Appendix A section.

Conclusion: This literature review and case series highlights which features of CDPX1 manifest prenatally, as well as introduces new phenotypes that have not been previously identified.

Summary

- **What is already known about this topic?**
  - CDPX1 is an X-linked recessive disorder of cartilage and bone which can present with prenatal findings.
  - There are currently seven publications about prenatal manifestations of CDPX1 in fetuses with *ARSL* variants.
- **What does this study add?**
  - We present the phenotype for 12 published cases and add 10 unpublished cases to summarize the current known prenatal phenotype.
  - Prenatal findings include: nasal hypoplasia (55%), bony stippling/calcifications (41%), polyhydramnios (32%), and shortened long bones (23%), among other findings.
  - Introduces unreported prenatal manifestations of CDPX1, including intracranial hemorrhage and stillbirth.

1 | Introduction

Chondrodysplasia punctata 1 (CDPX1) is an X-linked recessive disorder that affects bone and cartilage. It appears on X-rays as stippling on the bones and cartilage. CDPX1 is also typically accompanied by a flattened nasal bridge and brachydactyly or short fingers. CDPX1 has been associated with variants in the *ARSL* (legacy name *ARSE*) gene (Syndromic Disorders Gene Curation Expert Panel—ClinGen, definitive classification) [1]. *ARSL* encodes for arylsulfatase L, which is located at Xp22.33. In prior studies, *ARSL* activity has been noted to be inhibited by warfarin and the prenatal phenotype has similarities to warfarin embryopathy [2]. While the relationship between this gene and disease is well established, and CDPX1 is known to manifest prenatally, there has been no systematic literature review of the prenatal findings of CDPX1. Additional cases of CDPX1 and *ARSL* variants of uncertain significance have been noted to have intracranial bleeding as well as stillbirth or recurrent pregnancy loss that have not been previously described. Here, we provide a review of the current literature on prenatal manifestations of CDPX1, and introduce previously unpublished cases that offer additional insight into the prenatal phenotype of this disease.

2 | Methods

A review of the literature was conducted through searching PubMed, OMIM, and review of citations in previously published articles. The search terms utilized were "ARSL," "ARSE," "X-linked Chondrodysplasia Punctata," "binder anomaly," AND "prenatal".

Publications with relevant titles and abstract content were reviewed in full by two authors for potential relevance for inclusion (E.C.B., R.M.R.). The summarized data was initially presented at the ClinGen Prenatal Gene Curation Expert Panel (GCEP) and discussion among the members yielded additional unpublished cases.

A call for additional cases was presented at the Fetal Sequencing Consortium meetings hosted by the Women's Genetics program at Columbia University Department of Obstetrics and Gynecology [3]. Additionally, a GeneMatcher submission was created with phenotypic features such as microcephaly, micrognathia, cataract, epiphyseal abnormalities, punctate/stippled, intracranial hemorrhage, stillbirth or neonatal death, and Chondrodysplasia Punctata.

Informed consent for all subjects was obtained through the submitting clinical team according to local protocols for research inclusion during clinical care. Formal institutional review board approval was not required due to the small number of patients from each site. Patient consent for data sharing as a part of this case series was obtained from each treating clinical team who contributed to a previously unpublished case. Sequencing of unreported cases varied by location. All authors made substantial contributions to the design, data, and analysis and have had the opportunity to critically revise the content, and approve of the content in its final form.

3 | Results

To date, there are seven publications on the prenatal manifestations of *ARSL* and X-linked chondrodysplasia punctata 1, which report 12 fetuses [4–10]. In addition to these publications, we report 10 previously unpublished cases of variants in *ARSL* and CDPX1 with prenatal phenotypes. Of the 22 fetuses, 21 were reported to be XY and one was reported to be XX (Table 1). The XX fetus was included in a report of uniparental disomy [10]. There were no multiple pregnancies, only one case was a product of assisted reproductive technology (Case 7), and the average maternal age (reported only in 10 cases) was 28.9 years with a standard deviation of 3.6 years. Of the gestational age for abnormal ultrasounds noted for these fetuses, the earliest finding was at 16 weeks gestational age (WGA) and the latest at 32 WGA, with most initial abnormal ultrasound findings reported between 22 and 26 WGA (Table 1). For pregnancy outcomes, six pregnancies underwent an induced abortion, three infants were born via vaginal delivery, five were born via cesarean section, four were demised prior to birth, and four pregnancy outcomes were not available (Table 1).

