Author/s:
O'Keefe, D;Kennedy, J;McCombe, D;Coombs, C;Hui, L;Wilks, D;Halliday, J

Title:
Pre-natal and post-natal diagnosis of congenital upper limb differences: The first 3 years of the Australian Hand Difference Register

Date:
2022-01-01

Citation:
O'Keefe, D., Kennedy, J., McCombe, D., Coombs, C., Hui, L., Wilks, D. & Halliday, J. (2022). Pre-natal and post-natal diagnosis of congenital upper limb differences: The first 3 years of the Australian Hand Difference Register. Journal of Paediatrics and Child Health, 58 (1), pp.122-128. https://doi.org/10.1111/jpc.15673.

O'Keefe David (Orcid ID: 0000-0002-1666-3445)

Prenatal and Postnatal Diagnosis of Congenital Upper Limb Differences: The First 3 Years of the Australian Hand Difference Register

Running title: The Australian Hand Difference Register

Original article

Dr David O'Keefe[1], Ms Joanne Kennedy[2,4], A/Prof David McCombe[2,3,4], Prof Chris Coombs[2,3,4], A/Prof Lisa Hui[1,2,5], Mr Daniel Wilks[2,3,4], Prof Jane Halliday[2,4]

[1] Mercy Hospital for Women, Melbourne, Australia

[2] Murdoch Children's Research Institute, Melbourne, Australia

[3] Department of Plastic & Maxillofacial Surgery, The Royal Children's Hospital, Melbourne, Australia

[4] Department of Paediatrics, The University of Melbourne, Australia

[5] Department of Obstetrics & Gynaecology, The University of Melbourne, Australia

Corresponding author:

Dr Daniel Wilks

The Royal Children's Hospital

50 Flemington Rd, Parkville VIC 3052 Australia

E: Daniel.Wilks@rch.org.au **P:** +61 (3) 9345 5522

Acknowledgements: Thank you to Aussie Hands for engaging families and supporting the development of the register. We acknowledge our funders, The Aussie Hands Foundation Incorporated, McNally Family Foundation and Australasian Foundation for Plastic Surgery. LH was funded by a University of Melbourne Faculty of Medicine, Dentistry and Health Sciences Research Fellowship (2020), and a Medical Research Future Fund Emerging Leader fellowship (2021-2025).

Conflicts of interest: the authors declare no conflicts of interest.

Key words: congenital anomaly; upper extremity; prenatal diagnosis; hand; registries

Abstract

Background: Children with a congenital upper limb difference (CoULD) are a diverse group who often require multidisciplinary care and long-term support for functional and social impacts.

Aims: The Australian Hand Difference Register (AHDR) provides a national database of children born with a CoULD and aims to facilitate research and improve health care for affected children. Using data from the first three years of its operation, we analysed the demographic and clinical features of participating families, including type of CoULDs and the frequency of prenatal and syndromic diagnoses.

Methods: Families were recruited from tertiary plastic surgery, orthopaedic and genetics clinics, as well as by self-referral. Hand differences were classified by the consulting physician according to the Oberg-Manske-Tonkin (OMT) classification system. Primary carers were invited to complete an online questionnaire covering demographic information, pregnancy and newborn outcomes, and diagnostic details.

Results: Between August 2017 and September 2020, 822 families consented and 320 questionnaires were reviewed. CoULDs were detected prenatally in 66 (20.6%) and postnatally in 248 children (77.5%); data for six (1.9%) were missing. The most common CoULDs were radial polydactyly, symbrachydactyly with ectodermal elements, and radial longitudinal deficiency, hypoplastic thumb. Twenty-seven children (8.4%) had an associated syndrome, 7 diagnosed prenatally and 19 postnatally; the most common were VACTERL association, Poland anomaly, Holt-Oram, and Ectrodactyly-Ectodermal Dysplasia Clefting syndromes.

Conclusions: The AHDR is a valuable resource for understanding the relative frequencies of CoULDs. Participation will assist future research into the diagnostic journeys of children with CoULDs, including risk factors, diagnosis, and psychosocial impacts.

Keywords

congenital anomaly; upper extremity; prenatal diagnosis; hand; registries

Introduction

Children with a congenital upper limb difference (CoULD) are a diverse group who often require complex multidisciplinary care and may carry the associated functional and social impacts for life. These conditions can be caused by a range of environmental and genetic factors, including genetic syndromes.[1] The low birth prevalence of CoULDs, estimated at 5-27 per 10,000 live births in population-based studies,[2-5] and their clinical heterogeneity hamper evaluation of long-term outcomes. An adequate evidence-base upon which to inform management for these children and their families is often not available.

