Polydactyly: How Many Disorders and How Many Genes?

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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. Published 2002 Wiley-Liss, Inc.[†]

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*

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

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TABLE I. Disorder Data*

Disorder	OMIM mapped	Gene	Туре	S/NS
Acrocallosal syndrome	20099012p13.3-p11.2			s
Acrocephalopolydactylous dysplasia	200995			\mathbf{S}
Acrocephalopolysynd type II	201000			\mathbf{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			2
Bardet Biedl sundreme, type 1	20000111~12			2 2
Bardet-Biedl syndrome, type 1	20990111q13 20990016a21	BBS9	Unknown	S
Bardet-Biedl syndrome, type 2	6001513n13-n12	DD52	Clikilown	S
Bardet-Biedl syndrome, type 9	60037415g22 3-g23	BBS4	Unknown	S
Bardet-Biedl syndrome, type 5	6036502a31	2201		$\tilde{\mathbf{s}}$
Bardet-Biedl syndrome, type 6	60523120p12	MKS	Chaperonin	ŝ
Bardet-Biedl syndrome, type 7	Pending	-		S
Basal cell nevus syndrome, gorlin syndrome	1094009g22.3	PTCH1	Signal transduction	S
Beckwith-Wiedemann syndrome	13065011p15.5	p57kip2	Cell cycle	\mathbf{S}
Biemond syndrome II	210350	• •	·	\mathbf{S}
Bloom syndrome	21090015q26	RecQPL2	DNA repair	\mathbf{S}
Branchial clefts, char facies, growth retardation, etc.	113620		_	\mathbf{S}
C syndrome	211750			\mathbf{S}
Chondrodysplasia, Grebe type	20070020q11.2	CDMP1	Signal transduction	\mathbf{S}
Coach syndrome	216360			\mathbf{S}
Conradi-Hunnerman chondrodyspl punctata	302960Xp11.2	EBP	Metabolic	\mathbf{S}
Cran-fac malf, polysyndactyly, abnormal skin and gut development	601707			\mathbf{S}
Dandy-Walker malformation and postaxial polydactyly	220220			\mathbf{S}
Disorganization, mouse, homolog of	223200			\mathbf{S}
Ectrodactyly, ectodermal dysplasia, and cleft lip palate syndrome 1	1299007q11.2-q21.3	p63	Transcription factor	\mathbf{S}
Ectrodactyly-polydactyly	225290			NS
Ellis-van creveld syndrome	2255004p16	EVC	Unknown	\mathbf{S}
Fanconi anemia A	22765016q24	FACA	DNA repair	\mathbf{S}
Fanconi anemia B	227660			\mathbf{S}
Fanconi anemia C	2276459q22.3	FACC	DNA repair	\mathbf{S}
Fanconi anemia D1	605724	FACD1	DNA repair	\mathbf{S}
Fanconi anemia D2	2276463 p 25.3	FACD2	DNA repair	\mathbf{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	13575014q13			NS
absent tibla and radius	196760			C
Frontonasal dyspiasia	130700			a a
Frontonasai dyspiasia	303043 999090			2
Coltz focal dormal hypoplasia	305600			2
Greig cenhalonolysynd syndrome	1757007n13	GL13	Transcription factor	S
Hamifacial microsomia and radial defects	1/1/00	UL15	Transcription factor	S
Hirschsprung disease, congenital heart defect,	604211			$\ddot{\mathbf{s}}$
Hirschsprung disease, polydactyly,	235740			S
renal agenesis, and deatness Hirschsprung disease, polydactyly, polysyndactyly	235750			\mathbf{S}
of toes, and congenital heart defect			—	~
Holoprosencephaly 2, alobar	6037142p13	SIX3	Transcription factor	\mathbf{s}
Holoprosencephaly 1, alobar	23610021q22.3			S
Holoprosencephaly 2, alobar	1571702p21	CI III		S
Holoprosencephaly 3, alobar	1429457936	SHH	Signal transduction	8
Holoprosencephaly 4, alobar	14294018p 60207212-	TGIF	Transcription factor	D C
Holt Oram sundrome	14900019~94 1	LICZ TDV5	Transcription factor	20
Holzgreve syndrome	14230012424.1 236110	I DAU	rranscription factor	D D
Hydrolethalus syndrome	23668011a22 a25			D D
Joubert syndrome 1	2133009a34 3			S
Sousci i Synui onic I	21000004010			0