Several common features have been observed both prenatally and postnatally among the 22 fetuses. For prenatal features observed on either sonograms or radiographs, 55% (12/22) had nasal hypoplasia (used interchangeably with maxillonasal

TABLE 1 | Fetal sex, gestational age at first abnormal findings, outcome of pregnancy, type of genetic testing, inheritance, zygosity of proband, *ARSL* variant, and ACMG variant classification for published and previously unpublished CDPX1 cases. Probands 3 and 4 are siblings, 17, 18, and 19 are siblings, and 20 and 21 are cousins whose mothers are identical twin sisters.

Case #	Fetal sex	Gestational age at first (abnormal) ultrasound	Outcome	Test type (trio ES, ES, GS, gene panel)	Inheritance	Zygosity	HGVS coding (NM_000047.3 (*ARSL*) for all)	HGVS protein consequence	ACMG variant classification	ACMG criteria	Reference
Published cases											
1	XY	26	Termination at 26 WGA	ES	U	Hemi.	c.1743G>A	p.(Trp581*)	VUS	PS4_Moderate	Brunetti-Pierri et al. (2003) [4] (PMID: 12567415)
2	XY	32	Born at 34 WGA via vaginal delivery	ES	U	Hemi.	c.1063G>A	p.(Gly355Ser)	VUS	PM2_Supporting, PP3, PS3_Moderate	Garnier et al. (2006) [5] (PMID: 16937129)
3	XY	22	Termination at 27 WGA	ES	U		c.1442C>T	p.(Thr481Met)	VUS	None	
4	XY	21	Termination at 26 WGA	ES	U	Hemi.	c.1442C>T	p.(Thr481Met)	VUS	None	
5	XY	—	Born at 34 WGA via C-section	ES	M	Hemi.	c.119T>G	p.(Ile40Ser)	VUS	PM2_Supporting, PP3, PS3_Moderate	Nino et al. (2008) [6] (PMID: 18348268)
6	XY	—	Born at 38.5 WGA via C-section	ES	M	Hemi.	c.410G>C	p.(Gly137Ala)	VUS	BS1, PP3, PM5, PS4_Moderate, PS3_Moderate	
7	XY	—	Born at 34 WGA via C-section	ES	M	Hemi.	c.767dupT	p.(Met256Ilefs*32)	VUS	PM2_Supporting	
8	XY	—	Born at 40 WGA via vaginal delivery	ES	M	Hemi.	c.1226C>T	p.(Thr409Met)	VUS	PM2_Supporting, PP3, PS3_Moderate	
9	XY	23	Born at 35 WGA	—	U	Hemi.	c.1258C>T	p.(Arg420Trp)	VUS	BS1	Boulet et al. (2010) [7] (PMID: 20523025)
10	XY	23	—	ES	M	Hemi.	c.640G>A	p.(Gly214Arg)	VUS	PM2_Supporting	He et al. (2019) [8] (PMID: 31337364)
11	XY	24	—	ES	U	Hemi.	c.265A>G	p.(Ser89Gly)	VUS	PM2_Supporting, PP3, PS3_Moderate	Zhang et al. (2021) [9] (PMID: 33942288)
12	XX	—	Born at 39 + 5 WGA via vaginal delivery	Sanger sequencing	M	Hom.	c.1227_1228delinsAT	p.(Ser410Cys)	VUS	PM2_Supporting	Woods et al. 2022 [10] (PMID: 35256563)
Unpublished cases											
13	XY	28 + 6	Born at 37 + 6 WGA	Chondrodysplasia Punctata Panel (*AGPS, ARSE, EBP, GNPAT, PEX7*)	M	Hemi.	arr[GRCh37] Xp22.33 (2852428_2877779)x1	Deletion of exons 3–11 of *ARSL*	VUS	PM2_Supporting	
14	XY	20 + 2	IUFD at 25w3d	Trio ES	M	Hemi.	c.307G>T	p.(Gly103Trp)	VUS	PM2_Supporting, PP3	
15	XY	22 + 4	Termination at 23 + 5 WGA	Gene panel	U	Hemi.	c.1732C>T	p.(Pro578Ser)	VUS	BS1, PP3, PS4_Supporting, PS3_Moderate	
16	XY	19 + 5	Termination at 19 + 5 WGA	Gene panel	M	Hemi.	c.410G>C	p.(Gly137Ala)	VUS	BS1, PP3, PM5, PS4_Moderate, PS3_Moderate	
17	XY	19 + 3	IUFD at 19 + 3 WGA	Trio ES	M	Hemi.	c.332G>A	p.(Arg111His)	VUS	PM2_Supporting, PM5_Strong	
18	XY	19 + 1	IUFD at 20 + 1 WGA	Trio ES	M	Hemi.	c.332G>A	p.(Arg111His)	VUS	PM2_Supporting, PM5_Strong	
19	XY	21	IUFD at 21 WGA	Trio ES	M	Hemi.	c.332G>A	p.(Arg111His)	VUS	PM2_Supporting, PM5_Strong	
20	XY	20	C-section at 32 WGA	Blinded ES[a]	M	Hemi.	c.1692C>G	p.(Asn564Lys)	VUS	PM2_Supporting	
21	XY	20	C-section at 36 WGA	Blinded ES[a]	M	Hemi.	c.1692C>G	p.(Asn564Lys)	VUS	PM2_Supporting	
22	XY	16	Termination at 17 WGA	Trio ES	U	Hemi.	c.1126G>A	p.(Gly376Ser)	VUS	PM2_Supporting	

