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Polydactyly: How many disorders and how many genes: 2010 update

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Abstract

Limb development is clinically and biologically important. Polydactyly is common and caused by aberrant anterior-posterior patterning. Human disorders that include polydactyly are diverse. To facilitate an understanding of the biology of limb development, cataloging the genes that are mutated in patients with polydactyly would be useful. In 2002, I characterized human phenotypes that included polydactyly. Subsequently, many advances have occurred with refinement of clinical entities and identification of numerous genes. Here, I update human polydactyly entities by phenotype and mutated gene. This survey demonstrates phenotypes with overlapping manifestations, genetic heterogeneity, and distinct phenotypes generated from mutations in single genes. Among 310 clinical entities, 80 are associated with mutations in 99 genes. These results show that knowledge of limb patterning genetics is improving rapidly. Soon, we will have a comprehensive toolkit of genes important for limb development, which will lead to regenerative therapies for limb anomalies.

Keywords

malformations; genetic heterogeneity; medical diagnosis; pleiotropism

INTRODUCTION

Polydactyly results from defective patterning of the anterior-posterior axis of the developing limb and can occur as a simple or isolated malformation or as part of a pleiotropic developmental anomaly syndrome. Polydactyly is an important manifestation in clinical medicine not only because it has cosmetic and functional implications and often necessitates surgical treatment, but because it can serve as an immediately recognizable indicator that the patient, particularly a newborn, has a multiple congenital anomaly syndrome (pleiotropic developmental anomaly syndrome). For these reasons, it is important for the clinician to be prepared to evaluate the patient for polydactyly and consider the myriad syndromes that may be associated with this anomaly. In addition to the clinical manifestations, polydactyly can be considered by the scientist as an experiment of nature, in that the manifestation of this phenotype points to an underlying mutated gene or teratogen that is associated with a perturbation of the molecular machinery of limb development [Towers and Tickle 2009]. The elucidation of the etiologies of polydactyly can serve as a tool to facilitate the dissection of the genetic and signaling pathways that underlie polydactyly, specifically, that of anterior-posterior specification of the limb (for recent review, see [Butterfield et al., 2010]).

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Online sources: Mendelian Inheritance in Man: <http://www.ncbi.nlm.nih.gov/omim>

For both clinical utility and to facilitate basic science investigations, it is useful to catalog the phenotypes that include polydactyly as a manifestation. In 2002, I cataloged the entities recognized by geneticists in the clinic that included polydactyly as a manifestation [Biesecker 2002]. At that time, 97 clinical entities were listed, of which 37 were associated with mutations in one or more genes. Since that time, much progress has been made in molecular genetics of disease and it seemed appropriate to update this review*. In this article I will delineate the disorders that have been associated with polydactyly, delineate the genes that are altered in these disorders, and speculate on the future implications of these data.

Methods

To tabulate syndromic and isolated polydactyly clinical entities, I drew from several sources. First, Mendelian Inheritance in Man [Anon. 2010] was searched using the term “*polydactyl*”. Second, the Winter-Baraitser Medical Database (WBDD, Ref) was interrogated using the following terms: “postaxial polydactyly of fingers”, “postaxial polydactyly of toes”, “preaxial polydactyly of fingers”, “preaxial polydactyly of toes”, “meso-axial polydactyly of fingers”, “mesoaxial polydactyly of toes”, “palmar polydactyly”, “polydactyly/bifid thumb”, “polydactyly bifid hallux”, “mirror image polydactyly of fingers”, and “mirror image polydactyly of toes”. Third, the tabular listings of polydactyly in the appendix of Smith’s Recognizable Patterns of Malformation [Jones and Smith 2006] and Tables 21-1 – 21-7 of the chapter “Hands and Feet” in Human Malformations and Related Anomalies [Stevenson 2006], were reviewed. These lists were merged and duplicate entries were deleted, although, as will be noted in the discussion, this can be challenging. In contrast to the prior analysis, I included entities where only a single family or case was described. Some of these disorders must be considered as candidate polydactyly syndromes as it is possible in some cases that the association of polydactyly in these traits was coincidental. Many of these ultra rare or unique cases emanated from the Winter-Baraitser Dysmorphology Database. If a common malformation syndrome had a single case with polydactyly, that entity was deleted from this analysis, as it seemed more likely that it was coincidental, rather than causal. For rare malformation syndromes, it can be difficult to determine if a particular manifestation is uncommon or coincidental. In these cases, the entity was generally included in the listing. It can also be challenging to determine the boundaries of the descriptor of polydactyly itself. For example, broad thumbs or great toes are potentially mechanistically related to anterior-posterior patterning. There is a large degree of inter-individual variation in the width of these digits, arguing against inclusion of this finding as part of the spectrum of polydactyly. In contrast, in disorders with preaxial polydactyly (e.g., Greig cephalopolysyndactyly syndrome) a full spectrum of abnormalities are observed, including complete digit duplication, partial duplication, U shaped or forked distal phalanges, and broad digits, arguing for inclusion. In this review, I generally required frank polydactyly to be reported in the entity for it to be included. Next, entries that described polydactyly only in model organisms and entities that were associated with segmental aneuploidy (and not with a specific gene) or teratogens were deleted. This is not because these entities are unimportant for understanding limb development. Instead, this was done because the purpose of this review was to review the genes that contribute to polydactyly and it can be difficult to identify the gene products that are pathogenetically important in many teratogens and segmental aneuploidy syndromes. Entries that separately described a gene and a disorder (e.g., *GLI3* and Pallister-Hall syndrome) were reduced to a single clinical entry. In recent years, there has been evolution of the MIM database with regard to clinical and gene entries. For some disorders, MIM has consolidated the clinical

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*These data were presented at the 6th International Limb Development and Regeneration Conference in Williamsburg, Virginia, USA, July 16, 2010.

