Limb Abnormalities and Reduction Defects: Sequence Analysis and Exon-Level Deletion/Duplication Testing of 71 Genes

Panel Gene List:

*ANKRD11, ARHGAP31, ARID1A, ARID1B, BHLHA9, BMP2, BMPR1B, CC2D2A, CDH3, CEP290, CHSY1,DLL4, DLX5, DOCK6, DVL1, DVL3, **DYNC1I1, EOGT, ESCO2, FGF10, FGF16, FGFR1, FGFR2, FGFR3, GDF5, GLI3, GNAS, HDAC4, HDAC8, HOXD13, IHH, KIF7, KMT2A, LMBR1* (including *ZRS* regulatory region), *LRP4, MGP, MKS1, MYCN, NIPBL, NOG, NOTCH1, NSDHL, PHF6, PIGV, PTHLH, RAD21, RBPJ, RECQL4, RBM8A, ROR2, RPGRIP1L, SALL1, SALL4, SHH, SMARCA2, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SOX11, SOX9, TBX15, TBX3, TBX5, THPO, TP63, WNT10B, WNT3, WNT5A, WNT7A* and deletion/duplication coverage for 10q24.

**deletion/duplication only

Comprehensive Testing Options		
Test Code	**Test Description**	**Genes**
TA42	Limb Abnormalities and Reduction Defects	See above
Syndromic or Specific Testing Options *Testing includes sequencing plus deletion/duplication testing of genes listed as described within the Limb Abnormalities and Reduction Defects Test option.*		
Test Code	**Test Description**	**Genes**
TA46	Adams-Oliver Syndrome	*ARHGAP31, DLL4, DOCK6, EOGT, NOTCH1, RBPJ*
T993	Coffin-Siris Syndrome	*ARID1A, ARID1B, PHF6, SMARCA2, SMARCA4, SMARCB1, SMARCE1, SOX11*
584	Cornelia de Lange Syndrome	*ANKRD11, HDAC8, KMT2A, NIPBL, RAD21, SMC1A, SMC3*
TA39	Robinow Syndrome	*DVL1, DVL3, ROR2, WNT5A*
TA41	Split-Hand/Split Foot Malformations	*BHLHA9, CDH3, DLX5, DYNC1I1, FGFR1,TP63, WNT10B* including expanded deletion/duplication testing for chromosomal region 10q24

Clinical Features:

Limb abnormalities and reduction defects are a broad category of genetically heterogeneous syndromic and non-syndromic skeletal disorders. Pathogenic variants in the tested genes

cause a variety of limb malformations and reduction defects that range from complete absence of all four limbs to mild phalangeal abnormalities.

Syndromic Limb Abnormalities

Adams-Oliver Syndrome
(*ARHGAP31*, *DLL4*, *DOCK6*, *EOGT*, *NOTCH1*, and *RBPJ* genes)[1,2,3,4,5,6,7,8]
Adams-Oliver syndrome (AOS) is estimated to occur in approximately 4 per 1,000,000 live births. Affected individuals present with aplasia cutis congenita of the scalp and terminal transverse limb defects primarily affecting the lower extremites more severely than upper. Observed limb defects range from unilateral or bilateral short distal phalanges to complete absence of toes, fingers, feet or hands. Less common clinical features include cardiovascular (23%), neurological (~30% in autosomal recessive kindreds), renal (<5%), and opthalmologic abnormalities (<10%)[1,2] as well as cutis marmorata telangiectatica congenita (~20%). Autosomal dominant Adams-Oliver syndrome is associated with pathogenic variants in the *ARHGAP31, DLL4, NOTCH1,* and *RBPJ* genes. Autosomal recessive Adams-Oliver syndrome is associated with the *DOCK6* and *EOGT* genes[2].