Abbreviations: ES: exome sequencing; GS: genome sequencing; Hemi.: hemizygous; HGVS: human genome variation society; Hom.: homozygous; IUFD: intrauterine fetal demise; M: maternally inherited; U: unknown inheritance; VUS: variant of uncertain significance; WGA: weeks gestational age.

[a]For the probands that underwent blinded exome sequencing, only sequencing data from chromosome X was analyzed.

dysplasia or Binder anomaly in the literature), 41% (9/22) had bony stippling or calcifications, 32% (7/22) had polyhydramnios, 1 (5%) fetus had oligohydramnios, 23% (5/22) had shortened long bones, 23% (5/22) had spinal canal stenosis, 18% (4/22) had ventriculomegaly, 9% (2/22) had brachydactyly/brachytelephalangy, 9% (2/22) had clubbed feet, 9% (2/22) had premature rupture of membranes, and 9% (2/22) had intraventricular hemorrhage (Table 2). For postnatal features not visualized prenatally, 41% (9/22) had brachydactyly/brachytelephalangy, 41% (9/22) had stippling or calcifications, 23% (5/22) had nasal hypoplasia, 18% (4/22) had dysmorphic facies, 18% (4/22) had hypotonia, 14% (3/22) had intraventricular hemorrhage, 9% (2/22) had epicanthal folds, and 9% (2/22) had conductive hearing loss (Table 2). Detailed phenotypes for most probands can be found in the supplementary materials (Table S1).

Ultrasound and autopsy imaging were available for cases 14 and 15. For case 14, ultrasound imaging shows midface and nasal hypoplasia at 20 + 2 WGA (Figure 1A,C). Imaging from autopsy (IUFD occurred at 25 + 3 WGA) shows a flattened nasal bridge with an upturned nasal tip, mild macroglossia, and micro-retrognathia (Figure 1B,D). For case 15, the 3D surface rendering of fetal profile at 22 + 4 weeks gestation notes a flattened facial profile (Figure 1E), and the ultrasound image at 22 + 4 weeks gestational age of the fetal femur in a coronal plane depicts focal areas of increased echogenicity of the proximal femoral epiphysis consistent with stippling (Figure 1F).

TABLE 2 | Presence or absence of phenotypic features observed prenatally and postnatally.