Furthermore, families of children with CoULDs do not always receive adequate health information or sufficient attention to their emotional and psychological needs.[6]

A prenatal ultrasound diagnosis of a CoULD can facilitate multidisciplinary care including counselling with maternal-fetal medicine specialists, paediatricians, congenital hand surgeons and geneticists. However, prenatal ultrasound has variable sensitivity, depending on the specific anatomical characteristics of the CoULD and associated conditions.[7] It is not known, therefore, if prenatal diagnosis is beneficial or problematic for expectant couples.

The Australian Hand Difference Register (AHDR) is a national clinical register that aims to address issues that have the potential to improve health care for children with CoULDs and their families. It gathers information on frequency, demography, social experience, and long-term outcomes of CoULDs.[8] This study describes the participants in the first three years of the AHDR, based upon data collected at register recruitment and subsequent parent-completed questionnaires. We analysed the demographic and clinical features of participating families, including type of CoULD and the frequency of prenatal and syndromic diagnoses.

Materials and Methods

This is a retrospective observational study of clinical data and parental questionnaire responses collected during the first 37 months of the AHDR from August 2017 to September

2020. Clinicians were alerted to the study via known networks of paediatric hand and upper limb surgeons in the major population centres across the country.

A minimum dataset, including the child's diagnosis, sex, year of birth, and birth location, is gathered for children who present to tertiary plastic surgery, orthopaedic and genetics clinics (8 Australian centres), by the consulting physician. Diagnosis is categorised using the 2020 update of the Oberg-Manske-Tonkin (OMT) system;[9] each child is assigned up to two diagnoses, with free text entry available to capture additional information.

Those who consent to contact are sent a questionnaire to be completed by a parent/guardian of the child, or by themselves if considered a mature minor. This comprehensive questionnaire seeks general details (demographics, timing of diagnosis, health service usage), birth history, pregnancy history (antenatal care, maternal health, and antenatal exposures), and family history.

Children with trigger digits were accepted to the register given their inclusion in the OMT classification system at the time the AHDR was launched (2014 update).[10] However, trigger digits are now considered acquired rather than congenital and no longer included (2020 update).[9] Given acquired diagnoses cannot, by definition, be identified prenatally, children with isolated trigger digits are excluded from this study.

Data were collected and managed using REDCap (Vanderbilt University, Nashville, Tennessee)[11, 12] and electronic data capture tools hosted at Murdoch Children's Research Institute. Data for the study timeframe were de-identified and exported to Microsoft Excel for descriptive analysis of questionnaire responses.

Comparison of questionnaire responders with non-responders involved independent samples *t* test for continuous variables and chi-squared test for categorical variables.

Where participants had more than one diagnosis, the most physically prominent and non-syndromic diagnosis was identified by a study investigator with specialist paediatric hand surgery expertise (DW), henceforth referred to as "major limb diagnosis". Where only a syndromic diagnosis was provided by the consulting physician, the following major limb diagnoses were assumed: cleft hand for four children with ectrodactyly-ectodermal

dysplasia-clefting syndrome; radial longitudinal deficiency, hypoplastic thumb for one with Holt-Oram syndrome; and Apert hand for two with Apert syndrome. The major limb OMT diagnoses were transposed into the Swanson classification system for cross referencing,[13] as this system was previously used to classify hand differences prior to adoption of OMT by the International Federation of Societies for Surgery of the Hand (IFSSH).

This study was approved by The Royal Children's Hospital HREC (Project #36262). Parents/guardians or mature minors provided written consent for participation in the register.

Results

Participation

The minimum dataset was completed for 822 children in the study period, with completion of the questionnaire done by 352 of the families. Among responders, three cases with isolated lower limb differences and 29 with trigger digits were excluded. Questionnaires of 320 respondents (292 mothers, 25 fathers, 2 guardians, 1 mature minor) were analysed. Among non-responders, 51 cases with trigger digits were excluded. No differences were found between those who completed the questionnaire (n=320) and those who did not (n=419) (Table 1 and Table S1, Supporting Information).

Completion of the questionnaire was ethically approved as consent for the child to be included on the AHDR. The mean age of the child at time of consent to participation was 5.4 years.

Perinatal and demographic data

Key perinatal variables are presented in Table 2. There were 191 mothers (59.7%) and 169 fathers (52.8%) who were of English, Irish, Scottish or Welsh race. Mothers and fathers of Chinese race were next most represented (26 (8.1%) and 23 (7.2%) respectively). More than two-thirds of participants came from Victoria, where the AHDR was introduced, but all Australian jurisdictions are now represented (Table 3).

Upper limb differences

There were 332 CoULDs affecting 320 children. Ninety-eight (29.5%) were bilateral, 185 (55.7%) unilateral, and laterality was unrecorded for 49 (14.8%). Of the unilateral CoULDs, 95 affected the left, 79 affected the right and the affected side was unknown in 11.