Coffin-Siris Syndrome
(*ARID1A, ARID1B, PHF6, SMARCA2, SMARCA4, SMARCB1, SMARCE1*, and *SOX11* genes)[9,10,11,12,13]
Coffin-Siris syndrome (CSS) is classically characterized by aplasia or hypoplasia of the distal phalanx or the nail of the fifth digit, developmental delays, dysmorphic facial features, hypotonia, hirsutism/hypertrichosis, and sparse scalp hair. Congenital cardiac anomalies or renal and genitourinary malformations have been observed in ~35% of cases. Other common findings include feeding difficulties, poor growth, ophthalmologic abnormalities and hearing impairment. CSS is most commonly caused by de novo pathogenic variants in one of the eight genes: *ARID1A, ARID1B, PHF6, SMARCA2, SMARCA4, SMARCB1, SMARCE1*, and *SOX11*. However, individuals with *SMARCA2* or *PHF6* may have phenotypes more consistent with Nicolaides-Baraitser syndrome or Borjeson-Forssman-Lehmann syndrome, respectively[9].

Cornelia de Lange Syndrome
(ANKRD11, HDAC8, KMT2A, NIPBL, RAD21, SMC1A and SMC3 genes)[14,15,16,17,18]
Cornelia de Lange syndrome (CdLS) is a pan-ethnic disorder characterized by pre-and postnatal growth retardation and various congenital anomalies. Distinct craniofacial dysmorphisms include microbrachycephaly, synophrys, long eyelashes, long philtrum, thin upper lip, downturned mouth and small upturned nasal tip. Limb anomalies range from oligodactyly and small hands to absence of forearm. Gastrointestinal disorders and hirsutism are also common. Intellectual disability varies greatly, with an average IQ of 531. Less common features include psychomotor retardation, high arched palate with cleft, autism-like

behavior, self-injurious behaviors, speech impairment, sensorineural hearing loss, and ophthalmological, genito-urinary (cryptorchidism) and heart anomalies[14]. CdLS is estimated to occur in 1 in 10,000 to 1 in 100,000 individuals and presents in mild to severe forms with variable expressivity[15]. Pathogenic variants in six genes: *ANKRD11, HDAC8, KMT2A, NIPBL, RAD21, SMC1A*, and *SMC3* have been identified in patients with clinical features of CdLS[15,16,17,18].

Robinow Syndrome
(*DVL1, DVL3, ROR2*, and *WNT5A* genes)[19,20,21]
Robinow syndrome is characterized by distinct dysmorphic craniofacial features resembling a fetal face, skeletal features including short stature, acromesomelic or mesomelic limb shortening predominantly affecting the upper libs as well as brachydactyly, and genital abnormalities in males: micropenis/webbed penis, hypoplastic scrotum, cryptorchidism; in females: hypoplastic clitoris and labia majora. Growth retardation, dental abnormalities, bilobed tongue, prenatal macrocephaly, and postnatal microcephaly have also been reported as common features. Less common findings include renal abnormalities, radial head dislocation, vertebral anomalies, nail dysplasia, cardiac defects, cleft lip/palate and rarely cognitive delay. Milder autosomal dominant Robinow results from pathogenic variants in *DVL1*, *DVL3* or *WNT5A*[19,21], while autosomal recessive Robinow syndrome is caused by variants in the *ROR2* gene[20]. A variant of Robinow syndrome associated with osteosclerosis, normal stature, persistent macrocephaly, increased bone mineral density and hearing loss is also associated with heterozygous variants in *DVL1*[19].

Ciliopathies
(CC2D2A, CEP290, KIF7, MKS1, and RPGRIP1L genes)[22]
Ciliopathies comprise a group of disorders associated with abnormal formation or function of the cilia. Ciliary dysfunction can manifest as a constellation of features that include primary retinal degeneration, renal disease and cerebral anomalies. Skeletal dysplasia and polydactyly are common features in some ciliopathies, specifically those caused by pathogenic variants in the CC2D2A, CEP290, KIF7, MKS1, and RPGRIP1L genes[22]. Given the wide phenotypic variability in ciliopathies, we offer a Comprehensive Ciliopathy Test (https://www.genedx.com/test-catalog/available-tests/joubert-syndrome-and-related-disorders-panel/) for patients with clinical indications suggestive of this disorder.