	Case ID																					
	Previously published cases												Unpublished cases									
	1*	2	3*	4*	5	6	7	8	9	10	11	12	13	14*	15*	16*	17*	18*	19*	20	21	22*
Features noted prenatally																						
Bony stippling/calcifications	+	+	+	+	−	+	−	−	+	+	−	−	+	−	+	−	U	−	−	−	−	−
Nasal hypoplasia	−	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	U	−	−	−	−	−
Spinal canal stenosis	−	−	+	+	−	−	−	−	−	+	−	−	−	+	+	−	U	−	−	−	−	−
Short long bones	−	−	−	−	−	+	−	+	−	−	+	−	+	−	−	+	U	−	−	−	−	−
Brachydactyly/brachytelephalangy	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	U	−	−	−	−	−
Clubbed feet	−	−	+	+	−		−	−	−	−	−	−	−	−	−	−	U	−	−	−	−	−
Ventriculomegaly	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	U	+	+	+	−	+
Intraventricular hemorrhage	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	U	−	−	−	+	−
Polyhydramnios	−	+	−	−	+	−	+	−	−	−	−	+	+	−	−	−	U	+	−	+	−	−
Premature rupture of membranes	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	U	−	−	+	−	−
Postnatal features not visualized prenatally																						
Bony stippling/calcifications	+	−	+	U	−	−	+	−	+	U	U	+	−	+	+	U	−	−	−	+	+	−
Nasal hypoplasia	+	−	−	U	−	+	+	−	−	U	U	−	−	−	−	U	−	−	−	+	+	−
Dysmorphic facies	−	−	−	U	−	+	−	+	−	U	U	+	−	−	+	U	−	−	−	−	−	−
Brachydactyly/brachytelephalangy	+	+	−	U	+	+	+	+	−	U	U	−	+	+	+	U	−	−	−	−	−	−
Intraventricular hemorrhage	−	−	−	U	−	−	−	−	−	U	U	−	−	−	−	U	−	+	−	+	−	+
Hypotonia	N/A	+	N/A	N/A	+	+	−	+	−	U	U	−	−	N/A	N/A	N/A	N/A	N/A	N/A	−	−	N/A
Hearing loss	N/A	−	N/A	N/A	−	−	−	+	−	U	U	+	−	N/A	N/A	N/A	N/A	N/A	N/A	−	−	N/A
Ocular anomalies	−	−	−	U	−	+	+	+	−	U	U	−	−	+	−	U	−	−	−	−	−	−
Genitourinary anomalies	−	−	−	U	−	+	−	+	−	U	U	−	+	−	+	U	−	−	−	−	−	−

Note: A full list of phenotypic features can be found in Table S1.
Abbreviations: +: present; −: absent; N/A: not applicable; U: unknown.
* denotes IUFD or termination of pregnancy.