There were 246 malformations (74.1% of total CoULDs), 14 deformations (4.2%) and 69 dysplasias (20.8%). Three children (0.9%) were unclassifiable or could not have their OMT diagnosis confirmed despite attempts to contact referring clinicians. The most common malformations were radial polydactyly (52 cases), symbrachydactyly with ectodermal elements (30), and radial longitudinal deficiency, hypoplastic thumb (24). There were 12 cases of constriction ring sequence, the only specified deformation. Thumb in palm deformity was the most common dysplasia (17). Figure 1 displays the OMT diagnoses where 10 or more children were affected.

Timing of diagnosis

CoULDs were detected prenatally in 66 (20.6%) and postnatally in 248 (77.5%) participants; data for six (1.9%) were missing. Of the 248 postnatal diagnoses, 188 were diagnosed within one week of birth (75.8%); 60 (24.2%) were diagnosed one week after birth or later.

Where 10 or more children were affected, the CoULDs with the highest percentage of prenatal diagnosis were ulnar polydactyly (42% diagnosed prenatally), symbrachydactyly (33%), and constriction ring sequence (33%). The CoULDs with the highest percentage of postnatal diagnosis were radial longitudinal deficiency (94% diagnosed postnatally), thumb in palm deformity (94%), and cutaneous (simple) syndactyly (91%).

Prenatal investigations

Forty-two mothers (13.1%) recorded having amniocentesis, amongst whom eight recorded a test result, four of which described the result. The described amniocentesis results and the children's AHDR notification diagnoses were Apert syndrome (Apert syndrome), inversion of chromosome 2 (bilateral Ectrodactyly-Ectodermal Dysplasia-Clefting syndrome), *NRXN1* gene deletion (unilateral radial deficiency – thumb), and an unspecified duplication on chromosome 10 (bilateral complex cleft hand).

Seven mothers (2.2%) recorded undertaking chorionic villus sampling (CVS), one of whom had a chromosome condition detected (trisomy 21) in a child with radial polydactyly.

Of the genetic conditions identified on prenatal diagnosis, only two could be causally attributed to the CoULD, (Apert syndrome and trisomy 21,[14] while the other genetic findings were of uncertain significance. It was unknown if the *NRXN1* deletion was present in one or two copies. Pitt-Hopkins syndrome type 2 is caused by a biallelic insufficiency of *NRXN1*, while the spectrum of phenotypes associated with haploinsufficiency of neurexin-1 (NRXN1) is diverse.[15] The child with the *NRXN1* deletion also had renal and vertebral anomalies, and was classified in the VACTERL association group. Of the nine mothers with an abnormality detected on amniocentesis or CVS, three recorded having a prenatal diagnosis of a CoULD, five were diagnosed at birth or within one week, and one was diagnosed after the first week of birth.

Most mothers (284, 88.8%) recorded having at least one ultrasound in pregnancy. Five of these mothers did not record when the CoULD was diagnosed and three children with syndromes could not be assumed to have specific major limb diagnoses. The frequencies of major limb OMT diagnoses among the remaining 276 cases were categorised by prenatal versus postnatal diagnosis and OMT subcategory, shown in Table 4. These results, transposed to the Swanson classification system,[13] are shown in Table 5.

Total syndromal diagnoses

Twenty-seven children (8.4%) had a syndrome (Table 6). CoULDs were diagnosed prenatally in seven (25.9%), postnatally in 19 (70.4%) and data were missing for one. Age at enrolment of children with syndromes was significantly older than those without a syndromic diagnosis (7.6 vs 5.2 years, *p<0.05).*

Discussion

In this snapshot of the first three years of the AHDR, our participants most commonly had malformations such as radial polydactyly, symbrachydactyly, hypoplastic thumb and

cutaneous syndactyly. A prenatal diagnosis of a CoULD was made in 1 in 5 and almost 1 in 10 were born with a syndromal condition.

We include cases from every state and territory in Australia, though the majority were from Victoria, where the register was developed and the initial recruitment sites were opened. There were slightly more males registered, which may reflect the greater proportion of males to females affected by CoULDs described in a Western Australia population study.[2] Conversely, the distribution of gestational age at birth deviates from the same population study, with fewer preterm infants in our cohort (28.7% vs 13.4%), which may be accounted for by higher rates of neonatal deaths in preterm babies.

