

# Disorders caused by chromosome abnormalities

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**Abstract:** Many human genetic disorders result from unbalanced chromosome abnormalities, in which there is a net gain or loss of genetic material. Such imbalances often disrupt large numbers of dosage-sensitive, developmentally important genes and result in specific and complex phenotypes. Alternately, some chromosomal syndromes may be caused by a deletion or duplication of a single gene with pleiotropic effects. Traditionally, chromosome abnormalities were identified by visual inspection of the chromosomes under a microscope. The use of molecular cytogenetic technologies, such as fluorescence in situ hybridization and microarrays, has allowed for the identification of cryptic or submicroscopic imbalances, which are not visible under the light microscope. Microarrays have allowed for the identification of numerous new syndromes through a genotype-first approach in which patients with the same or overlapping genomic alterations are identified and then the phenotypes are described. Because many chromosomal alterations are large and encompass numerous genes, the ascertainment of individuals with overlapping deletions and varying clinical features may allow researchers to narrow the region in which to search for candidate genes.

**Keywords:** chromosome, deletion, duplication, telomere, segmental duplication

## Introduction

Humans have 23 pairs of chromosomes, ie, one pair of sex chromosomes (X and/or Y) and 22 pairs of autosomes (chromosomes 1–22). Many human genetic disorders result from unbalanced chromosome abnormalities, in which there is a net gain or loss of genetic material. Numeric and structural chromosomal abnormalities occur in approximately 0.6% of live births,<sup>1</sup> and often result in dysmorphism, malformations, and/or developmental disabilities. The resulting phenotypes are caused by the imbalance of one or more dosage-sensitive genes in a particular chromosome or chromosomal segment. Such gene imbalances often have devastating consequences and cause 25% of all miscarriages and stillbirths, and 50%–60% of first-trimester miscarriages.<sup>2</sup>

Numeric abnormalities, or aneuploidies, result from the gain or loss of an entire chromosome. Most aneuploidies result from improper segregation of the chromosome pairs during meiosis. Numeric abnormalities comprise the most common cytogenetic abnormalities. Numeric abnormalities are more tolerated for the sex chromosomes and only certain autosomes. The most common monosomy is that for the X chromosome (45,X) found in Turner syndrome. Trisomy, the presence of three, rather than two, copies of a particular chromosome, causes Down syndrome, or trisomy 21, and occurs in about 1/800 live births. Other common trisomies include trisomy 13 and 18. Mosaicism for a normal cell line and an abnormal cell line may occur in a single

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individual. Certain trisomies, such as trisomy 8 and 9, rarely occur in all cells and are mostly found in individuals with mosaicism.

In contrast with numeric abnormalities, structural chromosomal abnormalities result from the breakage and subsequent reunion of chromosome arms. Some structural chromosome abnormalities result in gain or loss of material. Deletions involve the loss of a segment of a chromosome and duplications result in a gain of a chromosome segment. Deletions may be terminal or interstitial; a terminal deletion results after one break in the chromosome with loss of the segment distal to the break, whereas an interstitial deletion results after two breaks in the chromosome, with the loss of the intervening segment, and rejoining of the remaining chromosome segments. A duplication is caused by the gain of a copy of a chromosomal segment at the original location on the chromosome. Duplications may be in an inverted orientation or in the original (direct) orientation.

Other structural chromosome abnormalities do not result in gain or loss of any genetic material. Such rearrangements include inversions, which are caused by a two-break event and the end-to-end reversal of the intervening chromosomal segment; translocations, which result from the exchange of chromosome segments between two or more chromosomes; and insertions, which occur when a segment of one chromosome is translocated and inserted into a new region of the same chromosome, the other homolog, or a nonhomologous chromosome. These rearrangements may be pathogenic if a gene(s) is disrupted by a rearrangement breakpoint, a novel fusion gene product is formed, or a position effect is exerted on genes neighboring the rearrangement.