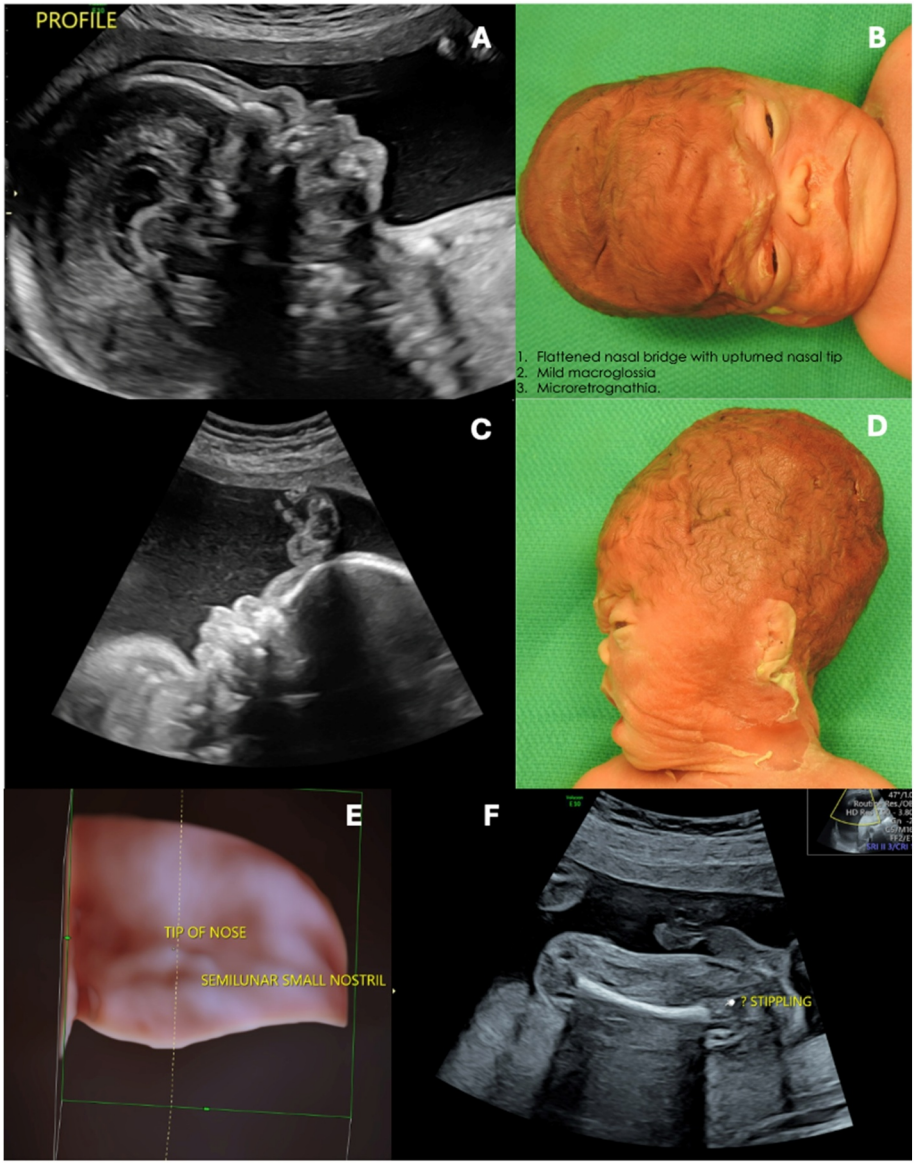

FIGURE 1 | Ultrasonographic and autopsy imaging for cases 14 and 15. (A) Ultrasound image at 20 + 2/7 weeks gestational age of the facial profile, noting flattening and midface retrusion (case 14). (B) Autopsy photo of the face after intrauterine fetal demise at 25 + 3 weeks gestational age, autopsy records noted a flattened nasal bridge with upturned nasal tip, mild macroglossia, and microretrognathia (Case 14). (C) Ultrasound image at 20 + 2/7 weeks gestational age of the fetal facial profile, noting a flattened facial profile (Case 14). (D) Autopsy photo of the side profile of the face after intrauterine fetal demise at 25 + 3 weeks gestational age with findings matching the previously described ultrasound images (Case 14). (E) 3D surface rendering of fetal profile at 22 + 4/7 weeks gestation noting a flattened facial profile (Case 15). (F) Ultrasound image at 22 + 4/7 weeks gestational age of the fetal femur in a coronal plane depicting focal areas of increased echogenicity of the proximal femoral epiphysis consistent with stippling (Case 15). [Colour figure can be viewed at wileyonlinelibrary.com]

Epiphyseal calcifications or stippling, and brachydactyly or brachytelephalangy, are common features of CDPX1 but are not always observed. For example epiphyseal calcifications or stippling was prenatally noted in 41% of ultrasounds/prenatal radiographs in this study, while in an additional nine cases, stippling or calcifications were first detected after delivery or upon autopsy, as opposed to prenatally. Of the cases that specified stippling localization prenatally, it was detected in the femoral and humeral epiphysis. For postnatally observed cases, stippling was noted in the vertebrae, femur, humerus, ribs, and cartilage. Additionally, calcification of the larynx was noted in three cases postnatally. The full natural history of these imaging findings is not currently known. Brachydactyly or brachytelephalangy was observed prenatally in five cases, postnatally in an additional nine cases, and was unspecified or not observed in eight cases. Although these features are common, their absence does not exclude a diagnosis of CDPX1 in this series.