Other syndromic limb abnormalities with limited genetic heterogeneity include Wolff-Parkinson-White syndrome (BMP2 gene)[35], Cousin syndrome (TBX15 gene)[23, 24], Al-Awadi-Raas-Rothschild syndrome (WNT7A gene)[25,26], Feingold syndrome (MYCN gene)[27,28], Robert's syndrome (ESCO2 gene)[29], Townes-Brocks syndrome (SALL1 gene)[30], Duane-radial ray syndrome (SALL4 gene)[31], Holt-Oram syndrome (TBX5 gene)[32], Lacrimo-auriculo-dental-digital syndrome (FGF10, FGFR2, FGFR3)[33,34,35], Cenani-Lenz syndrome (LRP4)[36], Keutel

syndrome (MGP)[37], CHILD syndrome (NSDHL)[38], Mabry syndrome (PIGV)[39], Rothmund-Thomson/RAPADILINO syndrome (RECQL4)[40,41], Ulnar-mammary syndrome (TBX3)[42], and multiple syndromes associated with pathogenic variants in the TP63 gene[43], and Thrombocytopenioa with Absent Radii (TAR) syndrome (RBM8A gene).[76]

Non-Syndromic limb abnormalities

Ectrodactyly or split hand/split foot malformations (SHSF) are unique to *BHLHA9, CDH3, DLX5, DYNC1I1, FGFR1, TP63,* and *WNT10B* variants[43-50, 53]. Non-syndromic or isolated SHSF malformations caused primarily by sequence variants involve the *TP63, CDH3*, and *FGFR1* genes[43,47,48,53]. Sequence variants as well as small copy number variants in *WNT10B* and *DLX5*, inherited in an autosomal recessive manner, have been reported to cause non-syndromic SHSF in multiple unrelated individuals[46,49]. Isolated split-hand/foot malformations may be associated with copy-number variations at 17p13.3 involving *BHLHA9*[44,45], at 7q21.3 involving *DYNC1I1*[50], and at chromosome 10q24[52]. Rare chromosomal abnormalities involving 2q31, 3q27, 17.q25, Xq26 and other loci have also been reported [44,45,50,51,52].

Other non-syndromic limb abnormalities and reduction defects include conditions such as non-syndromic syndactylies and polydactylies caused by pathogenic variants in *LRP4, HOXD13*, and *GLI3*[55-58]. Syndromic and non-syndromic brachydactyly is seen in patients with pathogenic variants in *BMPR1B, CHSY1, GDF5, HDAC4, IHH, NOG, PTHLH,* and *SOX9*[59-69]. Other limb abnormalities include metacarpal 4/5 fusion, reported to be caused by pathogenic variants in *FGF16*[70], Madelung deformity associated with pathogenic variants in *GNAS*[71], tetra-amelia caused by pathogenic variants in *WNT3*[72], and congenital transverse limb defects caused by pathogenic variants in *THPO*[73].

Pre-axial polydactyly and triphalangeal thumbs can be seen in patients with pathogenic variants in the *SHH* genes or its' regulatory element, the ZRS region of the *LMBR1* gene[74].

Because of the significant clinical overlap and phenotypic heterogeneity of disorders causing limb abnormalities and reduction defects, it can be difficult to make a clinical diagnosis. Additionally, variants in a single gene may be associated with a broad spectrum of clinical presentations (clinical heterogeneity). Therefore, testing of multiple genes is very useful in helping to establish the etiology of syndromic and non-syndromic limb malformations and reduction defects. A complete list of test offerings based on clinical presentations and additional gene information related to the disorders involving limb malformations and reduction defects are available below.

Inheritance Pattern/Genetics:

Autosomal dominant (AD), autosomal recessive (AR), and X-linked inheritance (XL).

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. For the DYCN1I1 gene and a 500kb region in 10q24 (chr10:102,962,134–103,476,346), copy number but not sequencing analysis is performed. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: FGF10 gene, only whole gene deletions or duplications may be detected.

Test Sensitivity:
Limb abnormalities and reduction defects are a genetically heterogeneous group of disorders with a wide variant spectrum. The clinical sensitivity of sequence and deletion/duplication analysis of the genes included in this panel depends on the clinical phenotype of the patient. Additional sensitivity information is available in the table below.