The relative frequencies of CoULDs typed by Swanson classification (shown in Table 5) are comparable to those identified in the Western Australia population study,[2] suggesting the broad spectrum of CoULDs seen in infants are well represented in the register. Two more recent population studies using the OMT system also describe a similar relative frequency of malformations (74-76%)[4, 16] to our database of 74%. Our study population were more affected by dysplasias (20.8%) than deformations (4.2%), in contrast to Ekblom et al[4] (2% and 22%, respectively). This is likely due to their exclusion of tumorous conditions and arthrogryposis, which are now classified as dysplasias by the current OMT system. The higher frequency of specific conditions such as radial polydactyly, symbrachydactyly and radial longitudinal deficiency in the AHDR cohort may reflect an ascertainment bias through limited recruitment from orthopaedic clinics compared to plastic surgery clinics, where these conditions are more commonly managed in Australia. Similarly, CoULDs which are not primarily managed surgically may not be well represented, for example, transverse arrest. In recent months the research group have expanded recruitment through contacting limb rehab clinics and genetics services in Victoria, Queensland and New South Wales, with a view to expand nationally, to gather more data about this cohort.

Prenatal ultrasound for structural anomalies is offered to all women at 18-22 weeks, and many women also access an 11-13 week ultrasound for early screening.[17] Many CoULDs involving the radius and ulna are detectable in first trimester, although some upper limb and hand conditions may not be evident until second or third trimester.[18] We included an analysis by the anatomy-based Swanson classification as this is more suited to considering

the relative prenatal ultrasound detection rates, compared with the OMT system which uses an embryology and dysmorphology framework. Two Swanson types with high prenatal detection rates were type I (failure of formation of parts) and type IV (undergrowth), which would be readily detected as absent or shortened bones on ultrasound respectively. Conversely, the low detection rate of overgrowth conditions likely reflects the fact that overgrowth is often not identifiable either at birth or prenatally and that soft tissue assessment on fetal ultrasound is difficult, especially in third trimester when the upper limbs are not routinely examined. While examination of the long bones, digits and hand posture/movement are routine components of the second trimester morphology scan,[18] the hands are not routinely assessed at third trimester ultrasound scans. Hence, the number of ultrasounds in third trimester would not be expected to correlate with the detection rate, particularly as advancing gestation may make the hands more difficult to assess due to crowding of fetal limbs.

Prenatal ultrasound diagnosis may be beneficial for many families, however only 1 in 5 of our cohort received this. When there is a suspected CoULD, tertiary fetal medicine referral for detailed ultrasound, genetic counselling, and an offer of prenatal diagnosis with chromosomal microarray would be routinely recommended. If a multisystem malformation syndrome or a skeletal dysplasia is present, fetal exome sequencing might also be considered if the chromosomal microarray is non-diagnostic.[19] The degree of additional investigations that are offered will be influenced by the nature of the CoULD, associated risk factors including family history, patient preference and local resources. Prenatal counselling following a suspected fetal CoULD is complex, as some degree of prognostic uncertainty is unavoidable, even after exhaustive work including fetal exome sequencing is completed.

We could not accurately determine the gestation at which prenatal diagnosis occurred as we relied on parental recall of events after a variable time period had elapsed. Some conditions cannot reasonably be expected to be identified on ultrasound, such as constriction ring sequences or syndactyly[20] and therefore postnatally diagnosed CoULDs should not necessarily be considered “missed” diagnoses. Our data does not allow for any specific conclusion regarding the sensitivity of prenatal ultrasound as pregnancies with a prenatal diagnosis of a CoULD may have ended in miscarriage, termination of pregnancy, or perinatal death and thus not be included in the AHDR. However, the prenatal diagnosis rate

in our paediatric cohort are considerably lower than reported from a large single centre prenatal study that reported sensitivities of 19.1% for polydactyly, 76% for clenched hands/overlapping digits, and 76% for limb reduction defects involving the long bones.[21] This difference may be due to ascertainment bias (severe, non-isolated fetal CoULD not being captured in a paediatric cohort), differences in ultrasound expertise (single centre tertiary fetal medicine unit versus general radiology practices), and other factors such as maternal body habitus and local ultrasound protocols.

The range of CoULDs represented in the AHDR reflects our postnatal ascertainment through tertiary hospital clinics. The high number of children with unilateral CoULDs in our cohort reflects the better prognosis for isolated lesions compared with bilateral anomalies.[22] In a prenatal setting, approximately 60% of fetal CoULDs involving the forearm are associated with aneuploidy (such as trisomy 18 or trisomy 13), or a single gene condition (e.g. thrombocytopenia-absent radius syndrome).[22] These syndromal associations are significantly higher in the presence of bilateral forearm anomalies, and is the likely reason for the relatively low representation of bilateral conditions and syndromal diagnoses in our paediatric referral cohort.