data into a single entry (e.g., Bardet-Biedl syndrome MIM 209900) with additional entries for the genes, and the gene entries have little or no clinical data. For other phenotypes, such as asphyxiating thoracic dystrophy (Jeune) and Meckel syndromes, there are multiple entries with genetic and clinical data. The general approach in this review was to treat clinically distinct phenotypes as single entities, independent of genotype [Robin and Biesecker 2001]. As is well known to clinical geneticists, it can be difficult to determine the boundaries that distinguish some clinical entities from overlapping disorders. For example, it can be challenging to clinically distinguish a mildly affected case of Jeune syndrome (MIM 208500) from Ellis-Van Creveld syndrome (MIM 225500). In addition, current standards of clinical data reporting and limitations of commonly used terminology limit the ability to finely parse the data in the clinical literature [Allanson et al., 2009; Biesecker 2005]. For this reason, it can be difficult to accurately determine the presence or absence of some malformations in clinical reports, much less to know the precise form of that manifestation – for example, whether a case of polydactyly was postaxial or central. As well, it can be difficult to distinguish entities that have both syndromic and non-syndromic manifestations, such as Greig Cephalopolysyndactyly syndrome (MIM 175700) and Crossed Polydactyly (MIM 174700), both of which can be caused by mutations in *GLI3* [Biesecker 2006]. In these cases, I generally deferred to the curators of MIM, WBDD, and the Stevenson et al textbook regarding the delineation of these entities. With respect to genes, this is generally straightforward to tabulate, with the exception of regulatory elements. Three entries were associated with such elements of the *SHH* and *SOX9* genes.

Results and Discussion

This resulting list comprised 310 entries of disorders that include polydactyly, including syndromic (290 entries) and nonsyndromic (20 entries) forms (Table I). This list is significantly larger than that from the 2002 review, primarily owing to the addition of the WBDD entities, improved curation, as well as general advances in medical knowledge. These 310 entities show a full range of Mendelian inheritance patterns, including autosomal dominant (73), autosomal recessive (103), X-linked (12), more than one inheritance pattern (9), but many had an unknown mode of inheritance (113).

Among the 310 entities, 80 have been associated with causative mutations in a total of 99 genes. This represents major progress, as the 2002 analysis identified only 39 entities associated with mutations. As before, these disorders illustrate another prominent feature, which is that of genocopies and pleiotropism. First, there are a number of entities that can be caused by mutations in more than one gene (genocopies). Among the entries with identified mutations, Fanconi anemia can be caused by homozygous or compound heterozygous mutations in one of 14 genes and Bardet-Biedl syndrome can be caused by mutations in at least 12 genes. These two disorders alone account for 26 of the 99 genes known to cause polydactyly when mutated. The remaining 308 entries are associated with mutations in 73 genes (note that *MKKS* is counted in both categories because distinct mutations in that gene can cause either McKusick-Kaufman syndrome or Bardet-Biedl syndrome). These 73 genes are associated with 95 distinct clinical entities, which is an expression of the concept of pleiotropy. A major culprit in this pleiotropy is the *GLI3* transcription factor gene, which can be attributed to five phenotypes [Elson et al., 2002; Kang et al., 1997; Radhakrishna et al., 1999; Radhakrishna et al., 1997; Vortkamp et al., 1991]. In the 2002 review, there were three genes associated with two phenotypes each: *MKKS*, *EVC*, and *DHCR7* [Cormier-Daire et al., 1996; Katsanis et al., 2000; Ruiz-Perez et al., 2000; Slavotinek et al., 2000; Stone et al., 2000; Wassif et al., 1998]. At the time of the present analysis, the Rutledge lethal multiple congenital anomaly syndrome, associated with *DHCR7* mutations, has been collapsed into Smith-Lemli-Opitz syndrome because it was determined that the two, previously considered distinct entities, actually formed a continuous spectrum of phenotype.

As of the present review, there are 15 sets of multiple phenotypic entities that have been shown to be caused by mutations in a single gene (Table II).

These results illustrate a number of important principles of clinical medicine, medical diagnosis, and the taxonomy of disease. The boundaries that delineate and demarcate disorders from other disorders can be difficult to determine. Essentially all human pleiotropic developmental anomaly syndromes overlap to a small, or sometimes large, extent with one or more other syndromes. It is not always possible to define unambiguous phenotypic categories and therefore there is debate about the boundaries of clinical entities. As noted above, it can also be difficult to rigorously distinguish syndromic from non-syndromic phenotypes. In the 1980's it was presumed that molecular diagnosis would solve these problems. In fact, an unsupported, but commonly held aphorism in those times was "one gene – one disease". A large body of work has overthrown that naïve view and we now recognize that the relationship of genotype and phenotype is much more complex and nuanced. An example of this is the situation with the McKusick-Kaufman and Bardet-Biedl syndromes. The McKusick-Kaufman syndrome comprises polydactyly, congenital heart disease, and hydrometrocolpos (obstruction secondary to imperforate uterovaginal plate) in females and hypospadias in males [Slavotinek and Biesecker 2000]. This phenotype is almost entirely limited to the Old Order Amish with ancestors in Southeastern Pennsylvania and is caused by a homozygous double mutation in the *MKKS* gene (homozygous c. [726C>G + 250C>T], p.[Ala242Ser + His84Tyr]) [Stone et al., 2000]. In contrast, all other homozygous or compound heterozygous mutations in *MKKS* cause the Bardet-Biedl syndrome (polydactyly, pigmentary retinal dystrophy, obesity, intellectual disability, hypogonadism, and other anomalies) [Katsanis et al., 2000; Slavotinek et al., 2000]. Although these two phenotypes can overlap in childhood, the adult manifestations are readily distinguished and the consequences for the patients are markedly distinct. In addition, the phenotypes breed true – that is, families with true McKusick-Kaufman syndrome do not have members affected with Bardet-Biedl syndrome and *vice versa*. They are therefore considered to be distinct clinical entities. To further complicate the situation, it is now known that Bardet-Biedl syndrome can be caused by mutations in at least 11 genes in addition to *MKKS*. This is an example of how mutations in one gene can cause more than one phenotype (as shown in Table II) and mutations in more than one gene can apparently cause a single phenotype (e.g., Table I entries for Bardet-Biedl or Fanconi syndromes). This means that the genetic etiology alone cannot completely solve the diagnostic challenges that clinicians face, although they can be extremely helpful in confirming or eliminating diagnoses and narrowing the list of potential disorders that the clinician must consider.