For each of the 22 probands, 17 unique variants in *ARSL* were observed. Fourteen were determined via exome sequencing, three determined via panel sequencing, two via blinded exome sequencing (only chromosome X was sequenced), one via genome sequencing, one was determined via Sanger sequencing, and one method of diagnosis was unspecified (Table 2). Of the

variants, 14 were missense variants, one was a nonsense variant, one was a multi-exon deletion, and one was a frameshift variant. The nonsense variant (c.1743G>A, p.Trp581Ter) is located in the final exon of *ARSL* and therefore escapes nonsense-mediated decay (Figure 2). All of these variants are currently categorized as variants of uncertain significance (VUS) upon reclassification by ACMG guidelines by the author; however, they are mostly incredibly rare missense variants, and each variant is usually only observed once per family [11].

4 | Discussion

We conducted a literature review of cases of CDPX1 with *ARSL* variants and known prenatal phenotypes and identified 12 published cases and 10 unpublished cases from colleagues and GeneMatcher collaborations. Similar combined case series and literature reviews have been published for other prenatal phenotype collections, including Kabuki syndrome, tuberous sclerosis, and Wolf–Hirschhorn syndrome [12–14].

A review of the literature has identified several prenatally observed phenotypes of CDPX1, with the most common being nasal hypoplasia, short long bones, and bony stippling or calcifications. This expanded case series highlights the challenge of prenatal phenotyping even for disorders with well-established postnatal phenotypes. Only 55% of fetuses were recognized to have nasal hypoplasia, 41% were noted to have bony stippling or calcifications, and 9% had brachytelephalangia, which are the hallmarks of the postnatal phenotype. This lack of classic phenotypic features in the prenatal period further emphasizes the need for thorough, systematic phenotyping in the prenatal period, annotated repositories of phenotypic information (such as MONDO or HPO terms), and a broad sequencing methodology in the prenatal period such as exome sequencing or genome sequencing. Prenatally diagnosed cases may also be enriched for presentation differences, such as polyhydramnios and stillbirth.

A previously unpublished association of *ARSL* variants with intrauterine fetal death or stillbirth was noted in this study. There were five fetuses with intrauterine fetal demise. The authors also observed that there were overall five cases noted (cases 14, 18, 20–22) in which an intraparenchymal cerebral hemorrhage was noted in the pregnancy or neonatal period. The definitive etiology of the hemorrhage in these cases is not known. In general, the differential diagnosis for fetal and neonatal intraparenchymal hemorrhage includes neonatal thrombocytopenia (including alloimmune), fetal coagulation disorders (including Factor V and X deficiency), alterations in maternal and fetal blood pressure, trauma, bacterial or viral infection, vascular malformations, and *COL4A1* and *COL4A2* pathogenic variation among other causes [15]. Intracranial hemorrhage has been reported in warfarin embryopathy, which is a phenocopy of CDPX, and maternal conditions resulting in vitamin K deficiency [16]. In the cases noted with intraparenchymal hemorrhage, there were no other noted risk factors or etiologies, but full workup for other etiologies was not available.

Hemorrhagic abnormalities and skeletal features consistent with CDPX1 have been reported in a stillborn male sibling of a child with postnatally diagnosed CDPX1 (*ARSL* c.949G>A, p.(Gly317Arg)) [17]. Other conditions within the vitamin K pathway have also been recently associated with fetal or neonatal intracranial hemorrhage, such as congenital combined vitamin K-dependent clotting factor deficiency [18]. It is possible that intracranial hemorrhage is an underrecognized feature associated with CDPX1 variation. Further research into the underlying biology and additional prenatal cases should be considered to refine this potential association.