TABLE I. (Continued)

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$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Meckel syndrome, type 1	24900017q22-q23			2
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an and relati Inpulation (year less), 500 - 120 S (Year Section 1), 500 - 120 S (Year Section 2), 500 - 120 - 1200	Migrocoph corpus collogum dysgonosis	601420			2
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	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, righthand 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 polydactyly, imperforate anus and vertebral anomalies (PIV) syn-

OMIM ENTRY	GENE	
BARDET-BIEDL SYN, TYPE 2	BBS2	
BARDET-BIEDL SYN, TYPE 4	BBS4	
BARDET-BIEDL SYN, TYPE 6	MKS	۱
BASAL CELL NEVUS SYN, GORLIN SYN	PTCH1	\
BECKWITH-WIEDEMANN SYN	p57kip2	<u> </u>
BLOOM SYN	RecQPL2	\rightarrow
CHONDRODYSPLASIA, GREBE TYPE	CDMP1	<u> </u>
CONRADI-HUNNERMAN CHONDRODYSPL	ASIA PUNCTATA EBP	<u> </u>
ECTRODACTYLY, ECTODERMAL DYSPLAS	SIA, & CLP SYN 1 p63	<u> </u>
ELLIS-VAN CREVELD SYN	EVC	· · ·
FANCONI ANEMIA A	FACA	ł /
FANCONI ANEMIA C	FACC	$t - \prime$
FANCONI ANEMIA D1	FACD1	<u>→</u>
FANCONI ANEMIA D2	FACD2	+ /
FANCONI ANEMIA E	FACE	\rightarrow /
FANCONI ANEMIA F	FACF	\rightarrow /
FANCONI ANEMIA G	FACG	<u> </u>
 GREIG CEPHALOPOLYSYND SYN 	GLI3	\sqrt{V}
HOLOPROSENCEPHALY 2, ALOBAR	SIX3	<u>→</u> _X
HOLOPROSENCEPHALY 3, ALOBAR	SHH	-///
- HOLOPROSENCEPHALY 4, ALOBAR	TGIF	- 7 /
HOLOPROSENCEPHALY 5, ALOBAR	ZIC2	- / \\
HOLT-ORAM SYN	TBX5	<i>≁</i> _\\
 MCKUSICK-KAUFMAN SYN 	MKS	/ \
ORAL-FACIAL-DIGITAL SYN I	CXORF5	— N
- PALLISTER-HALL SYN	GLI3	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
PFEIFFER SYN	FGFR1	- ^
PFEIFFER SYN	FGFR2	— // \
PFEIFFER SYN	FGFR3	H }
POLYD, POSTAXIAL, TYPE A1	GL13	///
POLYD, PREAXIAL IV	GLI3	
RUBINSTEIN SYN	CREBBP	/
RUTLEDGE LETHAL MULTIPLE CONGENIT	AL ANOMALY SYN DHCR7	
SIMPSON-GOLABI-BEHMEL SYN, TYPE 1	GPC3	\rightarrow
SMITH-LEMLI-OPITZ SYN	DHCR7	
SYNDACTYLY, TYPE II	HOXD13	\rightarrow
TOWNES-BROCKS SYN	SAL1	/-
ULNAR-MAMMARY SYN	TBX3	≁
 WEYERS ACROFACIAL DYSOSTOSIS 	EVC	/

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.

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