Notwithstanding the unavoidable ascertainment bias, the questionnaire captured fewer children with a syndromal diagnosis than previously reported in a population study of children with CoULDs (8.4% vs 15%).[16] Age at enrolment of children with syndromes in the present study was significantly older than those without a syndromic diagnosis, hence it may be that some syndromes remain undiagnosed at the time of enrolment. Similarly, decisions to continue a pregnancy following a prenatal syndromic diagnosis may have changed over time. Additionally, in the Western Australian study by Giele et al,[2] 90 babies with a CoULD (18% of cases) died after birth and before age 6, 91% of whom had other congenital anomalies (56% with syndromes). This study is unable to assess the effect of pre- or post-partum death that may result from syndromes.

The challenges in establishing a national register of this kind are mainly related to ethics (consent), governance across the many sites involved and maintaining engagement of the recruited families. These have been addressed and the AHDR is now increasing the number of recruitment sites. The standardised approach to collecting data ensures its high quality

and usefulness. It has been important to have regular engagement with AHDR registrants through newsletters providing aggregated data and requests for additional participation in research.[23] For the successful running and sustainability of such a register, consumer input into research ideas and feedback on results obtained is important.

The response rate of 43% to this multi-centre register, which requires patient input and consent to maintain re-identifiable data, is not optimal, but compares favourably to similar population-based, opt-in registries that often receive fewer responses compared to procedural or pathological data registries where data is harvested from existing sources. No pattern of diagnosis or ethnicity/cultural difference exist in preliminary analyses of those not completing the questionnaire.

Examining details of the diagnostic journey for families affected by CoULDs is important for improving care, as previous studies have identified deficiencies in emotional support for families receiving diagnoses of a congenital limb difference.[24] Our questionnaire included open-ended questions enquiring about the experience of families at the time of diagnosis: what information was provided, what would have been helpful and what supports were available. While not presented here, these responses will provide a springboard for further prospective qualitative studies investigating parental and their children's perceptions and experiences, with a view to improve patient and family-centred care. The participants of AHDR offer an opportunity for longer-term cohort outcome studies to monitor global hand function as well as general physical, social and mental health outcomes. In coming years, a more in-depth analysis of more questionnaire responses may be undertaken to evaluate trends in prenatal exposures, maternal conditions and socioeconomic status.

Conclusions

The first three years of the AHDR has achieved national participation with gradually increasing interstate uptake, building a cohort of families with a range of CoULD types similar to other paediatric population-based studies. The AHDR provides insight into demographic data of families affected by hand differences and will allow further research in this population. Only 1 in 5 children had a prenatal diagnosis of a CoULD, which could pose a

challenge for timely counselling of families, especially where a child has a severe or syndromal CoULD. Quantitative and qualitative information regarding the timing of diagnosis and parental experiences could identify areas for improvement in prenatal and postnatal communication, support, and referral. Improving national participation in the register will bolster the effort and contribute to improvement in health care for families and children.

Brief Points:

What is already known on this topic

1. Low birth prevalence and clinical heterogeneity of children with congenital upper limb differences make evaluation of long-term outcomes difficult.
2. Emotional and multidisciplinary support around the time of diagnosis can be improved.
3. Clinical registries are a powerful tool for improving health care.

What this paper adds

1. Only 1 in 5 children of AHDR questionnaire respondents received a prenatal diagnosis of their upper limb difference.
2. The AHDR provides a standardised national database of children and families affected by CoULDs and opportunities for further research.

References

1. Schwabe GC, Mundlos S. Genetics of congenital hand anomalies. Handchir Mikrochir Plast Chir. 2004;36(3):85-97.

2. Giele H, Giele C, Bower C, Allison M. The incidence and epidemiology of congenital upper limb anomalies: a total population study. J Hand Surg Am. 2001;26(4):628-34.

3. Koskimies E, Lindfors N, Gissler M, Peltonen J, Nietosvaara Y. Congenital upper limb deficiencies and associated malformations in Finland: a population-based study. J Hand Surg Am. 2011;36(6):1058-65.

4. Ekblom AG, Laurell T, Arner M. Epidemiology of congenital upper limb anomalies in Stockholm, Sweden, 1997 to 2007: application of the Oberg, Manske, and Tonkin classification. J Hand Surg Am. 2014;39(2):237-48.

5. Goldfarb CA, Shaw N, Steffen JA, Wall LB. The prevalence of congenital hand and upper extremity anomalies based upon the New York Congenital Malformations Registry. J Pediatr Orthop. 2017;37(2):144-8.

6. Andrews EE, Williams JL, VandeCreek L, Allen JB. Experiences of parents of children with congenital limb differences with health care providers: a qualitative study. Rehabil Psychol. 2009;54(2):217-21.

