American Journal of Medical Genetics 112:279–283 (2002)

Polydactyly: How Many Disorders and How Many Genes?

Leslie G. Biesecker
National Institutes of Health, National Human Genome Research Institute, Bethesda, Maryland

Disorders that include polydactyly as a manifestation are diverse and numerous. Cataloging these disorders by phenotype and genotype demonstrates numerous overlapping phenotypes, genetic heterogeneity of phenotypes, and distinct phenotypes generated from mutations in single genes. To assess these issues, a list of disorders with polydactyly has been compiled from several sources. Among 119 disorders, 39 disorders are associated with mutations in genes, and among these, genotypic and phenotypic overlap is demonstrated. These issues highlight the need for a diagnostic system that catalogs both genotype and phenotype.

KEY WORDS: malformations; genetic heterogeneity; medical diagnosis; pleiotropism

Polydactyly can occur as a simple or isolated malformation or as part of a pleiotropic developmental anomaly syndrome. Currently, there are 119 current entries that include polydactyly (Table I). Thirty-nine of these disorders are caused by mutations in known genes and 16 more are mapped to a locus in the genome. In this article I will describe these disorders, delineate the genes that are altered in these disorders, and finally attempt to organize the disorders and genes into a unifying framework.

To tabulate syndromic and isolated polydactyly syndromes, I drew from three primary sources. First, Online Mendelian Inheritance in Man [2000] was searched using the term "polydactyl*". Second, the tabular listings of polydactyly in the appendix of *Smith's Recognizable Patterns of Malformation* [Jones, 1997] and Tables 28–6, 28–7, and 28–9 of the chapter "Hands and Feet" in *Human Malformations and Related Anomalies* [Winter et al., 1993] were reviewed. These lists were merged and duplicate entries were deleted. Next, entries that described polydactyly only in model organisms and case reports of single families were deleted. Entries that solely referred to polydactyly in other disorders were also deleted. Entries that separately described a gene and a disorder (e.g., *FGFR1* and Pfeiffer syndrome) were reduced to a single entry.

This list comprised 119 entries of syndromic (97 entries) and nonsyndromic (22 entries) polydactyly (Table I). The latter entries generally follow the classic nomenclature of hand malformations [Temtamy and McKusick, 1969]. The approach of the present analysis was to be generally accepting of designations of the distinctness of an entity, although this leads to difficulties, as will be described below. Among the 39 entries associated with causative mutations, 36 are syndromic and three are nonsyndromic (Fig. 1). These 39 disorders illustrate another prominent feature, which is that of genocopies and pleiotropism. First, among the 39 entries with cloned genes, seven ($\sim$ 20%) are forms of Fanconi anemia (FA). All seven were included because there are not sufficient data to determine if the various FA types have significantly different frequencies of polydactyly. The remaining 32 entries are associated with mutations in 26 genes. A major culprit in this pleiotropy is the *GLI3* transcription factor gene, which can be attributed to four or five phenotypes [Vortkamp et al., 1991; Kang et al., 1997; Radhakrishna et al., 1997, 1999; Killoran et al., 2000], whereas the *MKS*, *EVC*, and *DHCR7* [Cormier-Daire et al., 1996; Wassif et al., 1998; Katsanis et al., 2000; Ruiz-Perez et al., 2000; Slavotinek et al., 2000; Stone et al., 2000] genes are associated with two phenotypes each.

The classes of genes represented in this group mostly reflect the types of genes known to be critical in mammalian development. Transcription factors are the largest group and account for 13 disorders, DNA repair genes account for eight, signal transduction molecules account for eight, chaperonins for two, and metabolic, growth factor receptors, and cell cycle one each. The predominance of transcription factors and signal transduction molecules in this list is not surprising, as the developmental program of the limb requires

Correspondence to: Leslie G. Biesecker, National Institutes of Health, National Human Genome Research Institute, Building 49, Room 4A80, Bethesda, MD 20892.
E-mail: leslieb@helix.nih.gov