Compared with, for example, single-gene mutations, chromosome abnormalities often disrupt large numbers of developmentally important genes. Such imbalances may alter the dosage of genes expressed within the affected chromosomal segment, resulting in clinical consequences for the individual (see Table 1). Some imbalances result in a contiguous gene syndrome, in which multiple genes within the deleted or duplicated region are affected, each contributing a discrete clinical feature to the phenotype.<sup>3</sup> Alternately, some chromosomal syndromes may be caused by a deletion or duplication of a single gene with pleiotropic effects. For most deletion syndromes, deletion causes haploinsufficiency of a gene or genes in the region, in which the remaining intact copy of the gene does not produce sufficient gene product for normal function. Haploinsufficiency for specific genes has been identified in several syndromes, including Williams

syndrome, Langer–Giedion syndrome, Miller–Dieker syndrome, and DiGeorge/velocardiofacial syndrome.

Traditionally, chromosome abnormalities were identified by visual inspection of the chromosomes under a microscope. Each chromosome can be divided into bands, which are sections of a chromosome that can be distinguishable from adjacent sections by lighter or darker variations in intensity following one or more staining methods. The original reports of chromosome rearrangements were made prior to the development of these staining techniques. Thus, any rearrangements recognized under the microscope were either numeric or an altered segment of the chromosome large enough so that the affected homolog could be easily distinguished from the normal homolog based on the overall size of the chromosome.<sup>4,5</sup> The development of banding techniques and high-resolution chromosome analysis enabled the detection of subtle rearrangements that affected one or a few chromosome bands. The use of molecular cytogenetic technologies, such as fluorescence in situ hybridization (FISH) and microarrays, has allowed for the identification of cryptic or submicroscopic imbalances, which are not visible under the light microscope (Figure 1). Numerous previously unrecognized microdeletion and microduplication syndromes have been identified by these molecular cytogenetic techniques.<sup>6–16</sup>

In 1986, Schmickel<sup>3</sup> first described contiguous gene syndromes (CGS) as involvement of multiple genes located in close proximity to each other on a chromosome. This term has been refined over the years and expanded to include a group of disorders defined by a deletion or duplication of a chromosomal segment spanning more than one disease gene, each affecting the phenotype independently. CGS have been described for many disorders mapping to various chromosomes. Disorders now recognized as CGS often have subtle cytogenetic changes that cannot always be resolved with conventional cytogenetic methods. Molecular cytogenetics, specifically FISH and microarray analysis, has helped to characterize many CGS.

## Terminal rearrangements

Of all cytogenetically visible structural abnormalities, the majority occur in the distal telomeric bands of the chromosomes.<sup>17</sup> Telomeres are specialized protein-DNA structures at the ends of all linear chromosomes that play numerous important cellular roles, including the prevention of chromosome degradation and end-to-end chromosome fusions,<sup>18</sup> as well as the proper pairing, recombination, and segregation of chromosome homologs during meiosis.<sup>19</sup>

Table 1

Microdeletion/ microduplication syndrome	Common features	OMIM#	Gene/locus	Location	Size of aberration	Detection rate for deletion/duplication by microarray	References
1p36 microdeletion	Dysmorphic facial features (deep-set eyes, flat nasal bridge, asymmetric ears, and pointed chin), seizures, cardiomyopathy, developmental delay, and hearing impairment	607872	Multiple	1p36	Variable	~99% have a detectable deletion	Heistedt et al <sup>93</sup> ; Heistedt et al <sup>94</sup> ; Yu et al <sup>95</sup>
1q21.1 microdeletion with susceptibility for thrombocytopenia-absent radius	Hypomegakaryocytic thrombocytopenia, upper extremity abnormalities ranging from bilateral absent radii to phocomelia; normal intellect	274000	Multiple	1q21.1	500 kb deletion mediated by LCRs	~99% have a detectable deletion	Klopocki et al <sup>96</sup>
1q21.1 microdeletion with susceptibility to mental retardation, autism, or congenital anomalies	Mild to severe mental retardation, microcephaly, occasional congenital heart disease; schizophrenia	612474	Multiple	1q21.1	1.5 Mb deletion mediated by LCRs	~99% have a detectable deletion	International Schizophrenia Consortium; <sup>97</sup> Stefansson et al; <sup>98</sup> Brunetti-Pierri et al; <sup>99</sup> Mefford et al <sup>100</sup> Willatt et al <sup>101</sup>
3q29 microdeletion	Mild-to-moderate mental retardation, with only slightly dysmorphic facial features that are similar in most patients: a long and narrow face, short philtrum, and high nasal bridge	609425	Multiple	3q29	1.5 Mb deletion mediated by LCRs	~99% have a detectable deletion	Balouniene et al <sup>90,91</sup>
10q22.3q23.2 microdeletion	Learning disabilities, speech and language delay, mild developmental delays, mild dysmorphic features	N/A	Multiple	10q22.3q23.2	7.95 Mb deletion mediated by LCRs	~99% have a detectable deletion	Wang et al <sup>102,103</sup>
15q11-15q13 microduplication*	Autism, mental retardation, ataxia, and seizures	608636	Multiple	15q11-15q13	Duplications most commonly occur between BP3B-BP3B and BP4-BP5	~99% have interstitial duplications; precise detection rate of markers depends on size of duplicated region	
15q13.3 microdeletion	Mental retardation, epilepsy, and variable dysmorphism of the face and digits	612001	Multiple	15q13.3	Deletions occur between BP3-BP5, 3.95 Mb; BP4-BP5, 1.6 Mb	~99% have a detectable deletion	Sharp et al; <sup>104,105</sup> Slavotinek <sup>106</sup>
15q24 microdeletion	Mild to moderate mental retardation, high anterior, hairline, downslanting palpebral fissures, long philtrum, digital abnormalities, genital abnormalities, loose connective tissue	N/A	Multiple	15q24.1q24.3	1.8 Mb deletion mediated by LCRs	~99% have a detectable deletion	Klopocki et al <sup>13,14</sup>
16p11.2p12.2 microdeletion	Severe developmental delay; hypotonia; flat facies, downslanting palpebral fissures, posteriorly rotated ears	N/A	Multiple	16p11.2p12.2	7.1-8.4 Mb deletions mediated by LCRs	~99% have a detectable deletion	Ballif et al <sup>6</sup>