7. Piper SL, Dicke JM, Wall LB, Shen TS, Goldfarb CA. Prenatal detection of upper limb differences with obstetric ultrasound. J Hand Surg Am. 2015;40(7):1310-7 e3.

8. McCombe DB, Coombs CJ. The Australian hand difference register: sharing clinical experience. Australas J Plast Surg. 2018;1(2):19-20.

9. Goldfarb CA, Ezaki M, Wall LB, Lam WL, Oberg KC. The Oberg-Manske-Tonkin (OMT) classification of congenital upper extremities: update for 2020. J Hand Surg Am. 2020;45(6):542-7.

10. Tonkin MA, Oberg KC. The OMT classification of congenital anomalies of the hand and upper limb. Hand Surg. 2015;20(3):336-342.

11. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.

12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

13. Swanson AB. A classification for congenital limb malformations. J Hand Surg Am. 1976;1(1):8-22.

14. Stoll C, Dott B, Alembik Y, Roth MP. Associated congenital anomalies among cases with Down syndrome. Eur J Med Genet. 2015;58(12):674-80.

15. Al Shehhi M, Forman EB, Fitzgerald JE, et al. NRXN1 deletion syndrome; phenotypic and penetrance data from 34 families. Eur J Med Genet. 2019;62(3):204-9.

16. Goldfarb CA, Wall LB, Bohn DC, Moen P, Van Heest AE. Epidemiology of congenital upper limb anomalies in a midwest United States population: an assessment using the Oberg, Manske, and Tonkin classification. J Hand Surg Am. 2015;40(1):127-32 e1-2.

17. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prenatal assessment of fetal structural conditions (C-Obs-60) [Internet]. East Melbourne (AU): The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; 2018 May [cited 2021 Mar 29]. 17 p. Available from https://ranzcog.edu.au/statements-guidelines/obstetrics/prenatal-assessment-of-fetal-structural-conditions.

18. Edwards L, Hui L. First and second trimester screening for fetal structural anomalies. Semin Fetal Neonatal Med; 2018;23(2):102-111.

19. Lord J, McMullan DJ, Eberhardt RY, Rinck G, Hamilton SJ, Quinlan-Jones E, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. Lancet. 2019;393(10173):747-57.

20. Gray BL, Calfee RP, Dicke JM, Steffen J, Goldfarb CA. The utility of prenatal ultrasound as a screening tool for upper extremity congenital anomalies. J Hand Surg Am. 2013;38(11):2106-11.

21. Dicke JM, Piper SL, Goldfarb CA. The utility of ultrasound for the detection of fetal limb abnormalities–a 20-year single-center experience. Prenat Diagn. 2015;35(4):348-53.

22. Pajkrt E, Cicero S, Griffin DR, van Maarle MC, Chitty LS. Fetal forearm anomalies: prenatal diagnosis, associations and management strategy. Prenat Diagn. 2012;32(11):1084-93.

23. McDougall L, Kennedy J, Coombs C, Penington A. The psychosocial impact of congenital hand and upper limb differences on children: a qualitative study. J Hand Surg Eur Vol. 2020;46(4):391-7.

24. Campbell T, Chen CJ, Chhina H, Chahal R, Cooper A, Elliott AM. Support, information, and integration of genetics for children with congenital lower limb deficiencies in British Columbia, Canada. Paediatr Child Health. 2019;24(6):395-401.

Tables

Table 1. Basic demographics of those who completed the questionnaire and those who did not

Variable	**Non-responder (n=419)**	**Responder (n=320)**	***p*-value**
Age at registration, years (95% CI)	4.7 (4.2 - 5.2)	5.3 (4.8 - 5.9)	NS
Male, %	57.1	55.3	NS
Unilateral CoULD, %	64.7	66.2	NS
Right sided CoULD, %	45.8	43.8	NS

NS, non-significant

Table 2. Key perinatal data

Variable	**Number (n=320)**
Child sex	
Male (%)	177 (55.3)
Female (%)	143 (44.7)
Gestational age at birth, weeks (median [range])	39 (26 – 42)
<37 weeks (%)	43 (13.4)
37-41 weeks (%)	232 (72.5)
≥42 weeks (%)	11 (3.4)
Unknown (%)	34 (10.6)
Birth weight, grams (median [range])	3230 (820 – 5670)
Plurality	
Singleton (%)	282 (88.1)
Multiple (%)	15 (4.7)
Unknown (%)	23 (7.2)
Parental age	
Maternal age at birth, years (median [range])	32 (18 – 44)
Paternal age at birth, years (median [range])	34 (20 – 52)

