Prenatal Diagnosis

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PRENATAL DIAGNOSIS

ORIGINAL ARTICLE OPEN ACCESS

Phenotype-to-Genotype Description of Prenatal Suspected and Postnatal Discovered Upper Limb Anomalies: A Retrospective Cohort Study

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Received: 16 July 2024 | **Revised:** 14 November 2024 | **Accepted:** 15 November 2024

Funding: The authors received no specific funding for this work.

Keywords: genetic counseling | polydactyly | prenatal ultrasound | reduction defect | syndactyly | upper limb anomalies

ABSTRACT

Objective: To evaluate phenotype and genotype characteristics of fetuses and children with upper limb anomalies.

Method: Retrospective cohort study of a prenatal and postnatal cohort with upper limb anomalies from January 2007 to December 2021 in a Fetal Medicine Unit. Prenatally on ultrasound suspected upper limb anomalies, such as transverse and longitudinal reduction defects, polydactyly, and syndactyly, and postnatally identified children referred to the Congenital Hand Team were evaluated separately.

Results: The prenatal group included 199 pregnancies: 64 transverse and 19 longitudinal reduction defects, 103 polydactylies, and 13 cases with syndactyly. The majority of cases with longitudinal reduction defects (n = 10, 52.6%), polydactyly (n = 62, 60.2%), and syndactyly (n = 10, 76.9%) were non-isolated, as opposed to transverse reduction defects, which were generally isolated (n = 41, 64.1%). The postnatal cohort included 362 children with upper limb anomalies with 49 transverse and 22 longitudinal reduction defects, 226 polydactylies, and 65 syndactylies. Chromosomal or monogenic abnormalities were identified in 76/199 (38.2%) cases of the prenatal cohort and in 31/362 (8.6%) cases of the postnatal cohort.

Conclusion: Prenatal identification of minor defects of the digits is a challenge, with more postnatal than prenatal cases. The majority of cases with isolated anomalies in both groups had no underlying chromosomal or monogenic cause, nor were they associated with a syndrome, as compared to the non-isolated cases. Conducting structural anomaly scans and genetic counseling are crucial to assess the risk of genetic abnormalities.

Summary

- What is already known about this topic?
  - The current Dutch and ISUOG guidelines for the second trimester anomaly scan require sonographers to visualize at least both the upper and lower limbs, along with the posture of the hands and legs. However, visualization of the digits is not explicitly mandated in these guidelines, although it remains an important aspect for thorough fetal assessment.
- What does this study add?
  - This study highlights the challenges associated with the prenatal identification of minor digit defects. This underscores that most isolated anomalies of the digits do not have an underlying chromosomal or monogenic cause and are not typically associated with syndromes, in contrast to non-isolated cases.

1 | Introduction

Congenital anomalies affect approximately 2.5% of all newborns [1]. Limb anomalies of the upper and lower limbs are frequently observed, with an estimated prevalence of 39 per 10,000 pregnancies in the Netherlands [1]. Polydactyly is the most frequently observed upper limb anomaly followed by reduction defects, and syndactyly [1]. Polydactyly is the occurrence of complete or partial extra digit(s) with or without a bony content on the thumb side or on the side of the little digit [2]. A reduction defect is the absence, aplasia, or hypoplasia of skeletal structures of the limb: transverse when the limb (distal or proximal arm, forearm and/or hand) is absent, and longitudinal when the long axis of a limb is affected [2, 3]. Syndactyly is the (partial or complete) fusion of two or more digits [2].

Considering the significant role that upper limbs play in a child's psychosocial and motor development, it is crucial to provide information, support, and guidance by a multidisciplinary team to parents and their child when an upper limb anomaly is identified in the prenatal or postnatal period. Although the majority of children appear to adjust well to their condition, this is by no means the case for all children [4]. Although surgeons and parents may be good judges of functional outcomes, quality of life can only really be accurately measured if self-reported [4]. Reconstructive operations could have a positive impact on the function of the limbs and a child's self-confidence and self-image [4]. Prenatal or postnatal genetic testing can be offered to define the underlying genetic etiology and the recurrence risk in a future pregnancy. Additionally, prenatal diagnosis empowers parents with informed reproductive choices and enables planning of optimal neonatal and surgical care [5].

The aim of this study was to evaluate the phenotype and genotype characteristics of a prenatal group of fetuses with suspected upper limb anomalies, including transverse and longitudinal reduction defects, polydactyly, and syndactyly. Additionally, a postnatal group of children with the same upper limb anomalies, not identified prenatally, was also described. The comparison in the phenotype-to-genotype characterization between the prenatal and postnatal groups will support healthcare providers in advising and informing parents during parental genetic counseling.

2 | Methods

2.1 | Dutch Prenatal Healthcare System

In the Netherlands, prenatal screening occurs majorly in primary and secondary healthcare centers as part of a government led national screening program [6–8]. All pregnant women are offered a first trimester viability and dating scan around 10 weeks of pregnancy. Additionally, women can opt for two structural anomaly scans, that is a second trimester anomaly scan since 2007 and in research setting a first trimester anomaly scan since 2021 [6, 7]. Both structural anomaly scans have a strict protocol and are performed by trained sonographers. The second trimester protocol included the visualization of the following structures of the upper arm solely by 2D ultrasound: upper arm (including humerus), forearm (including ulna and radius), position of the wrist, and hand. Evaluation of the digits is not mandatory. Moreover, all women are offered prenatal screening for fetal aneuploidy by the first trimester combined test (until 2021) or cell free fetal DNA testing (since 2017). Ultrasound examination in the third trimester is only performed for obstetric indications such as suspected growth restriction or abnormal presentation of the fetus. In contrast to low risk women, those with a high risk for fetal anomalies due to an obstetric history or underlying medical conditions can opt for medical ultrasounds in the first and second trimesters in a Fetal Medicine Unit. Invasive prenatal testing (chorionic villus sampling or amniocentesis) is offered in cases of parental chromosome rearrangement, familial pathogenic variants, or detected fetal abnormality.

If a fetal anomaly is suspected, the pregnant women are referred for an advanced ultrasound to a Fetal Medicine Unit [8]. In the North-West region of the Netherlands, this scan is conducted at Amsterdam University Medical Center (AUMC). Here, the length of the fetal limb bones is assessed using the charts of Chitty et al. [9]. If an upper limb anomaly is suspected, the possibility of genetic testing is discussed, depending on the findings. Moreover, referral to the Congenital Hand Team for additional counseling is also provided. This multidisciplinary team, consisting of clinical geneticists, plastic surgeons, rehabilitation doctors, and occupational therapists specialized in congenital anomalies of the upper limbs, offers prenatal and/or postnatal counseling and treatment until adulthood. Both the Fetal Medicine Unit and the Congenital Hand Team serve as referral centers for the same geographical area. Termination of pregnancy is permissible up to 24 weeks of gestation in the Netherlands.