(Continued)

Table 1 (Continued)

Microdeletion/ microduplication syndrome	Common features	OMIM#	Gene/locus	Location	Size of aberration	Detection rate for deletion/duplication by microarray	References
17q21.31 microdeletion	Mild to severe global developmental delay, childhood hypotonia, long face, tubular, or pear-shaped nose, bulbous nasal tip, friendly/amiable behavior	610443	Multiple	17q21.31	700 kb deletion mediated by LCRs	~99% have a detectable deletion	Koolen et al <sup>10-12</sup>
17q23.1q23.2 microdeletion	Speech delay, postnatal growth retardation, heart defects and hand, foot and limb abnormalities	N/A	Multiple	17q23.1q23.2	2.2–2.8 Mb deletions mediated by LCRs	~99% have a detectable deletion	Ballif et al <sup>107</sup>
22q11.2 distal microdeletion	Features mildly suggestive of DGS/VCFs, prematurity, prenatal and postnatal growth delay, developmental delay, and mild skeletal abnormalities	611867	Multiple	22q11.2	1.4 Mb–2.1 Mb deletion distal to the common 3Mb deletion of DGS/VCFs	~99% have a detectable deletion	Ben-Shachar et al <sup>108,109</sup>
22q11.21 microduplication	Failure to thrive, marked hypotonia, sleep apnea, and seizure-like episodes in infancy, delay of gross motor development with poor fine motor skills, velopharyngeal insufficiency, and a significant delay in language skills	608363	Multiple	22q11.21	3.0 Mb duplication	~99% have a detectable duplication	Ensenauer et al <sup>59,110-112</sup>
22q13.3 microdeletion	Neonatal hypotonia, global developmental delay, normal to accelerated growth, absent to severely delayed speech, autistic behavior, and minor dysmorphic features	606232	Multiple	22q13.3	130 kb deletion	~99% have a detectable deletion	Phelan et al <sup>35,113-115</sup>
Adrenal hypoplasia congenita	A rare developmental disorder of the human adrenal cortex caused by deletion or mutation of the <i>DAX-1</i> gene; hypogonadotropic hypogonadism is frequently associated with AHC	300200	NR0B1	Xp21.2	Generally part of a contiguous gene deletion with Duchenne muscular dystrophy and GK	~18% have a detectable deletion in isolated AHC; ~99% have a detectable deletion in AHC/GKD or AHC/GKD/DMD	Guo et al <sup>116,117</sup>
Alagille	Chronic cholestasis caused by intrahepatic biliary hypoplasia, cardiac disease, skeletal abnormalities, and a characteristic facial phenotype	118450	JAG1	20p12.2	Variability in deletion size	3%–7% have a detectable deletion	Krantz et al <sup>118,119</sup>
Angelman	Mental retardation, movement or balance disorder, characteristic abnormal behaviors, and severe limitations in speech and language	105830	UBE3A	15q11.2	Deletions spanning the segment between BP1 or BP2 to BP3 have been estimated at 6 Mb, although larger deletions occur	~70% have a detectable deletion	Magenis et al <sup>120,121</sup>
Beckwith-Wiedemann, IGF <sub>2</sub> -related*	Exomphalos, macroglossia, and gigantism in the neonate; an omphalocele or other umbilical abnormalities characteristic at birth	130650	IGF2	11p15.5	Duplications of IGF <sub>2</sub> have been reported	Majority have paternal isodisomy or mutations not detectable by array CGH	Henri et al <sup>122-124</sup>