Received 29 March 2002; Accepted 4 June 2002
DOI 10.1002/ajmg.10779

TABLE I. Disorder Data*

Disorder	OMIM mapped	Gene	Type	S/NS
Acrocallosal syndrome	20099012p13.3-p11.2			S
Acrocephalopolydactylous dysplasia	200995			S
Acrocephalopolysynd type II	201000			S
Acrocephalopolysynd type IV	201020			S
Acrofrontofacionasal dysostosis, severe	239710			S
Acromelic frontonasal dysostosis	603671			S
Acropectoral syndrome	6059677q36			S
Acropectorovertebral dysplasia, F-form of	102510			S
Alstrom syndrome	2038002p13			S
Jeune asphyxiating thoracic dystrophy	208500			S
Bardet-Biedl syndrome, type 1	20990111q13			S
Bardet-Biedl syndrome, type 2	20990016q21	*BBS2*	Unknown	S
Bardet-Biedl syndrome, type 3	6001513p13-p12			S
Bardet-Biedl syndrome, type 4	60037415q22.3-q23	*BBS4*	Unknown	S
Bardet-Biedl syndrome, type 5	6036502q31			S
Bardet-Biedl syndrome, type 6	60523120p12	*MKS*	Chaperonin	S
Bardet-Biedl syndrome, type 7	Pending			S
Basal cell nevus syndrome, gorlin syndrome	1094009q22.3	*PTCH1*	Signal transduction	S
Beckwith-Wiedemann syndrome	13065011p15.5	*p57kip2*	Cell cycle	S
Biemond syndrome II	210350			S
Bloom syndrome	21090015q26	*RecQPL2*	DNA repair	S
Branchial clefts, char facies, growth retardation, etc.	113620			S
C syndrome	211750			S
Chondrodysplasia, Grebe type	20070020q11.2	*CDMP1*	Signal transduction	S
Coach syndrome	216360			S
Conradi-Hunnerman chondrodyspl punctata	302960Xp11.2	*EBP*	Metabolic	S
Cran-fac malf, polysyndactyly, abnormal skin and gut development	601707			S
Dandy-Walker malformation and postaxial polydactyly	220220			S
Disorganization, mouse, homolog of	223200			S
Ectrodactyly, ectodermal dysplasia, and cleft lip palate syndrome 1	1299007q11.2–q21.3	*p63*	Transcription factor	S
Ectrodactyly-polydactyly	225290			NS
Ellis-van creveld syndrome	2255004p16	*EVC*	Unknown	S
Fanconi anemia A	22765016q24	*FACA*	DNA repair	S
Fanconi anemia B	227660			S
Fanconi anemia C	2276459q22.3	*FACC*	DNA repair	S
Fanconi anemia D1	605724	*FACD1*	DNA repair	S
Fanconi anemia D2	2276463p25.3	*FACD2*	DNA repair	S
Fanconi anemia E	6009016p22.1	*FACE*	DNA repair	S
Fanconi anemia F	60346711p15.5	*FACF*	DNA repair	S
Fanconi anemia G	6029569p13	*FACG*	DNA repair	S
Femoral-facial syndrome	134780			S
Fibula and ulna duplication and absent tibia and radius	13575014q13			NS
Frontonasal dysplasia	136760			S
Frontonasal dysplasia	305645			S
Fuhrmann syndrome	228930			S
Goltz focal dermal hypoplasia	305600			S
Greig cephalopolysynd syndrome	1757007p13	*GLI3*	Transcription factor	S
Hemifacial microsomia and radial defects	141400			S
Hirschsprung disease, congenital heart defect, laryngeal anomaly, and polydactyly	604211			S
Hirschsprung disease, polydactyly, renal agenesis, and deafness	235740			S
Hirschsprung disease, polydactyly, polysyndactyly of toes, and congenital heart defect	235750			S
Holoprosencephaly 2, alobar	6037142p13	*SIX3*	Transcription factor	S
Holoprosencephaly 1, alobar	23610021q22.3			S
Holoprosencephaly 2, alobar	1571702p21			S
Holoprosencephaly 3, alobar	1429457q36	*SHH*	Signal transduction	S
Holoprosencephaly 4, alobar	14294618p	*TGIF*	Transcription factor	S
Holoprosencephaly 5, alobar	60307313q	*ZIC2*	Transcription factor	S
Holt-Oram syndrome	14290012q24.1	*TBX5*	Transcription factor	S
Holzgreve syndrome	236110			S
Hydrolethalus syndrome	23668011q23-q25			S
Joubert syndrome 1	2133009q34.3			S