The classes of genes products can be interpreted as a reflection of categories of genes that are important in mammalian development. Whereas transcription factors were the largest group in the prior analysis, the current gene list is dominated by genes that encode proteins involved in cell signaling (21 genes) and genes that encode for proteins in the basal body and cilium (13 genes). The other major categories of gene products implicated in phenotypes associated with polydactyly are the DNA repair genes (15 genes, primarily attributable to the Fanconi anemia phenotypes), followed by the transcription factors (16 genes). Much less commonly involved (fewer than 5 identified) genes encode structural proteins, catalytic proteins, immunoglobulin superfamily proteins, chaperones, and gap junctions. This significant shift in the distribution of identified genes since 2002 reflects the rapidly increasing emphasis on signaling pathways in development [Duboc and Logan 2009] and the key role of the cilium and basal body in the Sonic hedgehog-GLI3 transcription factor pathway [Goetz and Anderson 2010].

Perspectives and Future Directions

From the data reviewed above, it is clear that a great deal of progress has been made in elucidating the etiology of polydactyly since the previous review in 2002. Recent technologic developments, especially that of massively parallel sequencing [Shendure and Ji 2008], have shown remarkable initial promise to accelerate the process of gene identification in rare disorders. The coupling of massively parallel sequencing to various implementations of target selection [Gnirke et al., 2009] to enrich DNA samples for protein-coding exons, has been shown to be effective for mutation detection. Several disorders have recently been elucidated by various implementations of this technology including Miller syndrome [Ng et al., 2010] and TARP syndrome [Johnston et al., 2010]. These technologies accelerate human genetic discovery because they have the capability not only to increase sequence acquisition, but to potentially bypass meiotic mapping, which can be limiting in ultra rare disorders. As many of the disorders in Table I that have not yet been associated with mutations in a gene are known to occur in only a few or even in single families, this technologic advance holds out the promise of elucidating the etiology of most, if not nearly all of these disorders. Therefore, one can anticipate that human geneticists will, in the next several years, have a catalog of nearly all of the genes that are mutated in patients with polydactyly phenotypes, thus comprising a rich catalog of pathologic variations as well as a large list of genes important in anterior-posterior patterning in the limb. One can readily imagine that massively parallel sequencing of transcripts in developing limbs will delineate another set of genes, and that these sets can be analyzed and intersected to develop a rich, and perhaps nearly complete catalog of genes important for the patterning of the limb. With this knowledge, one can further predict that developmental biologist will have the resources to characterize the key pathways in the development of the limb in humans and in model systems, which can be used to develop regenerative or cell replacement therapies for limb anomalies.

References

- Allanson JE, Biesecker LG, Carey JC, Hennekam RC. Elements of morphology: introduction. *American Journal of Medical Genetics Part A*. 2009; 149A:2–5. [PubMed: 19127575]
- Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University; Baltimore, MD: National Center for Biotechnology Information, National Library of Medicine; Bethesda, MD: 2010.
- Biesecker LG. Polydactyly: how many disorders and how many genes? *American Journal of Medical Genetics*. 2002; 112:279–283. [PubMed: 12357471]
- Biesecker LG. Mapping phenotypes to language: a proposal to organize and standardize the clinical descriptions of malformations. *Clinical Genetics*. 2005; 68:320–326. [PubMed: 16143016]
- Biesecker LG. What you can learn from one gene: GLI3. *J Med Genet*. 2006; 43:465–469. [PubMed: 16740916]
- Butterfield NC, McGlinn E, Wicking C. The molecular regulation of vertebrate limb patterning. *Curr Top Dev Biol*. 2010; 90:319–341. [PubMed: 20691854]
- Cormier-Daire V, Wolf C, Munnich A, Le Merrer M, Nivelon A, Bonneau D, Journel H, Fellmann F, Chevy F, Roux C. Abnormal cholesterol biosynthesis in the Smith-Lemli-Opitz and the lethal acrodysgenital syndromes. *Eur J Pediatr*. 1996; 155:656–659. [PubMed: 8839719]
- Duboc V, Logan MP. Building limb morphology through integration of signalling modules. *Curr Opin Genet Dev*. 2009; 19:497–503. [PubMed: 19729297]
- Elson E, Perveen R, Donnai D, Wall S, Black GC. De novo GLI3 mutation in acrocallosal syndrome: broadening the phenotypic spectrum of GLI3 defects and overlap with murine models. *J Med Genet*. 2002; 39:804–806. [PubMed: 12414818]
- Gnirke A, Melnikov A, Maguire J, Rogov P, LeProust EM, Brockman W, Fennell T, Giannoukos G, Fisher S, Russ C, Gabriel S, Jaffe DB, Lander ES, Nusbaum C. Solution hybrid selection with