Cat eye	Coloboma of the iris, anal atresia with fistula, downslanting palpebral fissures, preauricular tags and/or pits, frequent occurrence of heart and renal malformations, and normal or near-normal mental development	115470	Multiple	22q11.1	A small supernumerary chromosome is present, frequently has two centromeres, is bisatellited, and represents an inv dup(22)(q11)	Precise detection rate unknown, although, the supernumerary marker chromosome is detectable by array CGH	Bartsch et al <sup>125-127</sup>
Charcot-Marie-Tooth Type 1A	Slowly progressive distal muscle wasting, weakness and decreased nerve conduction velocities; the age of onset of symptoms is variable	118220	PMP22	17p12	1.5 Mb duplication mediated by LCRs		Lupski et al <sup>143,128,129</sup>
CHARGE	Coloboma of the eye, heart anomaly, atresia, choanal, retardation of mental and somatic development; microphallus; ear abnormalities and/or deafness; facial palsy, cleft palate, and dysphagia are commonly associated	214800	CHD7	8q12.2	2.3 Mb deletion	~10% have a detectable deletion	Visser et al <sup>130</sup>
Cri du chat	High-pitched cat-like cry, microcephaly, round face, hypertelorism, micrognathia, epicanthal folds, low-set ears, hypotonia, and severe psychomotor and mental retardation	123450	Multiple	5p15.2	Size is variable and may be terminal, interstitial or whole arm deletions	~99% have a detectable deletion	Church et al <sup>131-133</sup>
DiGeorge 1/velocardiofacial	Hypocalcemia arising from parathyroid hypoplasia, thymic hypoplasia, and outflow tract defects of the heart; disturbance of cervical neural crest migration into the derivatives of the pharyngeal arches and pouches can account for the phenotype; many patients die due to cardiac complications or poor immune function	188400	HIRA TBX1	22q11.21	3.0 Mb deletion mediated by LCRs	>95% have a detectable deletion	Shaikh et al <sup>136,134,135</sup>
DiGeorge 2	Features similar to DiGeorge 1, including mild mental retardation and slight dysmorphic features of the face, head, and skeletal system	601362	Multiple	10p14	2.0 Mb and has been reported both terminal and interstitial	<1% have a detectable deletion	Berend et al <sup>136,137</sup>
Duchenne muscular dystrophy	Progressive proximal muscular dystrophy with characteristic pseudohypertrophy of the calves; massive elevation of creatine kinase levels in the blood, myopathic changes by electromyography, and myofiber degeneration, with fibrosis and fatty infiltration on muscle biopsy, onset usually occurs before age three years, and the victim is usually wheelchair-ridden by age 12 and dead by age 20	310200	DMD	Xp21.2-p21.1	Deletions are most often associated with a contiguous gene deletion including AHC and GK		Del Gaudio et al <sup>138-140</sup>

(Continued)

Table 1 (Continued)