Clinical Sensitivity of Genes Associated with Limb Abnormalities & Reduction Defects:

Disorder(s)	Gene	Inh.	Diagnostic Yield for Disorder
Cornelia de Lange syndrome; KBG syndrome; Schizophrenia; Intellectual disability; Heart disease; Seizure; Autism spectrum disorder; KBG-like syndrome; Bile-duct dilatation; 16q24.3 microdeletion syndrome	*ANKRD11*	AD	Unknown

Disorder(s)	Gene	Inh.	Diagnostic Yield for Disorder
Adams-Oliver syndrome; Syndrome cutis aplasia and limb anomalies	*ARHGAP31*	AD	<5%[2]
Coffin-Siris syndrome; Intellectual disability and hexadactyly	*ARID1A*	AD	5%[8]
Coffin-Siris syndrome; Autism spectrum disorder; Intellectual disability; Short stature, non-syndromic; Schizophrenia; Corpus callosum abnormalities; Intellectual disability, plantar fat pads & facial dysmorphism; Nicolaides-Baraitser syndrome; Hirschsprung disease; Hypertrichosis; Limb anomalies and hearing loss	*ARID1B*	AD	37%[8]
Mesoaxial synostotic syndrome, Malik-Percin type; Split hand/foot malformation with long-bone deficiency	*BHLHA9*	AR	Unknown
Wolff-Parkinson-White syndrome; Orofacial cleft palate; Brachydactyly type A2	*BMP2*	AD	Unknown
Acromesomelic Chondrodysplasia, Grebe type; Brachydactyly type A2; Brachydactyly type A1; Chondrodysplasia, du Pan type	*BMPR1B*	AD AR	Unknown
Joubert syndrome; Meckel syndrome; Meckel-Gruber syndrome; Nephronophthisis-related ciliopathy; Mental retardation with retinitis pigmentosa	*CC2D2A*	AR	Unknown
Ectodermal dysplasia, ectrodactyly and macular dystrophy syndrome; Hypotrichosis with juvenile macular dystrophy; Retinitis pigmentosa, autosomal recessive; Increased promoter activity; Hypotrichosis, autosomal recessive	*CDH3*	AD	Unknown
Leber congenital amaurosis; Joubert syndrome, Senior-Loken type; Retinal disease; Schizophrenia; Cone-rod dystrophy; Nephronophthisis-related ciliopathy; Retinitis pigmentosa; Meckel syndrome; Bardet-Biedl syndrome; Meckel-Gruber syndrome; Intellectual disability; Heterotaxy	*CEP290*	AR	Unknown
Temtamy preaxial brachydactyly syndrome	*CHSY1*	AR	Unknown
Adams-Oliver syndrome; Schizophrenia; Multiple congenital anomalies	*DLL4*	AD	~9.9%[4]
Split hand/foot malformation; Pierre Robin sequence; Split hand/foot malformation with Mondini dysplasia	*DLX5*	AD	Unknown

Disorder(s)	Gene	Inh.	Diagnostic Yield for Disorder
Robinow syndrome, autosomal dominant; Robinow syndrome, osteosclerotic; Neural tube defects; Schizophrenia; Ventricular septal defect and pulmonary hypertension	*DVL1*	AD	Unknown
Robinow syndrome, autosomal dominant	*DVL3*	AD	Unknown
Adams-Oliver syndrome	*DOCK6*	AR	~17%[4]
Split hand/foot malformation	*DYNC1I1*	AD	Del/dup only, Unknown
Adams-Oliver syndrome	*EOGT*	AR	<10%[1]
Roberts syndrome; SC phocomelia syndrome	*ESCO2*	AR	100% for Roberts syndrome[29]
Aplasia of lacrimal and salivary glands; Lacrimo-auriculo-dento-digital syndrome; Extreme myopia, increased risk; Orofacial clefting; Tetralogy of Fallot	*FGF10*	AD	Unknown
Metacarpal 4/5 fusion	*FGF16*	XL	Unknown
Hypogonadotropic hypogonadism with split hand/foot malformation; Kallmann syndrome; Congenital anomalies of the kidney and urinary tract; Hartsfield syndrome; Holoprosencephaly, lobar; Pfeiffer syndrome; Hypothalamic amenorrhea; Non-syndromic trigonocephaly; Osteoglophonic dysplasia; Septic-optic dysplasia; Solitary median maxillary central incisor and pyriform aperture stenosis; Combined pituitary hormone deficiency	*FGFR1*	AD	Unknown
Lacrimo-auriculo-dento-digital syndrome; Ectrodactyly and acinar dysplasia; Crouzon syndrome; Cleft lip and palate; Craniosynostosis; Apert syndrome; Pfeiffer syndrome; Jackson-Weiss syndrome; Beare-Stevenson cutis gyrata syndrome; Bent bone dysplasia;Congenital anomalies of the kidney and urinary tract; Saethre-Chotzen syndrome; Renal agenesis; Scaphocephaly; Disorder of sexual development	*FGFR2*	AD AR	Unkown
Acromesomelic Chondrodysplasia, Grebe type; Acromesomelic dysplasia, Hunter-Thompson type; Brachydactyly, type A1, C; Du Pan syndrome; Proximal symphalangism 1B;	*GDF5*	AR	Unknown