TABLE I. (*Continued*)

Disorder	OMIM mapped	Gene	Type	S/NS
Klippel-Trenaunay-Weber syndrome	149000			S
Ladd lacrimo-auriculo-dento-digital syndrome	149730			S
Lenz micophthalmia syndrome	309800			S
Mckusick-Kaufman syndrome	23670020p12	*MKS*	Chaperonin	S
Meckel syndrome, type 1	24900017q22-q23			S
Meckel syndrome, type 2	60319411q13			S
Megalenceph-cutis marmorata telang congenita	602501			S
Microceph, corpus callosum dysgenesis, and cleft lip/palate	601420			S
Mohr syndrome	252100			S
Oral-facial-digital syndrome 1	311200Xp22.3-p22.2	*CXORF5*	Unknown	S
Oral-facial-digital syndrome and fibular aplasia	165590			S
Oral-facial-digital syndrome, type III	258850			S
Oral-facial-digital syndrome, type IV	258860			S
OTO-palato-digital type II	304120			S
Pallister-Hall syndrome	1465107p13	*GLI3*	Transcription factor	S
Pena-Shokeir syndrome, type I	208150			S
Pfeiffer syndrome	1016008p11.2-p11.1	*FGFR1*	Signal transduction	S
Pfeiffer syndrome	10160010q26	*FGFR2*	Signal transduction	S
Pfeiffer syndrome	1016004p16	*FGFR3*	Signal transduction	S
Polydactyly	603596			NS
Polydactyly, imperforate anus, and vertebral anomaly	174100			NS
Polydactyly, postaxial	263450			NS
Polydactyly, postaxial, type A1	1742007p13	*GLI3*	Transcription factor	NS
Polydactyly, postaxial, type A2	60208513q21-q32			NS
Polydactyly, postaxial, dental and vertebral anomaly	263540			NS
Polydactyly, postaxial, median cleft of upper lip	174300			NS
Polydactyly, postaxial, progressive myopia	174310			NS
Polydactyly, preaxial I	174400			NS
Polydactyly, preaxial II	174500q36			NS
Polydactyly, preaxial III	174600			NS
Polydactyly, preaxial IV	1747007p13	*GLI3*	Transcription factor	NS
Polysyndactyly and cardiac malformation	263630			NS
Polysyndactyly, crossed	175690			NS
Preaxial deficiency, postaxial polydactyly, and hypospadias	176305			S
Pseudotrisomy 13 syndrome	264480			S
Rubinstein syndrome	18084916p13.3	*CREBBP*	Transcription factor	S
Rutledge lethal multiple congenital anomaly syndrome	26867011q12-q13	*DHCR7*	Signal transduction	S
Scalp defects and postaxial polydactyly	181250			S
Schinzel-giedion midface-retraction syndrome	269150			S
Short rib-polydactyly syndrome, type I	263530			S
Short rib-polydactyly syndrome, type II	263520			S
Short rib-polydactyly syndrome, type III	263510			S
Short rib-polydactyly syndrome, type IV	269860			S
Simpson-Golabi-Behmel syndrome type 1	312870Xq26	*GPC3*	Growth factor	S
Smith-Lemli-Opitz syndrome	27040011q12-q13	*DHCR7*	Signal transduction	S
Syndactyly, type II	1860002q31-q32	*HOXD13*	Transcription factor	NS
Syndactyly, type IV	186200			NS
Tibia, absence of, and polydactyly	188740			NS
Tibia, of polydactyly and arachnoid cyst/hypoplasia	601027			S
Tibia, hypoplasia of, and polydactyly	188770			NS
Townes-Brocks syndrome	10748016q12.1	*SAL1*	Transcription factor	S
Triphalangeal thumb, nonopposable	190600			NS
Triphalangeal thumb-polysyndactyly syndrome	1906057q36			NS
Ulnar dysgen, polydactyly and renal cystic dysplasia	604380			S
Ulnar-mammary syndrome	18145012q24.1	*TBX3*	Transcription factor	S
Varadi-Papp syndrome	277170			S
Vater association	192350			S
Weyers acrofacial dysostosis	1935304p16	*EVC*	Unknown	S
Syndromic				97
Nonsyndromic				22

*OMIM: Online Mendelian Inheritance in Man entry number; type: the type of gene product.

careful regulation of gene expression and cell-cell communication during embryogenesis. The large number of DNA repair genes is attributable to two phenotypes, Fanconi anemia and Bloom syndromes, both of which have polydactyly (or partial digital duplication) as an infrequent manifestation [Auerbach et al., 2001; German and Ellis, 2001]. This list also includes five genes that have been shown to be mutated in a polydactyly disorder, although no functional information is currently assigned to those gene products.