Table 3. Location of birth

Location of birth	**Number (%)**
Australian Capital Territory	5 (1.6)
New South Wales	26 (8.1)
Northern Territory	3 (0.9)
Queensland	32 (10.0)
South Australia	9 (2.8)
Tasmania	9 (2.8)
Victoria	215 (67.2)
Western Australia	4 (1.3)
Born overseas	17 (5.3)

Table 4. Distribution of major CoULDs diagnosed prenatally and postnatally in infants who underwent ultrasound, according to OMT[9] classification† (n=276)

Type and subtype	**Prenatally diagnosed CoULD cases, n (%)**	**Postnatally diagnosed CoULD cases, n (%)**	**Proportion diagnosed prenatally (%)**
I. Malformations	Total 42 (80.8)	Total 168 (75.0)	20.0
A. Entire upper limb: abnormal axis formation			
1. Proximodistal axis	5	5	50.0
2. Radioulnar axis	3	19	14.3
3. Dorsoventral axis	0	0	NA
4. Unspecified axis	0	0	NA
B. Hand plate: abnormal axis formation			
1. Proximodistal axis (e.g. brachydactyly, symbrachydactyly, ectrodactyly, cleft hand)	12	33	26.7
2. Radioulnar axis (e.g. hypoplastic thumb, radial and ulnar polydactyly)	15	73	17.0
3. Dorsoventral axis	0	0	NA
4. Unspecified axis (e.g. Apert hand)	7	38	15.6
II. Deformations	Total 5 (9.6)	Total 8 (3.6)	38.5
A. Constriction ring sequence	4	7	36.4
B. Not otherwise specified	1	1	50.0
III. Dysplasias	Total 4 (7.7)	Total 46 (20.5)	8.0
A. Variant growth			
1. Diffuse	0	1	NA
2. Isolated	0	2	NA
B. Tumour conditions			

1. Vascular	0	1	NA
2. Neurological	0	0	NA
3. Connective tissue	0	1	NA
4. Skeletal	0	3	NA
C. Congenital contracture			
i. Arthrogryposis	3	15	16.7
ii. Isolated	1	23	4.2
Unable to classify	Total 1 (1.9)	Total 2 (0.9)	33.3
TOTAL	**52 (100)**	**224 (100)**	

† Where participants had more than one diagnosis, the most physically prominent and non-syndromic diagnosis was identified and included. Where only a syndromic diagnosis was provided by the consulting paediatrician, the following major limb diagnoses were assumed: cleft hand for four children with ectrodactyly-ectodermal dysplasia-clefting syndrome; radial longitudinal deficiency, hypoplastic thumb for one with Holt-Oram syndrome; and Apert hand for two with Apert syndrome.

NA, not applicable

Table 5. Distribution of major CoULDs diagnosed prenatally and postnatally in infants who underwent ultrasound, according to Swanson[13] classification† (n=276)

Type	Prenatally diagnosed CoULD cases, n (%)	Postnatally diagnosed CoULD cases, n (%)	Total, n (%)	Proportion diagnosed prenatally (%)
I. Failure of formation of parts (arrest of development)	15 (28.8)	48 (21.4)	63 (22.8)	23.8
II. Failure of differentiation (separation) of parts	7 (13.5)	60 (26.8)	67 (24.3)	10.4
III. Duplication	12 (23.1)	55 (24.6)	67 (24.3)	17.9
IV. Overgrowth	0 (0.0)	3 (1.3)	3 (1.1)	0
V. Undergrowth	10 (19.2)	29 (12.9)	39 (14.1)	25.6
VI. Congenital constriction band syndrome	4 (7.7)	7 (3.1)	11 (4.0)	36.4
VII. Generalised skeletal abnormalities	3 (5.8)	15 (6.7)	18 (6.5)	16.7
Unable to classify	1 (1.9)	7‡ (3.1)	8 (1.9)	12.5
TOTAL	**52 (100)**	**224 (100)**	**276 (100)**	**18.8 (100)**

† Where participants had more than one diagnosis, the most physically prominent and non-syndromic diagnosis was identified and included as the major limb diagnosis.