2.2 | Prenatal Group

This was a retrospective cohort study of pregnant women who underwent prenatal ultrasound examinations at the Fetal Medicine Unit of AUMC from January 2007 to December 2021. We included all fetuses with the following fetal upper limb

anomalies: transverse and longitudinal reduction defects, polydactyly, and syndactyly. After approval from the Medical Ethical Committee of AUMC (reference number W21_361 # 21.401), we extracted data on the medical and obstetric history of the mothers, prenatal ultrasound findings, results of invasive genetic tests, and postnatal follow-up of the newborns. Additional information regarding postnatal findings was evaluated using the children's electronic patient files. When data were missing, we contacted other healthcare providers (e.g., midwife or gynecologist) of the mothers for information on the outcome. We excluded pregnancies with other upper limb anomalies, such as dysplasia (e.g., contractures and lymphangioma).

In case of a termination of pregnancy, postnatal confirmation of the diagnosis occurred by external physical examination, autopsy, and/or X-ray. If no autopsy was performed, all fetuses were structurally examined externally by our medical professionals to see if the suspected anomalies were present in case of a medical termination. In cases without documentation of the postnatal examination, it was assumed that the postnatal findings were in accordance with prenatal findings.

2.3 | Postnatal Group

The postnatal group consisted of all live born children who were seen by the Congenital Hand Team of AUMC between January 2007 and December 2021 with a transverse and longitudinal reduction defect, polydactyly, and syndactyly. All mothers had received their second trimester anomaly scan in the North-West region of the Netherlands. Duplicate cases were removed when the case was already included in the prenatal group.

2.4 | Classification

Cases were grouped per affected axis (proximodistal, radioulnar or unspecified) according to the Oberg–Manske–Tonkin (OMT) classification for upper limb anomalies [2]. The anomalies were classified as isolated (ISO) if no other fetal abnormality was observed during prenatal sonography (prenatal group) or during postnatal physical examination (postnatal group), and as non-isolated (NISO) when other structural anomalies were identified. In case of multiple anomalies of the upper limb, the case was classified as isolated and scored according to the most severe upper limb anomaly. Pregnancy outcomes were classified as termination of pregnancy, stillbirth, neonatal death in the first 28 days of life, or live birth.

Outcomes of genetic testing were reported and classified as chromosomal or as monogenic. In cases with multiple anomalies without a genetic diagnosis, the case was classified as syndromic.

The genetic tests performed per case were dependent on the parents' request and year of diagnosis. In the last decades, advancements in genetic evaluation have shifted from karyotyping to whole exome sequencing (WES) [10–13]. In case of suspected anomalies, rapid aneuploidy testing is the first tier test to examine aneuploidies, followed by chromosomal microarrays. Targeted molecular testing was performed mainly in families with known genetic pathogenic variants. Prenatal WES has been offered since 2019 in our unit, as opposed to a postnatal WES, which is available since 2012 [13]. The approach to genetic testing differs between the prenatal and postnatal groups. During pregnancy, genetic tests such as rapid aneuploidy testing, microarray, or WES are routinely offered. In the postnatal group, the choice of genetic testing is guided by the physical examination of the newborn. In the prenatal period, only class 4 and 5 genetic variants (likely pathogenic or pathogenic variants) are reported in WES diagnostics. In contrast, variants of uncertain significance (VUS) are also reported in postnatal WES diagnostics.

2.5 | Descriptive Analysis

For the descriptive analysis of both groups, the findings of prenatal and postnatal genetic testing were reported in numbers and percentages. Furthermore, we estimated the prevalence (per 10,000 pregnancies) and prenatal detection rates of the specific limb anomalies.

3 | Results

3.1 | Prevalence and Detection Rate

In total, there were 561 cases with anomalies, of which 199 were identified in the prenatal period and 362 in the postnatal period. The estimated prevalence for the North-West region was 2.3 per 10,000 pregnancies for transverse reduction defects, 0.8 for longitudinal reduction defects, 6.7 for polydactyly and 1.6 for syndactyly, respectively. The estimated prenatal detection rates were 57% (64 of the 113) for transverse reduction defect, 46% (10 of the 41) for longitudinal reduction defect, 31% (103 of the 329) for polydactyly, and 17% (13 of the 78) for syndactyly.

3.2 | Prenatal Group

Between 2007 and 2021, 485.000 women received a structural anomaly scan within the North-West region of the Netherlands (source unpublished data from the yearly ultrasound unit audit files of the Fetal Medicine Unit of AUMC, including the region's primary care facilities). A total of 225 women were referred for ultrasound examinations due to suspected upper limb anomalies of which 26 (11.5%) could not be confirmed. A transverse reduction defect was finally identified in 66 cases, longitudinal reduction defect in 19, polydactyly in 124, and syndactyly in 16 cases, of which the majority was non-isolated (Figure 1). Of the 85 cases with a termination of pregnancy, 28 (32.9%) agreed for autopsy (Figure 2). There was one lost to follow-up in the polydactyly group. All cases with genetic abnormalities are summarized in Tables 1 and 2, including the phenotypes. Genetic testing was performed in 121 of the 199 cases (60%). A genetic abnormality was identified in 76 of the 199 (38.2%) cases. The most commonly observed monogenic syndromes were Cornelia de Lange for reduction defects (4x), Greig cephalopolysyndactyly (3x) and Bardet–Biedl (3x) for polydactyly,