- ultra-long oligonucleotides for massively parallel targeted sequencing. *Nat Biotechnol.* 2009; 27:182–189. [PubMed: 19182786]
- Goetz SC, Anderson KV. The primary cilium: a signalling centre during vertebrate development. *Nat Rev Genet.* 2010; 11:331–344. [PubMed: 20395968]
- Johnston JJ, Teer JK, Cherukuri PF, Hansen NF, Loftus SK, Chong K, Mullikin JC, Biesecker LG. Massively parallel sequencing of exons on the X chromosome identifies RBM10 as the gene that causes a syndromic form of cleft palate. *American Journal of Human Genetics.* 2010; 86:743–748. [PubMed: 20451169]
- Jones, KL.; Smith, DW. Smith's recognizable patterns of human malformation. Vol. xviii. Philadelphia: Elsevier Saunders; 2006. p. 954
- Kang S, Graham JM Jr, Olney AH, Biesecker LG. *GLI3* frameshift mutations cause autosomal dominant Pallister-Hall syndrome. *Nature Genetics.* 1997; 15:266–268. [PubMed: 9054938]
- Katsanis N, Beales PL, Woods MO, Lewis RA, Green JS, Parfrey PS, Ansley SJ, Davidson WS, Lupski JR. Mutations in *MKKS* cause obesity, retinal dystrophy and renal malformations associated with Bardet-Biedl syndrome. *Nat Genet.* 2000; 26:67–70. [PubMed: 10973251]
- Ng SB, Buckingham KJ, Lee C, Bigham AW, Tabor HK, Dent KM, Huff CD, Shannon PT, Jabs EW, Nickerson DA, Shendure J, Bamshad MJ. Exome sequencing identifies the cause of a mendelian disorder. *Nature Genetics.* 2010; 42:30–35. [PubMed: 19915526]
- Radhakrishna U, Bornholdt D, Scott H, Patel U, Rossier C, Engel H, Bottani A, Chandal D, Blouin J, Solanki J, Grzeschik K, Antonarakis S. The phenotypic spectrum of *GLI3* morphopathies includes autosomal dominant polydactyly type IV and postaxial polydactyly type A/B; no phenotype prediction from the position of *GLI3* mutations. *American Journal of Human Genetics.* 1999; 65:645–655. [PubMed: 10441570]
- Radhakrishna U, Wild A, Grzeschik K-H, Antonarakis SE. Mutation in *GLI3* in post-axial polydactyly type A. *Nature Genetics.* 1997; 17:269–270. [PubMed: 9354785]
- Robin NH, Biesecker LG. Considerations for a multiaxis nomenclature system for medical genetics. *Genet Med.* 2001; 3:290–293. [PubMed: 11478529]
- Ruiz-Perez VL, Ide SE, Strom TM, Lorenz B, Wilson D, Woods K, King L, Francomano C, Freisinger P, Spranger S, Marino B, Dallapiccola B, Wright M, Meitinger T, Polymeropoulos MH, Goodship J. Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrorenal dysostosis. *Nat Genet.* 2000; 24:283–286. [PubMed: 10700184]
- Shendure J, Ji H. Next-generation DNA sequencing. *Nat Biotechnol.* 2008; 26:1135–1145. [PubMed: 18846087]
- Slavotinek AM, Biesecker LG. Phenotypic overlap of McKusick-Kaufman syndrome with Bardet-Biedl syndrome: a literature review. *Am J Med Genet.* 2000; 95:208–215. [PubMed: 11102925]
- Slavotinek AM, Stone EM, Myktyyn K, Heckenlively JR, Green JS, Heon E, Musarella MA, Parfrey PS, Sheffield VC, Biesecker LG. Mutations in *MKKS* cause Bardet-Biedl syndrome. *Nature Genetics.* 2000; 26:15–16. [PubMed: 10973238]
- Stevenson, RE. Human malformations and related anomalies. Vol. xiv. Oxford; New York: Oxford University Press; 2006. p. 1495
- Stone DL, Slavotinek AS, Bouffard GG, Banerjee-Basu S, Baxevanis AD, Barr M, Biesecker LG. Mutations of a gene encoding a putative chaperonin causes McKusick-Kaufman syndrome. *Nature Genetics.* 2000; 25:79–82. [PubMed: 10802661]
- Towers M, Tickle C. Growing models of vertebrate limb development. *Development.* 2009; 136:179–190. [PubMed: 19103802]
- Vortkamp A, Gessler M, Grzeschik K-H. *GLI3* zinc finger gene interrupted by translocations in Greig syndrome families. *Nature.* 1991; 352:539–540. [PubMed: 1650914]
- Wassif CA, Maslen C, Kachilele-Linjewile S, Lin D, Linck LM, Connor WE, Steiner RD, Porter FD. Mutations in the human sterol delta7-reductase gene at 11q12-13 cause Smith-Lemli-Opitz syndrome. *Am J Hum Genet.* 1998; 63:55–62. [PubMed: 9634533]

Table I

Clinical Entities That Manifest Polydactyly

Source	Inheritance	Clinical Entity	Gene
147800	D	Aase Smith Syndrome Type I	
200610	R	Achondrogenesis, Type II	<i>COL2A1</i>
201050	R	Acro-Cranio-Facial Dysostosis	
200990	R	Acrocallosal Syndrome	<i>GLI3</i>
200995	R	Acrocephalopolysyndactylous Dysplasia	
201020	R	Acrocephalosyndactyly Type I	
*	U	Acrofacial Dysostosis	
201170	R	Acrofacial Dysostosis-Type Rodriguez	
201180	R	Acrofrontofacionasal Dysostosis Type 1	
239710	R	Acrofrontofacionasal Dysostosis Type 2	
603671	D	Acromelic Frontonasal Dysostosis	
605967	D	Acropectoral Syndrome	
102510	D	Acropectorovertebral Dysplasia, F-form of	
102520	U	Acrorenal	
200980	R	Acrorenal-Mandibular Syndrome	
*	U	Adamsbaum (1991) Syndrome	
600325	U	Aminopterin Syndrome <i>sine</i> Aminopterin	
*	U	Anandan (2008) Sternal Defects – Aplasia Cutis Congenita-Polydactyly	
101200	D	Apert Syndrome	<i>FGFR2</i>
*	U	Arens (1991) Acrofacial Dysostosis	
243910	R	Arimia Syndrome	
208500 611263 613091	R	Asphyxiating Thoracic Dystrophy	<i>IFT80, DYNC2H1</i>
108721	D	Atelosteogenesis Type III	<i>FLNB</i>
*	U	Baisch-Polydactyly; Absent Nails	
218600	R	Baller-Gerold Syndrome	<i>RECQL4</i>
*	U	Baraitser-Brachyphalangy-Polydactyly-Absent Tibiae	
*	U	Barakat (1996) Polydactyly-Osteopenia-Hypoplastic Kidney	
209900	R	Bardet-Biedl Syndrome	<i>BBS1, BBS2, ARL6, BBS4, BBS5, MKKS, BBS7, TTC8, BBS9, BBS10, BBS11, BBS12</i>
109400	D	Basal Cell Nevus Syndrome	<i>PTCH1</i>
*	U	Bates (2002) Acrofacial Dysostosis-Digital Anomalies-Renal Agenesis	
130650	D	Beckwith-Wiedemann Syndrome	<i>CDKN1C</i>
210350	R	Biamond Syndrome II	
*	U	Bitoun (1994)-Glaucoma-Thumb Anomalies-Joint Dislocations	
*	R	Blair (2000) Autosomal Recessive Craniosynostosis Syndrome	
210900	R	Bloom Syndrome	<i>RECQL3</i>
263630	R	Bonneau Syndrome	
112450	D	Brachydactyly (Preaxial) Hallux Varus-Thumb Abduction	