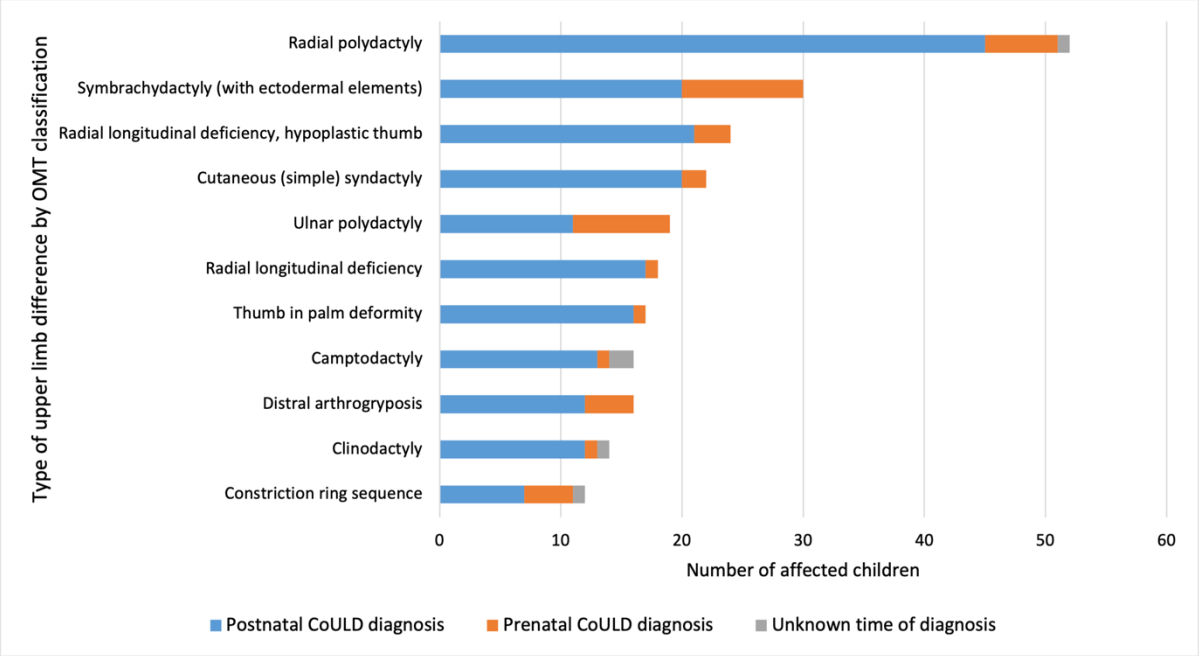
‡ Includes 5 cases of "tumorous condition" as per OMT classification e.g. vascular malformation, osteochondramatosis, enchondromatosis.

Table 6. Syndromal diagnoses among questionnaire participants and time at which upper limb difference was diagnosed (n=27)

OMT Code	Syndrome	Total, n	Prenatal diagnosis, n	Postnatal diagnosis, n	Unknown, n
IV-A-2	Apert Syndrome	3	2	1	
IV-A-12	Down (Trisomy 21)	1	1		
IV-A-13	Ectrodactyly-Ectodermal Dysplasia-Clefting Syndrome	4		4	
IV-A-17	Goltz Syndrome	1		1	
IV-A-19	Greig Cephalopolysyndactyly Syndrome	2	2		
IV-A-21	Hemifacial Microsomia (Goldenhar Syndrome)	1		1	
IV-A-22	Holt-Oram Syndrome	4		3	1
IV-A-38	Poland Anomaly	5	1	4	
IV-A-50	VACTERL Association	5	1	4	
IV-B	Other syndromes	1		1	

Figures

Figure 1. Most common CoULDs classified by OMT[9] system and distributed by timing of diagnosis, where ≥10 children were affected.



Prenatal and Postnatal Diagnosis of Congenital Upper Limb Differences: The First 3 Years of the Australian Hand Difference Register

Running title: The Australian Hand Difference Register

Original article

Dr David O'Keefe[1], Ms Joanne Kennedy[2,4], A/Prof David McCombe[2,3,4], Prof Chris Coombs[2,3,4], A/Prof Lisa Hui[1,2,5], Mr Daniel Wilks[2,3,4], Prof Jane Halliday[2,4]

[1] Mercy Hospital for Women, Melbourne, Australia

[2] Murdoch Children's Research Institute, Melbourne, Australia

[3] Department of Plastic & Maxillofacial Surgery, The Royal Children's Hospital, Melbourne, Australia

[4] Department of Paediatrics, The University of Melbourne, Australia

[5] Department of Obstetrics & Gynaecology, The University of Melbourne, Australia

Corresponding author:
Dr Daniel Wilks
The Royal Children's Hospital
50 Flemington Rd, Parkville VIC 3052 Australia
E: Daniel.Wilks@rch.org.au **P:** +61 (3) 9345 5522

Acknowledgements: Thank you to Aussie Hands for engaging families and supporting the development of the register. We acknowledge our funders, The Aussie Hands Foundation Incorporated, McNally Family Foundation and Australasian Foundation for Plastic Surgery. LH was funded by a University of Melbourne Faculty of Medicine, Dentistry and Health Sciences Research Fellowship (2020), and a Medical Research Future Fund Emerging Leader fellowship (2021-2025).

Conflicts of interest: the authors declare no conflicts of interest.

Key words: congenital anomaly; upper extremity; prenatal diagnosis; hand; registries