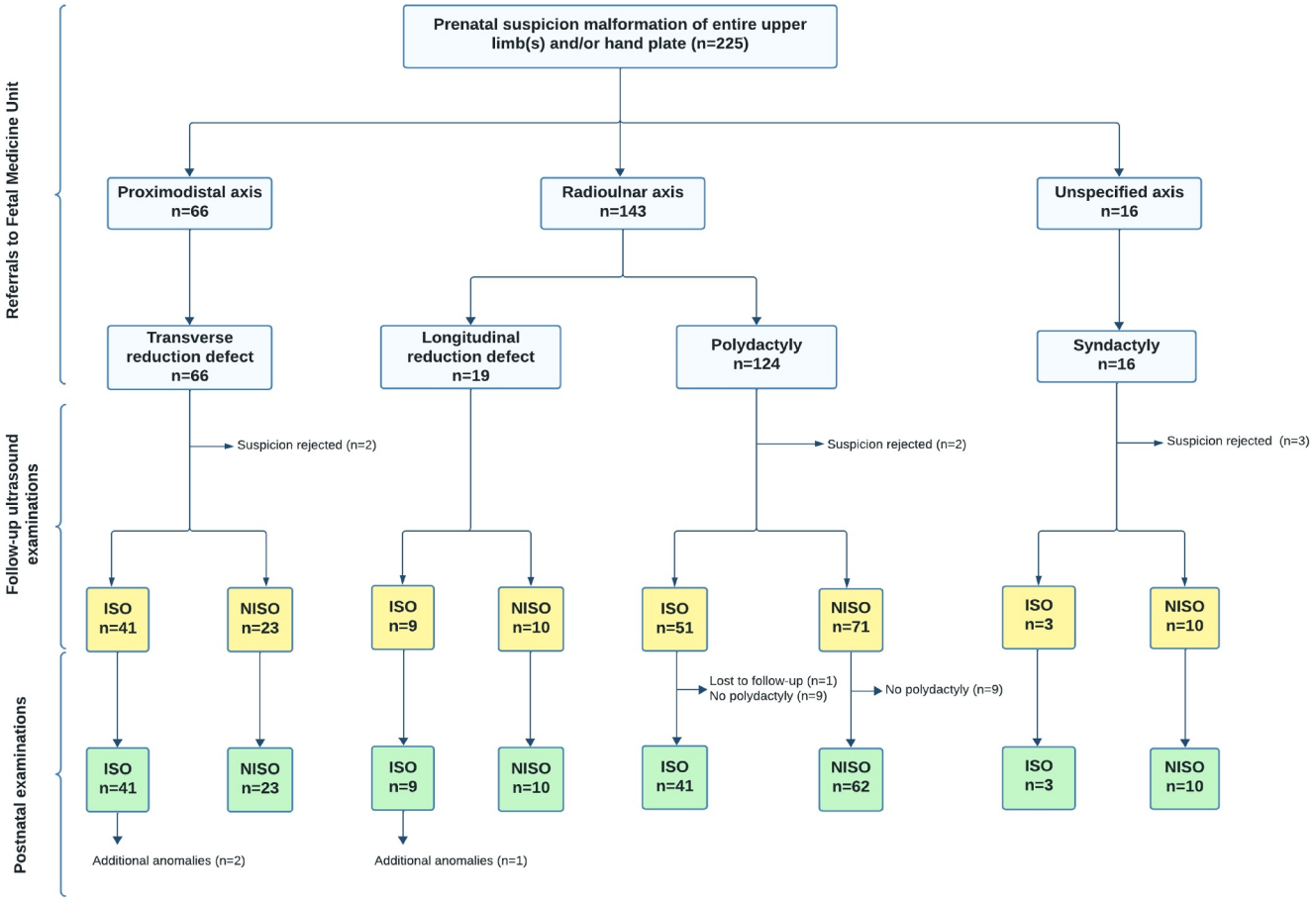

FIGURE 1 | Prenatal group: sonographic and postnatal findings. ISO = isolated, NISO = non-isolated.2 [Colour figure can be viewed at wileyonlinelibrary.com]

and Apert (2x) for syndactyly (Table 2). Among the 94 isolated cases, 90 (96%) had no underlying chromosomal or monogenic cause, nor were they associated with a syndrome, while 95 of the 105 (90%) non-isolated cases had a chromosomal or monogenic cause, or a suspected syndrome.

3.3 | Postnatal Group

The postnatal group consisted of 362 children. These cases included 49 transverse and 22 longitudinal reduction defects, 226 polydactylies, and 65 syndactylies, of which the majority was isolated (Figure 3). A total of 42 out of 49 (86%) children presented with a transverse reduction defect of the digits, 5 (10%) in the forearm (radius or ulna), and/or in 2 (4%) the whole hand was affected. In 14 out of 22 (64%) children with a longitudinal reduction defect, the anomaly occurred in the digit(s) only, in 5 (22%) in the forearm (radius or ulna) and in 3 (14%) children the whole hand was affected. Reduction defects involving the humerus were not observed. In cases with a polydactyly, we observed that 57 out of 226 (25%) children had other family members with a polydactyly, indicating a familial pattern. All cases with genetic abnormalities are summarized in Tables 1 and 3, including the phenotypes. A genetic abnormality was identified in 31 of the 362 (8.2%) cases. The most observed monogenic syndromes were brachydactyly type C (3x) for reduction defects, Bardet–Biedl (2x) for polydactyly, and oculo-dento-digital syndrome (3x) and Apert (2x) for syndactyly (Table 3). Among the 313 isolated cases, 298 (95%) had no underlying chromosomal or monogenic cause, nor were they associated with any syndrome, while 37 of the 49 (76%) non-isolated cases had a chromosomal or monogenic cause, or a suspected syndrome.

4 | Discussion

This study demonstrated that the majority of cases (90/94, 96%) with apparently isolated anomalies in the prenatal group had no underlying chromosomal or monogenic cause and were not associated with a syndrome. Similarity was observed in the postnatal group, where 298 of the 313 (95%) had no genetic cause or a syndrome (Tables 1–3). In contrast, the majority of the non-isolated cases in both groups (132/154, 86%) had an underlying genetic cause or a suspected syndrome. A higher percentage of genetic abnormalities was seen in the prenatal group in comparison with the postnatal group. The larger size of the postnatal group suggests that identifying mild anomalies of the digits during the prenatal period remains challenging.

The available literature on the prenatal detection of upper limb anomalies is primarily based on data gathered decades ago, while improvement in the prenatal anomaly identification has been observed on other fetal anomalies over the last few years