Source	Inheritance	Clinical Entity	Gene
113000	D	Brachydactyly Type B	<i>ROR2</i>
113100	D	Brachydactyly Type C	<i>GDF5</i>
609945	D	Brachyphalangy, Polydactyly, and Tibial Aplasia/Hypoplasia	
*	U	Braddock (2003) Laryngeal Webs; CHD; Vertebral Defects	
113620	D	Branchiooculofacial Syndrome	<i>TFAP2A</i>
256200	R	Braun (1962) Nephrosis; Deafness; Brachytelephalangy	
300404	X	BRESHECK	
*	U	Brunoni (1984) Radial Aplasia; Short Stature; Unusual Face	
211750	D	C Syndrome	<i>CD96</i>
605039	D	C-LIKE Syndrome	<i>CD96</i>
114150	R	Camptobrachydactyly	
201000	R	Carpenter Syndrome	<i>RAB23</i>
*	U	Carpenter-Hunter-Micromelia; Polysyndactyly; Encephalocele; Fragile Bones	
*	U	Cerebro-fronto-facial Syndrome Type III	
213980	R	Cerebrofaciothoracic Dysplasia	
605627	D	Cerebrooculonasal Syndrome	
169100	D	CHAR Syndrome	<i>TFAP2B</i>
214800	D	CHARGE Syndrome	<i>CHD7, SEMA3E</i>
*	U	Chitayat (1993) Hyperphalangism; Hallux Valgus; Bronchomalacia	
*	R	Chitty (1993) Bowed Tibiae; Radial Anomalies; Osteopenia; Fractures	
*	U	Chondrodysplasia-Situs Inversus-Cystic Pancreatic Dysplasia	
200700	R	Chondrodysplasia, Grebe Type	<i>GDF5</i>
302960	X	Chondrodysplasia Punctata 2, X-Linked Dominant	<i>EBP</i>
601165	R	Cleft Lip/Palate with Characteristic Facies, Intestinal Malrotation, and Lethal Congenital Heart Disease	
*	U	COH Syndrome-Craniosynostosis; Bifid Thumb; Micropenis	
120400	D	Colobomas-Brachydactyly (Type Sorsby)	
601707	U	Craniofacial Malformations, Asymmetric, with Polysyndactyly and Abnormal Skin and Gut Development	
304110	X	Craniofrontonasal Syndrome	<i>EFNB1</i>
*	D	Culler (1984) Hypopituitarism; Postaxial Polydactyly	
*	U	Cutis Aplasia-Blue Sclerae-Hypertelorism-Polydactyly-Hypoplastic Nipples	
219250	U	Cutis Marmorata Telangiectasia Congenita	
220220	R	Dandy-Walker Malformation with Postaxial Polydactyly	
*	D	De Smet Complex Synpolydactyly	<i>FBLN1</i>
124480	D	Deafness, Congenital and Onychodystrophy, Autosomal Dominant	
**	U	Deafness, Onychodystrophy, Triphalangeal Thumbs	
251450	R	Desbuquois (1966)-Chondrodystrophy; Advanced Bone Age	<i>CANT1</i>
105650	R	Diamond-Blackfan	<i>RPS19, RPL5, RPL11</i>
223200	U	Disorganization, Mouse, Homolog of	
*	U	Donnai (1988) Meckel-like Syndrome	
220500	R	DOOR	
126500	U	Double Nail For Fifth Toe	

Source	Inheritance	Clinical Entity	Gene
607323	D	Duane-Radial Ray Syndrome	<i>SALL4</i>
*	U	Duplication of Lower Limb-Plus	
129540	U	Ectodermal Dysplasia Syndrome with Distinctive Facial Appearance and Preaxial Polydactyly of Feet	
183600	M	Ectrodactyly-Autosomal Dominant	<i>WNT10A</i>
225290	R	Ectrodactyly-Polydactyly	
600002	R	Eiken (1984) Retarded Ossification; Abnormal Modeling of Bones	<i>PTHR1</i>
225500	R	Ellis-Van Creveld Syndrome	<i>EVC, EVC2</i>
*	R	Encephalocele-Radial, Cardiac, Gastrointestinal, Anal/renal Anomalies	
612651	R	Endocrine-Cerebrostodysplasia	<i>ICK</i>
*	R	Engelhard (1979) Pre- and Postaxial Polysyndactyly; Ptosis	
612731	R	Faciocardiomeic Syndrome	
227650	R	Fanconi Pancytopenia Syndrome	<i>FANCA, FANCB, BANCC, FANCD1, FANCD2, FANCE, FANCF, XRCC9, FANCI, FANCI, PHF9, FANCM, FANCN, FANCO</i>
228930	R	Fibular Aplasia or Hypoplasia, Femoral Bowing and Poly-, Syn-, and Oligodactyly	<i>WNT7A</i>
134780	U	Femoral-Facial Syndrome	
*	U	Ferda Percin-Yilmaz-Syn-Poly-Oligo-Brachydactyly	
*	U	Fibular Aplasia-Anonychia-Finger Polydactyly-Toe Oligodactyly	
*	U	Fibular Hemimelia-Polysyndactyly	
136140	D	Floating-Harbor-Short Stature-Delayed Bone Age-Broad Nose	
*	U	Focal Dermal Hypoplasia, Morning Glory Anomaly, and Polymicrogyria	
305600	X	Focal Dermal Hypoplasia	<i>PORCN</i>
*	U	Franceschini (1994) Mask-Like Face; Ear Anomalies; Digital Malformations	
609640	D	Frias Syndrome	
136760	M	Frontonasal Dysplasia	<i>ALX3</i>
606155	U	Fryns-Aftimos	
*	U	Fryns-Lagae-Rizzo-Polydactyly-Growth Retardation-Spasticity-Urogenital	
*	U	Gandhi (2008)	
*	U	Garrett-Tripp-MR; Polydactyly; Hair Absence; Dermatitis; Perthe's Disease	
*	U	Giant Diencephalic Hamartoma-Facial Cleft-Ear and Eye Anomalies	
138790	U	Goiter, Multinodular, Cystic Renal Disease, and Digital Anomalies	
*	R	Goossens (2006) Congenital Heart Disease-Polydactyly-Ectopic Neuropituitary	
175700	D	Greig Cephalopolysyndactyly Syndrome	<i>GLI3</i>
610536	U	Growth and Mental Retardation, Mandibulofacial Dysostosis, Microcephaly, and Cleft Palate	
*	U	Gül (2000)-Craniofacial Anomalies	
*	R	Guschmann (2001) Mesomelic Campomelia-Polydactyly-Dandy-Walker	
234280	R	Hallux Varus and Preaxial Polysyndactyly	
*	U	Hameed (1999) Acrocraniofacial Syndrome	
*	U	Happle-Tinschert Syndrome	
*	U	Hartsfield (1984) Holoprosencephaly; Ectrodactyly; Cleft Face	
249670	R	Heart-hand-Type 4-with Mesoaxial Hexadactyly	