The above discussion approaches the entries from two distinct vantages: molecular genetic and phenotypic. Depending on one's interest, expertise, and purpose, categorizing the entries different ways can make a great deal of sense and lead to productive generalizations. However, it can also lead to confusion. The list of the 39 entries with cloned genes provides ample evidence of this. First, how many disorders are really represented by this list? The strict clinician would probably say that there are 26 disorders (Fig. 1, left-hand bars), whereas the molecular biologist would claim 34 (Fig. 1, right-hand bars). Some illustrative examples will be considered. Among the entries, the *GLI3* gene makes four appearances (Greig cephalopolysyndactyly syndrome, Pallister-Hall syndrome, postaxial polydactyly type A1, and preaxial polydactyly type IV; five if the *p*olydactyly, *i*mperforate anus and *v*ertebral anomalies (PIV) syn-

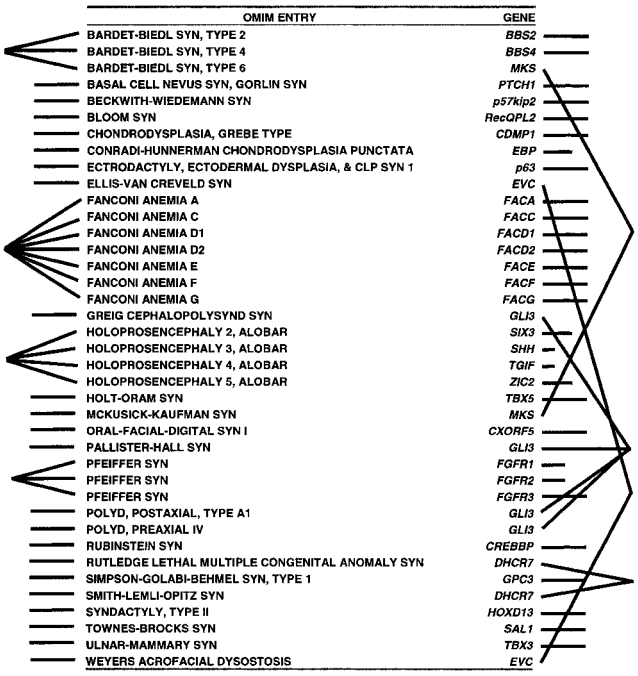

Fig. 1. Disease entries can be clustered either by phenotype or genotype, yielding different patterns. Phenotypes and genes are listed in the center. The bars flanking the left side of the phenotypes either designate distinct entities (unconnected horizontal bars) or separately listed entries that are a single phenotype (connected clusters of bars). There are four clusters and 22 individual phenotypes. The bars flanking the right side of the genes designate either unique gene entries (unconnected horizontal bars) or repetitive gene entries (connected clusters of bars). There are 29 unique genes and four clusters. The length of the bars has no significance and was adjusted to prevent spurious overlaps of bars.

drome is counted, though it is almost certainly not a valid diagnostic entity). Although one could argue that these are four distinct but allelic disorders, other views may be entertained. One view is that these four entries describe recognizable points of two distinct spectra. The first is the Pallister-Hall to postaxial polydactyly type A1 spectrum, and the second is the GCPS to preaxial polydactyly type IV spectrum. It is well recognized that the nonlimb manifestations of these two spectra are quite variable within families and so there is little reason to believe that these spectra can not encompass the particular manifestations that comprise such recognizable patterns. In this view, we can reduce the four entries to two spectra, but the molecular biologist intervenes at this point to suggest that genes are what matter, that the two phenotypic spectra are different in biologically unimportant ways and should be considered *"GLI3* morphopathies" [Radhakrishna et al., 1999], collapsing them further to a single entity.