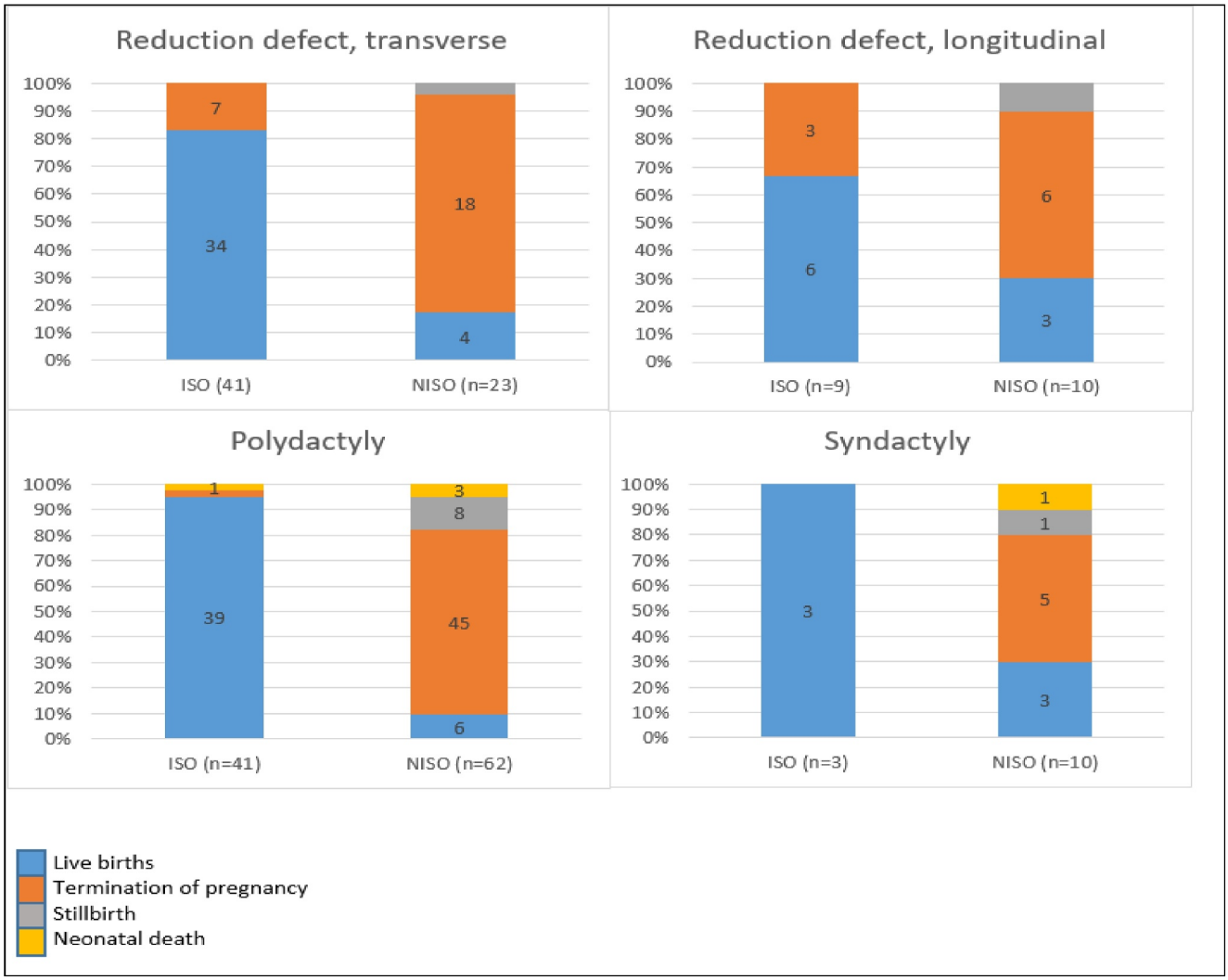

FIGURE 2 | Percentages (*y*-axis) and numbers (in the colored bars) of terminations of pregnancy, stillbirths, neonatal deaths (death in the first 28 days of life), and live births for each prenatal suspected and postnatal confirmed isolated and non-isolated anomaly. ISO = isolated, NISO = non-isolated. [Colour figure can be viewed at wileyonlinelibrary.com]

[14–22]. Reported prenatal detection rates of upper limb anomalies range between 22.8% and 42% (period 1990–2010) [14–22]. Anomalies of the entire upper limb have higher sensitivities (70%–100%), whereas anomalies affecting only the digits had the lowest sensitivities (4%–19%) [21, 22]. This is in line with our finding that in 56 of the 71 (78.9%) children with postnatally discovered reduction defects, the anomaly occurred in the digit(s). Prenatal detection rates in our study varied from 17% to 57%, depending on the anomaly. Since digit evaluation is not included in current (inter)national guidelines for second-trimester anomaly scans, it is likely that these specific anomalies are often missed during routine structural anomaly scans [6].

The high occurrence of chromosomal abnormalities in the non-isolated prenatal group of our study (26%) was similar to the findings of Paladini et al. (28%) [23]. In contrast, the postnatal group exhibited a lower percentage of chromosomal abnormalities (7/365, 1.9%). Additionally, the occurrence of monogenic abnormalities was higher in the prenatal group (21/199, 10.5%) than in the postnatal group (24/362, 6.6%). The expected structural anomalies were mainly in the urogenital, heart and nervous systems [22, 23]. Table 1 suggests that genetic abnormalities are more frequently associated with bilateral cases than with unilateral cases, which is in line with the findings of Pajkrt et al. [19]. Their study also found that cases with bilateral lesions have a significantly higher association with aneuploidy and genetic abnormalities, whereas those with sonographically isolated unilateral forearm defects had a very low incidence of other underlying pathology.

The findings of this study are useful for healthcare providers who want to inform parents about the potential prenatal and postnatal outcomes. Notably, this study has one of the largest study populations with upper limb anomalies that has been described, with a total of 561 included cases.

The retrospective nature of this study is one of the study's limitations. In the prenatal group, findings about postnatal examination were not always well documented after a termination of pregnancy and we assumed that all these cases were correctly identified when no additional specific classification was made postnatally. Moreover, since not all other fetuses have been systematically evaluated externally after a

TABLE 1 | Genetic testing and results in *n* (%), divided into prenatal identified (only cases that were prenatally identified on sonography and confirmed after birth) and postnatal discovered (prenatally not identified during ultrasound examination, but discovered after birth). All the cases were categorized into three groups with abnormalities: chromosomal, monogenic, or syndromic. Chromosomal cases involve abnormalities in the chromosomes, monogenic cases are linked to single gene mutations, and syndromic cases exhibit multiple abnormalities without a known chromosomal or monogenic disorder causing them. It is expected that cases without any suspected chromosomal, monogenic, or syndromic causes are generally in good health.

	Prenatally identified *n* (%)					Postnatally discovered *n* (%)				
		Genetic		Non-genetic			Genetic		Non-genetic	
Sonographic characteristics	Tested/ total (*n*)	Chromosomal	Monogenic	Syndromic	No additional diagnosis	Tested/ total (*n*)	Chromosomal	Monogenic	Syndromic	No additional diagnosis
Reduction defect, transverse	64					49				
Isolated, unilateral	14/40	—	—	—	40 (100%)	5/34	—	—	—	34 (100%)
Isolated, bilateral	1/1	—	—	—	1 (100%)	5/8	1 (12.5%)	3 (37.5%)	—	4 (50%)
Non-isolated	19/23	7 (30.4%)	4 (17.4%)	9 (39.1%)	3 (13.1%)	3/7	1 (14.3%)	—	5 (71.4%)	1 (14.3%)
Reduction defect, longitudinal	19					22				
Isolated, unilateral	2/6	—	—	—	6 (100%)	2/11	—	—	—	11 (100%)
Isolated, bilateral	3/3	2 (66.7%)	1 (33.3%)	—	—	2/2	1 (50%)	—	—	1 (50%)
Non-isolated	9/10	3 (30%)	3 (30%)	2 (20%)	2 (20%)	6/9	—	1 (11.1%)	7 (77.8%)	1 (11.1%)
Polydactyly	103					226				
Isolated, unilateral	2/12	—	—	—	12 (100%)	7/110	1 (0.9%)	1 (0.9%)	—	108 (98.2%)
Isolated, bilateral	6/29	—	1 (3.4%)	—	28 (76.6%)	10/94	—	2 (2.1%)	—	92 (97.9%)
Non-isolated	55/62	39 (62.9%)	7 (11.3)	11 (18.1%)	2 (3.2%)	16/22	2 (9.1%)	7 (31.8%)	6 (27.3%)	7 (31.8%)
Syndactyly	13					65				
Isolated, unilateral	0/2	—	—	—	2 (100%)	2/32	—	1 (3.1%)	—	31 (96.9%)
Isolated, bilateral	0/1	—	—	—	1 (100%)	9/22	—	5 (22.7%)	—	17 (77.3%)
Non-isolated	10/10	1 (10%)	5 (50%)	4 (40%)	—	9/11	1 (9.1%)	4 (36.3%)	3 (27.3%)	3 (27.3%)

Note: *n* = number.