Disorder(s)	Gene	Inh.	Diagnostic Yield for Disorder
Brachydactyly, type A1, C; Brachydactyly type A2; Brachydactyly type C; Multiple synostoses syndrome, type 2	*GDF5*	AD	Unknown
Greig cephalopolysyndactyly syndrome; Pallister-Hall syndrome; Sub-Greig cephalopolysyndactyly syndrome; Sub-Pallister-Hall syndrome; Oral-facial-digital syndrome	*GLI3*	AD	~15% (~2.5% for indidivuals with limb abnormalities, 29% of individuals with overlapping features[56,58])
Arcoscyphodysplasia; Albright hereditary osteodystrophy; Progressive osseous heteroplasia	*GNAS*	AD	Unknown
Brachydactyly type E; Craniofacial and skeletal abnormalities; Autism spectrum disorder	*HDAC4*	AD	Unknown
Cornelia de Lange syndrome 5	*HDAC8*	XLD	~4% of CdLS[15]
Limb malformation; Synpolydactyly	*HOXD13*	AD	~3% of congenital limb abrnomalities[58,75]
Brachydactyly type A1; Acrocallosal syndrome Acrocallosal syndrome; Pallister-Hall syndrome; Bardet-Biedl syndrome; Intellectual disability; Oral-facial-digital syndrome type VI / Bardet-Biedl syndrome; Meckel syndrome / hydrolethalus; Joubert syndrome; Hydrolethalus	*IHH* *KIF7*	AD AR	Unknown Unknown
Cornelia de Lange syndrome; Wiedemann-Steiner syndrome; Autism; West syndrome; High myopia; Epileptic encephalopathy with infantile spasms	*KMT2A*	AD	Unknown[16]
Acheiropody (AR); Hypoplastic or aplastic tibia with polydactyly; Laurin-Sandrow syndrome; Polydactyly, preaxial type II; Syndactyly, type IV; Triphalangeal thumb, type I; Triphalangeal thumb-polysyndactyly syndrome	*LMBR1** including ZRS regulatory region of *SHH*	AD AR	Unknown
Cenani-Lenz syndrome	*LRP4*	AR	Unknown
Keutel syndrome	*MGP*	AR	Unknown
Joubert syndrome; Cone-rod dystrophy; Parkinson disease, early onset; Meckel syndrome; Bardet-Biedl syndrome; Meckel-Gruber syndrome	*MKS1*	AR	Unknown