The opposite problem arises for Fanconi anemia. In this case, one considers eight entries that are not clinically distinguishable, separated only by the in vitro complementation assay. However, these complementation groups correlate with the genetics, being associated with mutations in seven distinct genes (FA group H being the exception, having been shown to be allelic to FA group A). In this case, then, the molecular biologist sees six disorders and the clinician sees one.

Things get even more peculiar with the Bardet-Biedl and McKusick-Kaufman syndromes. The former has been known to have genetic heterogeneity for some time [Sheffield et al., 2001]. The latter is extraordinarily rare (and may actually be private to the Old Order Amish), as most infants diagnosed with McKusick-Kaufman syndrome develop additional manifestations and have their diagnosis changed to Bardet-Biedl syndrome later in life. Two groups subsequently showed that mutations in the MKKS gene that causes McKusick-Kaufman syndrome can also cause the Bardet-Biedl syndrome [Katsanis et al., 2000; Slavotinek et al., 2000]. Subsequently, two additional genes were found to be mutated in Bardet-Biedl patients (BBS2 and BBS4). It turns out that a substantial number of patients have two mutations in one of these genes and a second, heterozygous mutation in another of the three, consistent with a model of oligogenic inheritance or a modifier locus [Burghes et al., 2001; Katsanis et al., 2001]. In this case, the strict clinician would argue for two disorders. However, the molecular biologist is in trouble with this situation as the genes do not cleave the patients into discrete categories.

Much of this confusion and debate stems from the fact we cannot decide whether to label patients based on their genotype or their phenotype. This dichotomous thinking (genotype vs. phenotype) leads to confusion because for some groups of conditions genotypic labeling works very well and for others phenotypic labeling makes much more sense. Using different systems for different sets of disorders is untenable and will lead to further problems. To address this issue, a multiaxis nomenclature system has been proposed [Robin and Biesecker, 2001]. In this scheme, patients are coded

by two or three attributes simultaneously: genotype (axis I), phenotype (axis II), and environmental factors (axis III). This scheme acknowledges that all three attributes are important and necessary for many disorders (environmental influences are not coded in the examples here as there are no data to suggest that such influences are important in these disorders). It rejects the notion that disorders can only be named for any one of these attributes. An application of this scheme to some of the disorders in this analysis is shown below.

Example 1, a patient with Fanconi anemia syndrome. Axis I: Fanconi anemia syndrome; axis II: complementation group A, *FACA* del1671-1944, *FACA* del938-1050; axis III: N/A.

In this example, the phenotypic label is specified in axis I and would be the same for any patient with FA, regardless of which complementation group they were assigned to or which (if any) mutation they were found to have.

Example 2, two patients, one with McKusick-Kaufman syndrome and one with Bardet-Biedl syndrome. Axis I: McKusick-Kaufman syndrome; axis II: *MKKS* H84Y, *MKKS* H84Y; axis III: N/A.

Axis I: Bardet-Biedl syndrome; axis II: *MKKS* 1168delT, *MKKS* 429–430 delCT; axis III: N/A.

Here, the system simply and unambiguously describes the two patients as having a different phenotype but mutations in the same gene. The recent description of triallelic or major modifier genes in Bardet-Biedl syndrome can easily be accommodated in the system.

Example 3, a Bardet-Biedl patient with a mutation in a modifier gene. Axis I: Bardet-Biedl syndrome; axis II: *BBS2* Y24X, *BBS2* Y24X, *MKKS* A242S; axis III: N/A.

In this case, axis II is used to specify multiple genomic alterations as there are no constraints on the number of alterations that can be included.

In the end, there is no single answer to the question of how many disorders and how many genes are involved in polydactyly and limb development. The answer will always depend on why the question is being asked, what biologic question is being addressed, and who is asking. The method by which patients are diagnosed and described should be comprehensive in order to capture all relevant biologic data in a coherent and efficient manner. In human genetics and dysmorphology, the goal is twofold: to provide optimal care and counseling to the patients and to promote improved understanding of mammalian development through the study of human malformations. There is little argument that genes and environment interact to generate phenotypes; what we need is a diagnostic coding system that reflects our understanding of all three.

REFERENCES

Auerbach AD, Buchwald M, Joenje H. 2001. Fanconi Anemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. New York: McGraw-Hill. p 753–768.