Source	Inheritance	Clinical Entity	Gene
141400	U	Hemifacial Microsomia-Radial Defects	
*	U	Hemihypertrophy-Hemimegalencephaly-Polydactyly	
218010	R	Hernandez (1985) Cortical Blindness; Polydactyly; Mental Retardation	
604211	R	Hirschsprung Disease with Heart Defects, Laryngeal Anomalies, and Preaxial Polydactyly	
235740	R	Hirschsprung Disease with Polydactyly, Renal Agenesis, and Deafness	
235750	R	Hirschsprung Disease with Ulnar Polydactyly, Polysyndactyly of Big Toes, and Ventricular Septal Defect	
*	U	Ho (1975) Cleft Palate; Congenital Heart Disease; Absent Tibia; Polydactyly	
*	U	Holmes-Schimke-Microcephaly; CHD; Skeletal Abnormalities	
610829	D	Holprosencephaly 9	<i>GLI2</i>
142900	D	Holt-Oram Syndrome	<i>TBX5</i>
236110	R	Holzgrev Syndrome	
*	R	Huang (1999) Hirschsprung, Congenital Heart Defect, Laryngeal Anomalies	
236680	R	Hydrolethrus Syndrome 1	<i>HYLS1</i>
215140	R	Hydrops-Ectopic Calcification-Moth-Eaten Skeletal Dysplasia	<i>LBR</i>
146160	D	Hypomelia with Müllerian Duct Anomalies	
*	M	Hypoplastic Left Heart-Postaxial Polydactyly	
*	U	Johnson (1974) Glossopalatine Ankylosis; Cataracts; Abnormal Digits	
147770	U	Johnson Neuroectodermal Syndrome	
213300	M	Joubert Syndrome; JBTS	<i>CXORF5, INPP5E, TMEM216, RPGRIP1L</i>
, 300804			
, 608091			
, 611560			
*	U	Kantaputra (2003) Symphalangism; Multiple Frenula; Polydactyly; Dental Anomalies	
149000	D	Klippel-Trenaunay-Weber Syndrome	
606242	R	Kondoh (2001) Microcephaly-growth Retardation-Atopic Dermatitis-Mental Retardation	
*	R	Kozlowski-Krajewska-Polydactyly-Brachydactyly-Uncombable Hair-Mental Retardation	
149730	D	Lacrimoauriculodentodigital Syndrome	<i>FGFR2, FGFR3, FGF10</i>
**	R	Lambotte (1990) Microcephaly, Large Ears, Polydactyly, Hypoplastic Thumb	
*	U	Lampert (1984)-Craniostenosis; Polydactyly	
*	U	Landy-Donnai-Split Hand; Hydrops; Renal Anomalies	
*	U	Laryngomalacia-Plus	
607330	R	Lathosterolosis	<i>SC5DL</i>
135750	D	Laurin-Sandrow Syndrome	
309800	X	Lenz Microphthalmia	
163200	U	Linear Nevus Sebaceous Syndrome	
605944	R	Liver Fibrocystic Disease and Polydactyly	
602501	U	Macrocephaly-Capillary Malformation	
*	U	Mandibulofacial Dysostosis-Type Guion-Almeida	
*	U	Mardini (1985) Lung Agenesis; Congenital Heart Disease; Thumb Anomalies	
*	D	Martin-Gorski-Ocular Malformations-polydactyly-membranous Bone Abnormal	

Source	Inheritance	Clinical Entity	Gene
600384	D	Martinez-Frias (1995) Distal Aphyalangia; Syndactyly; Microcephaly	
*	U	Martsof (1977) Skeletal Dysplasia; Polydactyly; Pierre Robin	
*	U	McGaughan (1998) Micrognathia-Syndactyly	
246000	R	McKusick (1968) Cataract; Unilateral Limb Defects	
236700	R	McKusick-Kaufman Syndrome	<i>MKKS</i>
249000	R	Meckel Syndrome	<i>CC2D2A, CEP290, MKS1, TMEM67, RPGRIP1L</i>
, 603194			
, 607361			
, 611134			
, 611561			
, 612284			
603387	R	Megalencephaly Polymicrogyria-Polydactyly Hydrocephalus Syndrome	
249310	R	Megalocornea-Mental Retardation Syndrome	
*	U	Meningocele-Renal Dysplasia-Postaxial Polydactyly	
249620	R	Mental Retardation, Congenital Heart Disease, Blepharophimosis, Blepharoptosis and Hypoplastic Teeth	
610156	R	Mental Retardation, Truncal Obesity Retinal Dystrophy, and Micropenis	<i>INPP5E</i>
251255	R	Microcephaly with Mental Retardation and Digital Anomalies	
601420	U	Microcephaly, Corpus Callosum Dysgenesis, and Cleft Lip/Palate	
206920	R	Microphthalmia with Limb Anomalies	
607932	D	Microphthalmia, Syndromic 6	<i>BMP4</i>
*	R	Mildenberger (1998) Diffuse Mesangial Sclerosis-Dandy-Walker-polydactyly	
606850	U	Mirror-Image Polydactyly	<i>MIPOL1</i>
157900	M	Moebius	
252100	R	MOHR Syndrome	
*	U	Morava (2004) Focal Skin Defect-Microphthalmia-Limb Defects	
*	R	Morton (1998) Lethal Skeletal Dysplasia-Ectopic Digits	
235255	R	Müllerian Derivatives Persistence of, with Lymphangiectasia and Postaxial Polydactyly	
*	R	Multiple Maternal Hypomethylation Syndrome	
312150	X	Multiple Pterygium Syndrome, X-Linked	
601076	U	MURCS	
154400	D	Nager Acrofacial Dysostosis	
*	U	Neural Tube Defect-Preaxial Polydactyly-Vertebral Anomalies	
256690	R	Neuro-Facio-Digito-Renal Syndrome	
*	U	NevusComedonicus Syndrome	
251260	R	Nijmegen Immunodeficiency Syndrome	<i>NBN</i>
*	U	Occult Toe	
164200	D	Oculo-dento-digital Syndrome	<i>GJA1</i>
273400	R	Odontotrichomelic Syndrome	
258040	U	OEIS	
258200	R	Oliver Syndrome	