TABLE 2 | Phenotype, genotype and postnatal findings of the prenatal group.

Number	Prenatal phenotype	Genotype	Diagnosis (by which test)	Sonographic characteristics and additional postnatal findings
1–2	Reduction defect, isolated, bilateral	TAR syndrome (microdeletion 1q21.1)	TAR syndrome (micro array)	Radial ray defect
3	Reduction defect, isolated, bilateral	Pathogenic variant in FGFR2 gene	FGFR2 related syndrome (WES)	Radial ray defect. Postnatal additional findings: Bilateral renal agenesis and syndactyly
4–5	Reduction defect, non-isolated, unilateral	Trisomy 21	Down syndrome (QF PCR)	
6–11	Reduction defect, non-isolated	Trisomy 18	Edwards syndrome (karyotyping or QF PCR)	
12	Reduction defect, non-isolated	PIK3CA gene mutation	PIK3CA related syndrome (gene panel)	Transversal reduction defect or the right hand, oligodactyly, lymphangioma from head to thorax
13	Reduction defect, non-isolated	FANCB gene mutation	Fanconi anemia type B (WES)	Fetal growth restriction, ventriculomegaly, small cerebellum, bilateral short humerus and ulna with radial ray defects. Left hand with rudimental thumb, contractures of both legs
14	Reduction defect, non-isolated	NIPBL gene mutation	Cornelia de Lange syndrome (targeted molecular testing)	Brachycephaly, hydrops, Dandy walker malformation, dextrocardia, hypoplastic left heart, bilateral radial ray defects, oligodactyly and rocker bottom feet
15	Reduction defect, non-isolated	Tetrasomy 9p	(Micro array)	Mild ventriculomegaly, vermis hypoplasia, abnormal corpus callosum, retrognathia, AVSD, empty stomach, single umbilical artery, talipes equinovarus, and syndactyly
16	Reduction defect, non-isolated	DYNC2H1-gene mutations	Jeune syndrome (gene panel)	Bilateral short humerus and femur with an abnormal stature, short ribs and bilateral polydactyly
17	Reduction defect, non-isolated	NIPBL gene mutation	Cornelia de Lange syndrome (WES)	Micrognathia, clubfeet, reduction defect lower legs, polydactyly unilateral, radial ray defect unilateral, oligodactyly hand
18	Reduction defect, non-isolated	NIPBL gene mutation	Cornelia de Lange syndrome (targeted molecular testing)	Split hand, radius aplasia, rudimentary fingers, hypoplastic nasal bone, ventricular septal defect
19	Reduction defect, non-isolated	NIPBL gene mutation,	Cornelia de Lange syndrome (targeted molecular testing)	Thick nuchal translucency, diaphragmatic hernia, micrognathia, absent nasal bone, absence of three fingers unilateral
20	Reduction defect, non-isolated	Triploidy (diandric)	Triploidy (QF PCR)	Holoprosencephaly, cardiomegaly, (A)VSD, oligodactyly unilateral, omphalocele, echogenic kidneys and bowels, growth restriction
21	Polydactyly, isolated, bilateral	Trisomy 13	Patau syndrome (QF PCR)	

(Continues)

TABLE 2 | (Continued)

Number	Prenatal phenotype	Genotype	Diagnosis (by which test)	Sonographic characteristics and additional postnatal findings
22	Polydactyly, isolated, bilateral	GLI3 gene mutation	Greig cephalopolysyndactyly syndrome (targeted molecular testing)	Polydactyly both hands. Sibling of number Case 70
23–52	Polydactyly, non-isolated	Trisomy 13	Patau syndrome (karyotyping or QF PCR)	
52–58	Polydactyly, non-isolated	Trisomy 18	Edwards syndrome (karyotyping or QF PCR)	
59	Polydactyly, non-isolated	1q21.1 duplication	1q21.1 duplication syndrome (micro array)	Diaphragmatic hernia, postaxial polydactyly both hands and feet, echogenic kidneys
60	Polydactyly, non-isolated	TMEM218 gene mutations	Meckel Gruber syndrome (WES)	Encephalocele, polydactyly, polycystic dysplastic kidneys
61	Polydactyly, non-isolated	GLI3 gene mutation	Greig cephalopolysyndactyly syndrome (WES)	Polydactyly (preaxial) hands and feet, mild ventriculomegaly
62	Polydactyly, non-isolated	BBS4 gene mutations	Bardet–Biedl syndrome type 4 (WES)	Polydactyly bilateral hands and feet, echogenic kidneys
63	Polydactyly, non-isolated	MKKS gene mutations	Bardet–Biedl syndrome type 6 (WES)	Ulnar polydactyly hands and feet, echogenic kidneys
64	Polydactyly, non-isolated	TMEM218 gene mutations	Meckel Gruber syndrome (WES)	Encephalocele, bilateral polycystic kidneys, polydactyly bilateral hands and legs, single ventricle heart, talipes equinovarus
65	Polydactyly, non-isolated	EVC gene mutations	Ellis van Crefeld syndrome (WES)	Ulnar polydactyly, short bones
66	Polydactyly, non-isolated	DHCR7 gene mutations	Smith Lemli Opitz syndrome (targeted molecular testing)	Polydactyly, overlapping fingers
67	Polydactyly, non-isolated	Trisomy 21	Down syndrome (QF PCR)	Hydrops and bilateral polydactyly (pre- or postaxial unknown), miscarriage at a gestational age of 11 weeks
68	Polydactyly, non-isolated	BBS5 gene mutations	Bardet–Biedl syndrome type 5 (WES)	Polycystic kidneys, hypospadias, postaxial polydactyly, oligohydramnios
69	Polydactyly, non-isolated	Trisomy 13	Patau syndrome (NIPT only)	
70	Polydactyly, non-isolated	GLI3 gene mutation	Greig cephalopolysyndactyly syndrome (targeted molecular testing)	Sibling of Case 22. Prenatal suspicion of CCAM and polyhydramnios. CCAM was not confirmed after birth
71	Syndactyly, non-isolated	Triploidy (maternal)	Triploidy (QF PCR)	Large head, small abdomen, horseshoe kidney, syndactyly unilateral, growth restriction
72	Syndactyly, non-isolated	FGFR2 gene mutation	Apert syndrome (targeted molecular testing)	Dolichocephaly, syndactyly bilateral, thick nuchal translucency
73	Syndactyly, non-isolated	TP63 gene mutation	Ectrodactyly—ectodermal dysplasia—cleft syndrome (targeted molecular testing)	Bilateral cleft lip, VSD, abnormal position of the toes and fingers, syndactyly dig 3–4 bilateral hands and also feet
74	Syndactyly, non-isolated	FGFR2 gene mutation	Apert syndrome (targeted molecular testing)	Abnormal profile (frontal bossing), large cerebellum, bilateral syndactyly
75			Triploidy (QF PCR)	