Disorder(s)	Gene	Inh.	Diagnostic Yield for Disorder
Feingold syndrome; Bilateral nephroblastomatosis; Neuroblastoma; Multiple congenital anomalies with bilateral Wilms tumor	*MYCN*	AD	Unknown
Cornelia de Lange syndrome 1	*NIPBL*	AD	~60% of CdLS[15]
Multiple synostoses syndrome; Tarsal-Carpal coalition syndrome stapes ankyloses with broad thumb and toes; Brachydactyly, type B2	*NOG*	AD	Unknown
Adams-Oliver syndrome; Bicuspid aortic valve; Left-ventricular outflow tract obstructions; Congenital heart disease; Aortic valve disease; Hypogonadotropic hypogonadism; Hypoplastic left heart syndrome; Aortic stenosis; Sudden infant death syndrome; Mental retardation, autosomal dominant; Epilepsy, infantile-onset; Tetralogy of Fallot	*NOTCH1*	AD	~23%[5,6]
CHILD syndrome	*NSDHL*	XL	Unknown
Coffin-Siris-like syndrome; Borjeson-Forssman-Lehmann syndrome; Intellectual disability; Neurological disease	*PHF6*	AD	5%[12]
Mabry syndrome	*PIGV*	AR	Unknown
Liebenberg syndrome; Clubfoot with or without deficiency of long bones	*PITX1*	AD	Unknown
Brachydactyly, type E	*PTHLH*	AD	Unknown
Cornelia de Lange syndrome 4	*RAD21*	AD	<1% CdLS[15]
Adams-Oliver syndrome; Proximal 4p deletion syndrome and epilepsy	*RBPJ*	AD	<10%[2,7]
Baller-Gerold syndrome; RAPADILINO syndrome; Rothmund-Thomson syndrome	*RECQL4*	AR	100% for BGS[40]. ~66% for RTS[41]
Thrombocytopenia-absent radius syndrome	*RBM8A*	AR	95%[77]
ROR2-Related Robinow syndrome	*ROR2*	AR	≥63% for *ROR2*-Related Robinow syndrome[19]
Brachydactyly, type B	*ROR2*	AD	Unknown

Disorder(s)	Gene	Inh.	Diagnostic Yield for Disorder
Meckel syndrome; Leber congenital amaurosis; Retinal degeneration in ciliopathies; Joubert syndrome; Bardet-Biedl syndrome; Meckel-Gruber syndrome; Retinitis pigmentosa; COACH syndrome	*RPGRIP1L*	AR	Unknown
Townes-Brocks syndrome; Townes-Brocks branchiootorenal-like syndrome	*SALL1*	AD	~75% for Townes-Brocks syndrome[30]
Duane-radial ray syndrome; IVIC syndrome; Holt-Oram syndrome, Okihiro syndrome	*SALL4*	AD	~90-95% for DDRS[31]
Nicolaides-Baraitser syndrome; Coffin-Siris syndrome; Severe intellectual disability, seizures, absent speech, rounded premaxilla & decreased subcutaneous fat; Schizophrenia, Multiple congenital anomalies	*SMARCA2*	AD	2%[9,10]
Coffin-Siris syndrome	*SMARCA4*	AD	7%[8]
Coffin-Siris syndrome; Nicolaides-Baraitser syndrome; Intellectual disability	*SMARCB1*	AD	7%[8]
Coffin-Siris syndrome; Multiple spinal meningiomas; Spinal clear cell meningiomas; Spinal/cranial clear cell meningiomas	*SMARCE1*	AD	2%[8]
Cornelia de Lange syndrome 2	*SMC1A*	XLD	~5% of CdLS[15]
Cornelia de Lange syndrome 3	*SMC3*	AD	1-2% of CdLS[15]
Acampomelic campomelic dysplasia (ACD); Campomelic dysplasia	*SOX9*	AD	~92% for Campomelic dysplasia[69]. 10% for sequence variants of ACD[69]
Coffin-Siris syndrome; Mental retardation, autosomal dominant	*SOX11*	AD	2%[11]
Ulnar-Mammary syndrome	*TBX3*	AR	Unknown
Holt-Oram syndrome; Ulnar-mammary syndrome	*TBX5*	AD	>70% for HOS[32]
Cousin syndrome	*TBX15*	AR	Unknown
Hereditary thrombocythemia; Congenital transverse limb defects	*THPO*	AD	Unknown

Disorder(s)	Gene	Inh.	Diagnostic Yield for Disorder
ADULT syndrome; Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3; Hay-Wells syndrome; Limb-mammary syndrome; Orofacial cleft 8; Rapp-Hodgkin syndrome; Split-hand/foot malformation 4	*TP63*	AD	~98% for EEC. ~10% for SHFM[43]
Tetra-amelia	*WNT3*	AR	Unknown
Robinow syndrome, autosomal dominant	*WNT5A*	AD	Unknown
Al-Awadi-Raas-Rothschild syndrome; Ulnar and fibula absence, with severe limb deficiency	*WNT7A*	AR	Unknown
Split hand/food malformation	*WNT10B*	AR	Unknown

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