Source	Inheritance	Clinical Entity	Gene
106995	D	Onychonychia-Acral Defects-Cooks	<i>SOX9</i>
*	U	Opitz (1989) Mandibulofacial Dysostosis; Hexadactyly; Lymphoedema	
*	U	Oral-Facial-Digital Syndrome-Cerebral Dysgenesis	
612913	U	Oral-Facial-Digital Syndrome-Type Gabrielli	
*	U	Oral-Facial-Digital Syndrome-Type Stenram	
*	U	Oral-Facial-Digital Syndrome-Type XII	
311200	X	Oral-Facial-Digital Syndrome Syndrome I; OFD1	<i>CXORF5</i>
258850	R	Oral-Facial-Digital Syndrome Syndrome III; OFD3	
258860	R	Oral-Facial-Digital Syndrome Syndrome IV; OFD4	
258865	R	Oral-Facial-Digital Syndrome Syndrome IX; OFD9	
174300	D	Oral-Facial-Digital Syndrome Syndrome V; OFD5	
277170	R	Oral-Facial-Digital Syndrome Syndrome VI; OFD6	
300484	X	Oral-Facial-Digital Syndrome Syndrome VIII; OFD8	
165590	D	Oral-Facial-Digital Syndrome Syndrome X; OFD10	
217085	R	Orstavik (1992) Oral-Cardiac-Digital Syndrome	
*	U	Osteochondrodysplasia-Osteopenia-Preaxial Polydactyly	
304120	X	Otopalatodigital Syndrome, Type II	<i>FLNA</i>
146510	D	Pallister-Hall Syndrome; PHS	<i>GLI3</i>
*	R	Panigrahi (2002) Ptosis Polydactyly Mental Retardation	
*	U	Parentin-Perissutti Single Incisor-Duane-Bifid Thumb	
*	U	Pavone (1991) Connective Tissue Disorder; Polydactyly	
*	U	Percin and Percin (2003) An Unusual Syndactyly	
*	R	Peters' Anomaly-Microphthalmia-Arhinia	
*	U	Pfeiffer-Angerstein-Bowing-Bone Dysplasia	
*	R	Pfeiffer-Mayer-Coloboma; Polydactyly; Mental Retardation	
607539	R	Phadke (1999) Complex Camptopolydactyly	
*	U	Piepkorn (1977) Short Ribs; Polydactyly	
*	U	Polydactyly-Colobomata-Hypopituitarism-Cleft Palate	
*	U	Polydactyly-Palmar Type	
*	U	Polydactyly-Panfollicular Nevus	
*	U	Polydactyly-Renal Vascular Malformation	
*	U	Polydactyly-Obstructive Uropathy	
174200 , 263450 , 602085 , 607324 , 608562	M	Polydactyly, Postaxial	<i>GLI3</i>
263540	U	Polydactyly, Postaxial, with Dental and Vertebral Anomalies	
174310	D	Polydactyly, Postaxial, with Progressive Myopia	
174400	D	Polydactyly, Preaxial I	
174500	D	Polydactyly, Preaxial II; PPD2	<i>SHH ZRS</i>
174600	D	Polydactyly, Preaxial III	

Source	Inheritance	Clinical Entity	Gene
174700	D	Polydactyly, Preaxial IV	<i>GLI3</i>
*	U	Polymetatarsia-Without Polydactyly.	
*	U	Polysyndactyly-Delta Phalanges	
263630	R	Polysyndactyly with Cardiac Malformation	
175690	D	Polysyndactyly, Crossed	
263750	R	Postaxial Acrofacial Dysostosis	<i>DHODH</i>
176240	D	Postaxial Oligodactyly, Tetramelic	
*	U	Postaxial Polydactyly-Atrium Anomaly	
*	U	Postaxial Polydactyly-Single Atrium-Mental Retardation	
176305	D	Preaxial Deficiency Postaxial Polydactyly, and Hypospadias	<i>HOXA13</i>
264480	R	Pseudotrisomy 13 Syndrome	
147750	D	Radial Defects-Deafness (IVIC)	
300233	X	Radioulnar Synostosis-Radial Ray Anomalies	
612095	R	Reinitis Pigmentosa 41	<i>PROML1</i>
266910	R	Renal Dysplasia; Limb Defects	
208540	R	Renal-Hepatic-Pancreatic Dysplasia	<i>NPHP3</i>
*	M	Rhombencephalosynapsis	
*	U	Rippberger (1976) BBB-like Syndrome with Brachydactyly	
180700	D	Robinow Syndrome	<i>ROR2</i>
180750	D	Robinow-Sorauf Syndrome	<i>TWIST</i>
180849	D	Rubinstein-Taybi Syndrome	<i>CBP</i>
101120	U	Sakati-Nyhan-Acrocephalopolysyndactyly Type III	
*	U	Say (1987) Clover-leaf Skull; Skeletal Dysplasia	
181250	U	Scalp Defects and Postaxial Polydactyly	
269150	R	Schinz-Giedion Midface-Retraktion Syndrome	<i>SETBP1</i>
179250	D	Schmitt Hypoplastic Radius, Hypospadias, Maxillary Diastema	
*	R	Sener (1990) Synpolydactyly	
*	U	Shepherd (1989) Noonan-like Syndrome	
*	U	Short Rib-polydactyly Syndrome (Kannu-Aftimos)	
263530	R	Short Rib-Polydactyly Syndrome, Type I	
263520	R	Short Rib-Polydactyly Syndrome, Type II	
263510	R	Short Rib-Polydactyly Syndrome, Type III	<i>DYNC2H1</i>
269860	R	Short Rib-Polydactyly Syndrome, Type IV	
300263	X	Siderius X-Linked Mental Retardation Syndrome	<i>PHF8</i>
312870	X	Simpson-Golabi-Behmel Syndrome, Type I	<i>GPC3</i>
*	D	Sinha-Verma-Postaxial and Mesoaxial Polydactyly	
*	U	Situs Inversus-Polydactyly-Broad Thumbs	
*	R	Sjogren-Larsson-Like Syndrome with Bone Dysplasia	
270400	R	Smith-Lemli-Opitz Syndrome	<i>DHCR7</i>
600095	D	Split-Hand/Foot Malformation	
272460	R	Spondylocaroptarsal Synostosis Syndrome	<i>FLNB</i>
*	U	Spondylocostal Dysostosis-Preaxial Polydactyly	