(Continues)

TABLE 2 | (Continued)

Number	Prenatal phenotype	Genotype	Diagnosis (by which test)	Sonographic characteristics and additional postnatal findings
	Syndactyly, non-isolated	Triploidy (maternal)		Syndactyly hands, small thorax, AC and FL<p3, micrognathia, VSD, empty stomach
76	Syndactyly, non-isolated	GLI3 gene mutation	Greig cephalopolysyndactyly syndrome (targeted molecular testing)	Ventriculomegaly, poly- and syndactyly, VSD

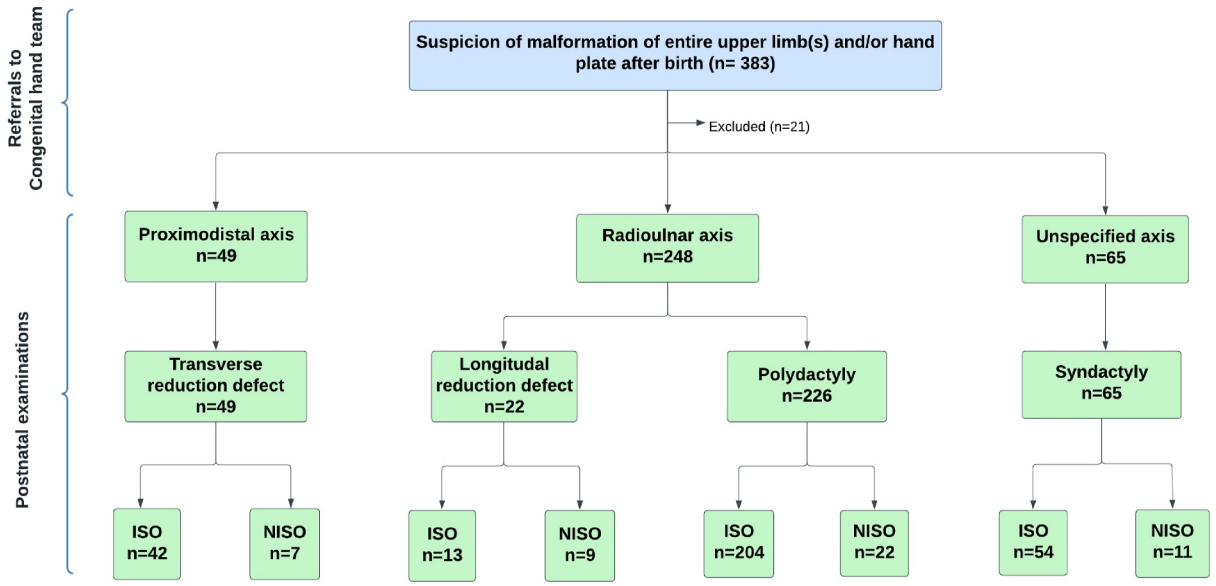

FIGURE 3 | Postnatal group: findings of physical examination. All cases were not identified during pregnancy but discovered after birth. ISO = isolated, NISO = non-isolated. [Colour figure can be viewed at wileyonlinelibrary.com]

termination of pregnancy, some upper limb anomalies may have been missed leading to an underestimation. Another limitation is that not all cases underwent autopsy, likely resulting in some anomalies not being confirmed postnatally. In the postnatal group, we expect that all children with clinically relevant upper limb anomalies will be referred to the Congenital Hand Team. However, we expect that simple forms of polydactyly may also have been treated outside our tertiary hospital. Regional guidelines allow plastic surgeons in secondary hospitals to treat simple forms of polydactyly, which may also have contributed to an underestimation of the postnatal group. Therefore, we think that the actual prenatal detection rate for polydactyly is lower.

An early prenatal identification of abnormalities allows parents more time to consider whether they wish to undergo prenatal invasive testing. A genetic consultation should be offered as a standard workup to define the underlying genetic causes if an upper limb anomaly is suspected [22, 23]. Evaluation of the prenatal phenotype can help to determine if it is part of a genetic syndrome [24]. For example, radial polydactylies are more frequently observed in non-isolated cases compared with ulnar polydactylies [25]. Furthermore, it is important to enquire about family history for upper limb anomalies, maternal medication use and intoxication to identify factors related to the anomaly [19, 26].

If invasive diagnostics are requested by parents, rapid aneuploidy testing and microarray analysis are highly recommended as a first step, particularly in non-isolated cases [19, 27]. In the prenatal group, 53 of the 76 (70%) abnormalities were detectable by these tests (Table 2). Finally, WES can be used to detect other genetic disorders. In case of isolated upper limb anomalies, particularly in unilateral anomalies, parents can be informed that chromosomal, monogenic and syndromic underlying causes are rare.

In conclusion, this study showed that the majority of cases with isolated limb anomalies in both the prenatal and postnatal groups had no underlying chromosomal or monogenic cause, and were not associated with syndromes, whereas in the majority of the non-isolated cases an underlying genetic cause was found. For isolated unilateral anomalies, parents should be informed that most cases do not have an underlying genetic cause. Identification of minor defects of the hand and digits poses a challenge, given the larger size of the postnatal group compared with the prenatal group.

TABLE 3 | Phenotype, genotype and postnatal findings of the postnatal group.