Burghes AH, Vaessin HE, de La Chapelle A. 2001. Genetics: the land between Mendelian and multifactorial inheritance. Science 293:2213–2214.

Cormier-Daire V, Wolf C, Munnich A, Le Merrer M, Nivelon A, Bonneau D, Journel H, Fellmann F, Chevy F, Roux C. 1996. Abnormal cholesterol biosynthesis in the Smith-Lemli-Opitz and the lethal acrodysgenital syndromes. Eur J Pediatr 155:656–659.

German J, Ellis NA. 2001. Bloom syndrome. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. New York: McGraw-Hill. p 733–751.

Jones KL. 1997. Smith's recognizable patterns of human malformation. Philadelphia: W.B. Saunders. p 816.

Kang S, Graham JM Jr, Olney AH, Biesecker LG. 1997. *GLI3* frameshift mutations cause autosomal dominant Pallister-Hall syndrome. Nat Genet 15:266–268.

Katsanis N, Beales PL, Woods MO, Lewis RA, Green JS, Parfrey PS, Ansley SJ, Davidson WS, Lupski JR. 2000. Mutations in MKKS cause obesity, retinal dystrophy and renal malformations associated with Bardet-Biedl syndrome. Nat Genet 26:67–70.

Katsanis N, Ansley SJ, Badano JL, Eichers ER, Lewis RA, Hoskins BE, Scambler PJ, Davidson WS, Beales PL, Lupski JR. 2001. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. Science 293:2256–2259.

Killoran CE, Abbott M, McKusick VA, Biesecker LG. 2000. Overlap of PIV syndrome, VACTERL and Pallister-Hall syndrome: clinical and molecular analysis. Clin Genet 58:28–30.

Online Mendelian Inheritance in Man (OMIM). 2000. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University, Baltimore, MD, and National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD (http://www.ncbi.nlm.nih.gov/omim/).

Radhakrishna U, Wild A, Grzeschik K-H, Antonarakis SE. 1997. Mutation in *GLI3* in post-axial polydactyly type A. Nat Genet 17:269–270.

Radhakrishna U, Bornholdt D, Scott HS, Patel UC, Rossier C, Engel H, Bottani A, Chandal D, Blouin JL, Solanki JV, Grzeschik KH, Antonarakis SE. 1999. The phenotypic spectrum of GLI3 morphopathies includes autosomal dominant preaxial polydactyly type-IV and postaxial polydactyly type-A/B: no phenotype prediction from the position of *GLI3* mutations. Am J Hum Genet 65:645–655.

Robin NH, Biesecker LG. 2001. Considerations for a multiaxis nomenclature system for medical genetics. Genet Med 3:290–293.

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. 2000. Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrodental dysostosis. Nat Genet 24:283–286.

Sheffield VC, Nishimura D, Stone EM. 2001. The molecular genetics of Bardet-Biedl syndrome. Curr Opin Genet Dev 11:317–321.

Slavotinek A, Stone E, Mykytyn K, Heckenlively J, Green J, Heon E, Musarella M, Parfrey P, Sheffield V, Biesecker L. 2000. Mutations in *MKKS* cause Bardet-Biedl syndrome. Nat Genet 26:15–16.

Stone D, Slavotinek A, Bouffard G, Banerjee-Basu S, Baxevanis A, Barr M, Biesecker L. 2000. Mutations of a gene encoding a putative chaperonin causes McKusick-Kaufman syndrome. Nat Genet 25:79–82.

Temtamy S, McKusick VA. 1969. Synopsis of hand malformations with particular emphasis on genetic factors. Birth Defects Orig Artic Ser 5(3):125–184.

Vortkamp A, Gessler M, Grzeschik K-H. 1991. *GLI3* zinc finger gene interrupted by translocations in Greig syndrome families. Nature 352:539–540.

Wassif CA, Maslen C, Kachilele-Linjewile S, Lin D, Linck LM, Connor WE, Steiner RD, Porter FD. 1998. Mutations in the human sterol delta7-reductase gene at 11q12-13 cause Smith-Lemli-Opitz syndrome. Am J Hum Genet 63:55–62.

Winter RM, Schroer RJ, Meyer LC. 1993. Hands and feet. In: Stevenson RE, Hall JG, Goodman RM, editors. Human malformations and related anomalies. New York: Oxford University Press. p 805–843.