Source	Inheritance	Clinical Entity	Gene
277300	R	Spondylocostal Dysostosis	<i>DLL3</i>
*	U	Stoll-Gasser-Hepatic Ductal Plate Anomalies; Digital Anomalies; Congenital Heart Disease	
*	U	Sugiura-Lenz (1999) Polysyndactyly	
*	U	Sulko (2010) Tibial Hemimelia-Preaxial Polydactyly-Heart Defects	
186350	D	Syndactyly-Polydactyly-Earlobe Syndrome	
186200	D	Syndactyly, Type IV	<i>SHH ZRS</i>
186000	D	Synpolydactyly 1; SPD1	<i>HOXD13</i>
608180	D	Synpolydactyly 2; SPD2	<i>FBLN1</i>
*	D	Tabatznik Syndrome	
*	U	Tarhan (2004) Mental Retardation, Polysyndactyly, Deafness, Facial Dysmorphism	
608028	U	Thai Symphalangism Syndrome	
187600	D	Thanatophoric Dysplasia, Type I	<i>FGFR3</i>
*	U	Thumb Hypoplasia-Preaxial Toe Polydactyly	
601027	R	Tibia, Absence of Hypoplasia of, with Polydactyly, Retrocerebellar Arachnoid Cyst, and Other Anomalies	
188740	U	Tibia, Absence of, with Polydactyly	
188770	D	Tibia, Hypoplasia of, with Polydactyly	
119100	D	Tibial Aplasia Ectrodactyly Syndrome	
275220	M	Tibial Hemimelia	
*	D	Tibial Hemimelia-Polydactyly-Club Foot	<i>PITX1</i>
*	U	Tollner (1981) Polydactyly; Visceral Anomalies	
107480	D	Townes-Brocks Syndrome	<i>SALL1</i>
*	U	Triangular Thumb Epiphysis-Angulation Deformity	
190600	D	Triphalangeal Thumb, Nonopposable	
190650	D	Triphalangeal Thumbs and Dislocation of Patella	
190680	D	Triphalangeal Thumbs with Brachyectrodactyly Ulna and Fibula, Absence of, with Severe Limb	
276820	R	Deficiency	<i>WNT7A</i>
276821	R	Ulnar Hypoplasia with Mental Retardation	
604380	M	Ulnar Ray Dysgenesis with Postaxial Polydactyly and Renal Cystic Dysplasia	
181450	D	Ulnar-Mammary Syndrome	<i>TBX3</i>
268250	R	Urbach (1986) Skeletal Dysplasia; Rhizomelia of Humeri	
*	R	Urioste (1996) Limb Deficiency-Vertebral Hypersegmentation-Absent Thymus	
*	U	VACTERL Association-Tibial Aplasia	
192350	U	VATER Association	
608406	R	VATER-Like Defects with Pulmonary Hypertension, Laryngeal Webs, and Growth Deficiency	
277590	U	Weaver Syndrome	<i>NSD1</i>
193530	D	Weyers Acrofacial Dysostosis	<i>EVC</i>
*	U	Wieczorek (2002) Thumb Aplasia-Radial Aplasia-Microcephaly	<i>ZBTB16</i>
*	U	Wiedemann (1985c) Macrocephaly; Polydactyly of Toes; Tibial Defect	
*	U	Wolter (1971) Papilla Nigra; Cleft Palate; Extra Thumb	
194350	D	WT Syndrome-Pancytopenia-Hand Defects	

Source	Inheritance	Clinical Entity	Gene
*	D	Zannolli (2008) Polydactyly-Ectodermal Dysplasia	

* Indicates that the entry was sourced from the Winter-Baraitser Dysmorphology Database,

** Indicates that the entry was sourced from the Stevenson et al text {Stevenson, 2006 #1688}, D: Autosomal dominant inheritance, R: Autosomal recessive inheritance, X: Sex-linked Inheritance, M: Multiple modes of inheritance, U: Unknown inheritance. Highlighted clinical entities are non-syndromic.

Table II

Genes that, when mutated, can cause more than one clinically distinct phenotype in humans

Gene	Clinical Entity
<i>CD96</i>	C syndrome C-like syndrome
<i>CXORF5</i>	Joubert syndrome* Oral-facial-digital syndrome type I
<i>DYNC2H1</i>	Asphyxiating thoracic dystrophy type 3 Short-Rib polydactyly syndrome
<i>EVC</i>	Ellis-Van Creveld syndrome Weyers acrofacial dysostosis
<i>FBLN1</i>	De Smet complex synpolydactyly Synpolydactyly*
<i>FGFR2</i>	Apert syndrome Lacrimoauriculodentodigital syndrome
<i>FLNB</i>	Atelosteogenesis type III Spondylocarpotarsal dysostosis
<i>GDF5</i>	Brachydactyly type C Chondrodysplasia, Grebe type
<i>GLI3</i>	Greig cephalopolysyndactyly syndrome Pallister-Hall syndrome Acrocallosal syndrome Polydactyly, postaxial Polydactyly, preaxial*
<i>INPP5B</i>	Joubert syndrome* Mental retardation, truncal obesity, retinal dystrophy, and micropenis
<i>MKKS</i>	Bardet-Biedl syndrome McKusick-Kaufman syndrome
<i>ROR2</i>	Brachydactyly type B Robinow syndrome
<i>RPGRIP1L</i>	Joubert syndrome* Meckel Syndrome
<i>SHH</i> **	Polydactyly, preaxial* Synpolydactyly*
<i>WNT7A</i>	Fibular a/hypoplasia, femoral bowing and poly-, syn-, and oligodactyly Ulna and fibula, absence of, with severe limb deficiency

* Note that these phenotypes can be caused by mutations in more than one of the genes listed in the left column.

** Note that these mutations are in the SHH ZRS (ZPA regulatory sequence) and not in the SHH gene proper.