Number	Postnatal phenotype	Genotype	Diagnosis (by which test)	Characteristics on postnatal physical examination and other comments
1	Reduction defect, isolated, bilateral	Duplication 20q11.22	(Micro array)	Hypoplastic thumb/brachydactyly
2	Reduction defect, isolated, bilateral	Duplication 10q24	Split-hand-split-foot malformation (micro array)	Cleft hand and foot syndrome
3–5	Reduction defect, isolated, bilateral	GDF5 gene mutation	Brachydactyly type C (WES)	Reduction defect dig 2–5
6	Reduction defect, non-isolated	Mosaic trisomy 18	(FISH/micro array)	Longitudinal defect of both lower arms with hypoplastic thumbs, proximal radio-ulnar synostosis, clinodactyly dig 5 bilateral, syndactyly toes
7	Reduction defect, non-isolated	TBX5 gene mutation	Holt-Oram syndrome (targeted molecular testing)	Radius hypoplasia, partial syndactyly dig 2 unilateral, VSD
8	Polydactyly, isolated, unilateral	Deletion 17p12-17p11.2	(Micro array)	Postaxial polydactyly
9	Polydactyly, isolated, unilateral	FANCA gene mutations	Fanconi anemia (mitomycine-C test)	Radial polydactyly, fanconi anemia
10	Polydactyly, isolated, bilateral	ERF gene mutation	Chitayat syndrome (WES)	Central polydactyly bilateral (dig 2)
11	Polydactyly, isolated, bilateral	GLI3 gene mutation	Greig cephalopolysyndactyly syndrome (unknown)	Polydactyly all limbs, syndactyly foot
12	Polydactyly, non-isolated	Deletion 1q21,1-q21.2	(Micro array)	Bilateral preaxial polydactyly, microcephaly
13	Polydactyly, non-isolated	TBX3 gene mutation	Ulnar-mammary syndrome (WES)	Bilateral polydactyly, VSD, tracheomalacia, mamma aplasia
14	Polydactyly, non-isolated	TFAP2A gene mutation	Branchio-oculo-facial syndrome (targeted molecular testing)	Cleft palate, polydactyly
15	Polydactyly, non-isolated	HNRNPU gene mutation	Early infantile epileptic encephalopathy type 31 (unknown)	Scoliosis, syndactyly feet, preaxial polydactyly hands and feet, epilepsy, psychomotor retardation
16	Polydactyly, non-isolated	PUF60 gene mutation, BTD gene mutations	Verheij syndrome (WES)	Cleft lip, polydactyly unilateral hand, coloboma. BTD gene mutation is a VUS
17	Polydactyly, non-isolated	CHD4 gene mutation	Sifrim-Hitz-Weiss syndrome (unknown)	Postaxial polydactyly hand (not typical for mutation, VUS), pes planovalgus deformity, cryptorchidism
18	Polydactyly, non-isolated	Trisomy 21	Down syndrome (QF PCR, karyotyping)	AVSD, radial polydactyly unilateral
19	Polydactyly, non-isolated	BBS10 gene mutations	Bardet–Biedl syndrome (WES)	Large kidneys, postaxial polydactyly unilateral
20	Polydactyly, non-isolated	BBS12 gene mutations	Bardet–Biedl syndrome (gene panel)	Polydactyly unilateral hand and both feet, dysplastic kidneys

(Continues)

TABLE 3 | (Continued)

Number	Postnatal phenotype	Genotype	Diagnosis (by which test)	Characteristics on postnatal physical examination and other comments
21–23	Syndactyly, isolated, bilateral	GJA1 gene mutation	Oculo-dento-digital syndrome (targeted molecular testing)	Syndactyly dig 4 and 5 hands
24	Syndactyly, isolated, bilateral	BBS7 gene mutations	Bardet–Biedl syndrome (gene panel)	Syndactyly and polydactyly
25	Syndactyly, isolated, unilateral	RAF1 gene mutation	Noonan syndrome (targeted molecular testing)	Syndactyly hand dig 3–4, learning difficulties, clinodactyly
26	Syndactyly, isolated, unilateral	PIK3CA gene mutation	Megalencephaly-capillary malformation (gene panel)	Syndactyly dig 3–4, syndactyly feet, cutis marmorata telangiectatica congenita
27	Syndactyly, non-isolated, bilateral	FGFR2 gene mutation	Apert syndrome (targeted molecular testing)	Syndactyly and craniosynostosis
28	Syndactyly, non-isolated, bilateral	FGFR2 gene mutation	Apert syndrome (targeted molecular testing)	Frontal bossing, syndactyly both hands and feet, craniosynostosis
29	Syndactyly, non-isolated	BPTF gene mutation	Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies (WES)	VSD, bilateral syndactyly
30	Syndactyly, non-isolated	Distal deletion of 22q11	22q11 deletion syndrome (micro array)	Unilateral syndactyly dig 3 and 4, ASD, retrognathia
31	Syndactyly, isolated, bilateral	GJA1 gene mutation	Oculo-dento-digital syndrome (targeted molecular testing)	Syndactyly dig 4 and 5 both hands

Acknowledgments

The authors have nothing to report.

Ethics Statement

Approval from the Medical Ethical Committee of Amsterdam UMC (reference number W21_361 # 21.401).

Consent

The manuscript does not contain any identifying clinical information, videos, or photographic material. We confirm that written permission was obtained from the participants or their parent(s)/guardian(s) where appropriate for diagnostic and/or research purposes.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. EUROCAT, Prevalence Charts and Tables, The Netherlands 2007–2019, https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en.

2. C. A. Goldfarb, M. Ezaki, L. B. Wall, W. L. Lam, and K. C. Oberg, "The Oberg-Manske-Tonkin (OMT) Classification of Congenital Upper Extremities: Update for 2020," *Journal of Hand Surgery* 45, no. 6 (June 2020): 542–547. Epub 2020 Feb 21. Erratum in: J Hand Surg Am. 2020 Aug;45(8):771–772. PMID: 32093994, https://doi.org/10.1016/j.jhsa.2020.01.002.

3. M. L. Schmitz, C. P. Coulter, and M. L. Schmitz, "Congenital Limb Deficiency Disorders," *Clinics in Perinatology* 42, no. 2 (2015): 281–300. ISSN 0095-5108, ISBN 9780323356626, https://doi.org/10.1016/j.clp.2015.02.004.

4. R. Miller, H. Samarendra, and M. Hotton, "A Systematic Review of the Use of Psychological Assessment Tools in Congenital Upper Limb Anomaly Management," *Journal of Hand Therapy* 33, no. 1 (January–March 2020): 2–12.e1. Epub 2019 Mar 8. PMID: 30857895, https://doi.org/10.1016/j.jht.2018.11.001.

5. A. D. Clelland, R. Lester, Ó Duncan, and W. L. Lam, "Parental Experience After Diagnosis of a Congenital Upper Limb Difference: A National Survey," *Journal of Hand Surgery (European Volume)* 49, no. 11 (2024): 1327–1333, https://doi.org/10.1177/17531934241249014.

6. "Kwaliteitseisen tweede trimester SEO (structureel echoscopisch onderzoek), versie 8.1," NVOG. Kwaliteitseisen Tweede Trimester SEO (Structureel Echoscopisch Onderzoek) (pns.Nl) (2022), https://www.pns.nl/professionals/nipt-seo/seo/tweede-trimester-seo/kwaliteitseisen/uitvoering-kwaliteitseisen-tweede-trimester-seo.

7. "Kwaliteitseisen eerste trimester SEO (structureel echoscopisch onderzoek), versie 2.1," NVOG. Kwaliteitseisen Eerste Trimester SEO (pns.Nl) (2022), https://www.pns.nl/professionals/nipt-seo/seo/eerste-trimester-seo/kwaliteitseisen-eerste-trimester-seo/uitvoering-kwaliteitseisen-eerste-trimester-seo.

8. "Leidraad indicatiestelling prenatale diagnostiek, versie 7," NVOG. definitieve-NVOG-Leidraad-indicatiestelling-PND-aangepaste-versie-10-juli-2019.pdf (2019), https://www.nvog.nl/wp-content/uploads/2024/10/

definitieve-NVOG-Leidraad-indicatiestelling-PND-aangepaste-versie-10-juli-2019-def-21-2-2023-e-2.pdf.