There have been additional challenges in applying ACMG criteria to *ARSL*, a gene without an associated Variant Curation Expert Panel (VCEP). The first challenge is that CDPX1 is noted to have minimal mortality and skeletal findings that improve with age [19]. Because of this, it is highly likely that there are individuals with the condition reporting as "unaffected" in population databases such as GnomAD. For example, one publication notes that the variant c.1743G>A, p.(Trp581*) accounts for 24% of the cases in their study [4]. However, it is also present in eight hemizygotes in GnomAD (v4.1.0), so it is

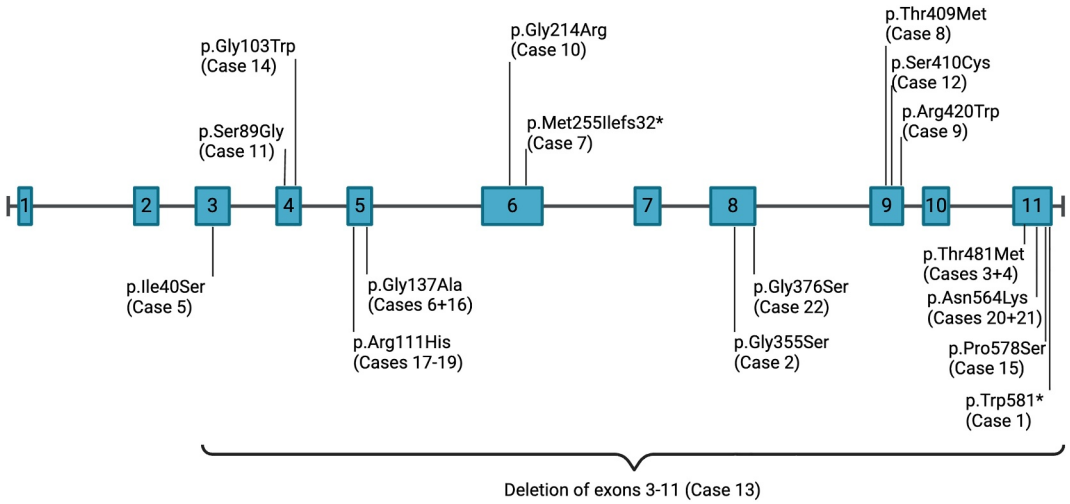

FIGURE 2 | Structure of Arylsulfatase L (*ARSL*) gene with variants from previously published and unpublished cases in this study. The protein consequences of the variant as well as the case it is associated with are indicated in the figure. Figure created in BioRender.com. [Colour figure can be viewed at wileyonlinelibrary.com]

possible that these individuals may have reduced penetrance. As for applying codes to variants in *ARSL*, PVS1 cannot be applied because the mechanism of disease has not been shown to be loss of function. Additionally, PP4 could not be applied because there is no expert panel to set phenotypic specifications, and there are no specific thresholds to apply PM2 or BA1/BS1 from an expert panel. For this publication, the Rett and Angelman-like Disorders VCEP specifications were followed since they are X-linked disorders, but they are not exact for *ARSL*. While we have performed a preliminary classification for these variants, a VCEP will need to be created to officially classify these variants and potentially boost pathogenicity.

This retrospective data series is limited by the currently available cases for inclusion and there could be selection bias. Attempts at broad inclusion were made including announcements at international prenatal sequencing groups and GeneMatcher submission. In the future, further broad collaborations for the purpose of curating prenatal phenotypes for well characterized postnatal disease presentations will be helpful for establishing gene-disease and prenatal phenotype associations.

This systematic review of known cases and additional published cases of the prenatal manifestations of CDPX1 includes nasal hypoplasia, polyhydramnios, shortened long bones, and bony stippling or calcifications. Additional, but possibly less common, features include intracranial hemorrhage or other hemorrhagic changes, stillbirth, or recurrent pregnancy loss. This information can be used to better phenotype and potentially diagnose CDPX1 prenatally.

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As many of the described patients were treated by a multidisciplinary team, we would like to acknowledge all those who provided care for these patients. We would also like to acknowledge Victoria McKay, MD, for her significant contribution of cases to this series. We would also like to thank the ClinGen Prenatal GCEP for their contribution in identifying this previous gap in the literature. Finally, we would like to thank the families for allowing their stories to be shared, without whom this work would not be possible.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. Patient-specific data are not publicly available due to privacy or ethical restrictions. Additionally, previously published cases are available in the public domain in the cited references.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

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