9. L. S. Chitty and D. G. Altman, "Charts of Fetal Size: Limb Bones," *BJOG: An International Journal of Obstetrics & Gynaecology* 109, no. 8 (August 2002): 919–929, https://doi.org/10.1111/j.1471-0528.2002.01022.x.

10. A. Tekcan, S. Tural, M. Elbistan, N. Kara, D. Guven, and I. Kocak, "The Combined QF-PCR and Cytogenetic Approach in Prenatal Diagnosis," *Molecular Biology Reports* 41, no. 11 (November 2014): 7431–7436. Epub 2014 Jul 31. PMID: 25078985, https://doi.org/10.1007/s11033-014-3630-7.

11. J. L. Brewster, K. B. Beason, T. T. Eckdahl, and I. M. Evans, "The Microarray Revolution: Perspectives From Educators," *Biochemistry and Molecular Biology Education* 32, no. 4 (2004): 217–227, https://doi.org/10.1002/bmb.2004.494032040362.

12. F. Sanger, S. Nicklen, and A. R. Coulson, "DNA Sequencing With Chain-Terminating Inhibitors," *Proceedings of the National Academy of Sciences of the United States of America* 74, no. 12 (December 1977): 5463–5467. PMID: 271968; PMCID: PMC431765, https://doi.org/10.1073/pnas.74.12.5463.

13. C. D. N. S. KuCooper, D. N. Cooper, and G. P. Patrinos, "The Rise and Rise of Exome Sequencing," *Public Health Genomics* 19, no. 6 (2016): 315–324, https://doi.org/10.1159/000450991.

14. J. H. Fleurke-Rozema, T. A. Vogel, B. J. Voskamp, et al. "Impact of Introduction of Mid-Trimester Scan on Pregnancy Outcome of Open Spina Bifida in The Netherlands." *Ultrasound in Obstetrics and Gynecology* 43, no. 5 (2014): 553–556, https://doi.org/10.1002/uog.12546.

15. C. L. Van Velzen, S. A. Clur, M. E. Rijlaarsdam, et al. "Prenatal Detection of Congenital Heart Disease: Results of a National Screening Programme." *BJOG* 123, no. 3 (2016): 400–407, https://doi.org/10.1111/1471-0528.13274.

16. S. Ensing, C. E. Kleinrouweler, S. M. Maas, C. M. Bilardo, C. M. Van der Horst, and E. Pajkrt, "Influence of the 20-Week Anomaly Scan on Prenatal Diagnosis and Management of Fetal Facial Clefts," *Ultrasound in Obstetrics and Gynecology* 44, no. 2 (August 2014): 154–159. PMID: 24375841, https://doi.org/10.1002/uog.13291.

17. E. Vasluian, C. K. van der Sluis, A. J. van Essen, et al., "Birth Prevalence for Congenital Limb Defects in the Northern Netherlands: A 30-Year Population-Based Study," *BMC Musculoskeletal Disorders* 14, no. 1 (November 2013): 323. PMID: 24237863; PMCID: PMC3840683, https://doi.org/10.1186/1471-2474-14-323.

18. H. Grandjean, D. Larroque, and S. Levi, "The Performance of Routine Ultrasonographic Screening of Pregnancies in the Eurofetus Study," *American Journal of Obstetrics and Gynecology* 181, no. 2 (August 1999): 446–454. PMID: 10454699, https://doi.org/10.1016/s0002-9378(99)70577-6.

19. E. Pajkrt, S. Cicero, D. R. Griffin, M. C. van Maarle, and L. S. Chitty, "Fetal Forearm Anomalies: Prenatal Diagnosis, Associations and Management Strategy," *Prenatal Diagnosis* 32, no. 11 (November 2012): 1084–1093. Epub 2012 Aug 18. PMID: 22903415, https://doi.org/10.1002/pd.3962.

20. B. L. Gray, R. P. Calfee, J. M. Dicke, J. Steffen, and C. A. Goldfarb, "The Utility of Prenatal Ultrasound as a Screening Tool for Upper Extremity Congenital Anomalies," *Journal of Hand Surgery* 38, no. 11 (November 2013): 2106–2111. Epub 2013 Sep 19. PMID: 24055134, https://doi.org/10.1016/j.jhsa.2013.08.091.

21. S. L. Piper, J. M. Dicke, L. B. Wall, T. S. Shen, and C. A. Goldfarb, "Prenatal Detection of Upper Limb Differences With Obstetric Ultrasound," *Journal of Hand Surgery* 40, no. 7 (July 2015): 1310–1317.e3. Epub 2015 May 28. PMID: 26026354; PMCID: PMC4568827, https://doi.org/10.1016/j.jhsa.2015.04.013.

22. G. Tonni, G. Grisolia, M. P. Bonasoni, et al., "Fetal Hands: A Comprehensive Review of Prenatal Assessment and Diagnosis Over the Past 40 Years," *Ultrasound in Medicine and Biology* 49, no. 3 (March 2023): 657–676, https://doi.org/10.1016/j.ultrasmedbio.2022.09.022.

23. D. Paladini, E. Greco, G. Sglavo, M. R. D'Armiento, I. Penner, and C. Nappi, "Congenital Anomalies of Upper Extremities: Prenatal Ultrasound Diagnosis, Significance, and Outcome," *American Journal of Obstetrics and Gynecology* 202, no. 6 (June 2010): 596.e1–10, https://doi.org/10.1016/j.ajog.2009.11.040.

24. H. Ahmed, H. Akbari, A. Emami, and M. R. Akbari, "Genetic Overview of Syndactyly and Polydactyly," *Plastic and Reconstructive Surgery Global Open* 5, no. 11 (November 2017): e1549. PMID: 29263957; PMCID: PMC5732663, https://doi.org/10.1097/GOX.0000000000001549.

25. M. W. F. Rac, J. McKinney, and M. Gandhi, "Polydactyly," *American Journal of Obstetrics and Gynecology* 221, no. 6 (December 2019): B13–B15. PMID: 31787158, https://doi.org/10.1016/j.ajog.2019.09.023.

26. U. G. Froster and P. A. Baird, "Maternal Factors, Medications, and Drug Exposure in Congenital Limb Reduction Defects," supplement, *Environmental Health Perspectives* 101, no. S3 (October 1993): 269–274. PMID: 8143629; PMCID: PMC1521174, https://doi.org/10.1289/ehp.93101s3269.

27. J. E. H. Bergman, K. Löhner, C. K. van der Sluis, P. Rump, and H. E. K. de Walle, "Etiological Diagnosis in Limb Reduction Defects and the Number of Affected Limbs: A Population-Based Study in the Northern Netherlands," *American Journal of Medical Genetics* 182, no. 12 (December 2020): 2909–2918. Epub 2020 Sep 21. PMID: 32954639; PMCID: PMC7756893, https://doi.org/10.1002/ajmg.a.61875.