Microdeletion/ microduplication syndrome	Common features	OMIM#	Gene/locus	Location	Size of aberration	Detection rate for deletion/duplication by microarray	References
Greig cephalopolysyndactyly	Polydactyly, macrocephaly, and hypertelorism; may be associated with cognitive deficits and abnormalities of the corpus callosum	175700	GLI3	7p14.1	Contiguous gene deletion with variable sizes from 151 kb to 10.6 Mb	~30% have a detectable deletion	Johnston et al <sup>141</sup>
Glycerol kinase deficiency	Mental retardation, growth retardation, elevated urinary glycerol and pseudo-hypertriglyceridemia	300474	GK	Xp21.2	Deletions are most often associated with a contiguous gene deletion including AHC and GK	Deletions uncommon; majority have mutations not detectable by array CGH	Sargent et al <sup>142</sup>
Hereditary liability to pressure palsies	Recurrent episodes of truncular palsies	162500	PMP22	17p12	1.5 Mb deletion mediated by LCRs	~99% have detectable deletion	Inoue et al <sup>128,143-145</sup>
Kallmann I	Congenital, isolated, idiopathic hypogonadotropic hypogonadism and anosmia.	308700	KALI	Xp22.31	Isolated deletions are rare, often found as a contiguous gene deletion with steroid sulfatase deficiency	10%–12% have a detectable deletion	Ballabio et al <sup>146-148</sup>
Langer-Giedion	Multiple dysmorphic facial features including large, laterally protruding ears, a bulbous nose, an elongated upper lip, as well as sparse scalp hair; winged scapulae, multiple cartilaginous exostoses, redundant skin, and mental retardation	150230	TRPS1 EXT1	8q23.3 8q24.11	Contiguous gene deletion including TRPS1 and EXT1	~75% have a detectable deletion	Ludecke et al <sup>149,150</sup>
Microphthalmia 7 with linear skin defects	Unilateral or bilateral microphthalmia and linear skin defects limited to the face and neck, consisting of areas of aplastic skin that heal with age to form hyperpigmented areas in affected females and in utero lethality for males	309801	Multiple	Xp22.2	Deletions are variable in size	Precise detection rate unknown, although majority of reported deletions are detectable by array CGH	Kayserili et al <sup>151-153</sup>
Miller-Dieker/Lissencephaly I	Lissencephaly (pachygyria, incomplete or absent gyration of the cerebrum), microcephaly, wrinkled skin over the glabella and frontal suture, prominent occiput, narrow forehead, downward slanting palpebral fissures, small nose and chin, cardiac malformations, hypoplastic male external genitalia, growth retardation, and mental deficiency with seizures and electroencephalographic abnormalities. Life expectancy is grossly reduced, with death most often occurring during early childhood	247200	PAFAH1B1 (LIS1)	17p13.3	Contiguous gene deletion with a minimum size of 400 Kb	85%–90% have a detectable deletion	Dobyns et al <sup>154,155</sup>

Neurofibromatosis 1/MR	Variable facial dysmorphisms, mental retardation, developmental delay, and an excessive number of neurofibromas for age	162200	NFI	17q11.2	~5%–20% of all NFI patients carry a 1.5 Mb deletion (NFI and contiguous genes) mediated by LCRs	5%–20% have a detectable deletion	Crossen et al <sup>156,157</sup>
Pelizaeus–Merzbacher	Nystagmus, spastic quadriplegia, ataxia, and developmental delay.	312080	PLPI	Xq22.2	Duplications are variable in size and deletions have been reported in a few cases	60%–70% have a detectable duplication	Inoue et al <sup>158,159</sup>
Potocki–Lupski/17p11.2 microduplication*	Infantile hypotonia, failure to thrive, mental retardation, autistic features, sleep apnea, and structural cardiovascular anomalies	610883	Multiple	17p11.2	Two categories of duplications: recurrent 3.7 Mb duplication mediated by LCRs and non-recurrent duplications ranging in size from 1.3 to 15.2 Mb	~99% have a detectable duplication	Potocki et al <sup>160,161</sup>
Potocki–Shaffer	Mental retardation, biparietal foramina, minor facial anomalies, and multiple cartilaginous exostoses	601224	EXT2 ALX4	11p11.2	2.1 Mb deletion	~99% have a detectable deletion	Wakui et al <sup>160,161</sup>
Prader–Willi	Obesity, muscular hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism, and small hands and feet; the face is characterized by a narrow bifrontal diameter, almond-shaped eyes (often in mild upslanted position), strabismus, full cheeks, and diminished mimic activity due to muscular hypotonia	176270	SNRPN	15q11.2	Type 1 mediated by LCR, BPI-BP3; Type 2 mediated by BP2 and BP3	~70% have a detectable deletion	Magenis et al <sup>162,163</sup>
Retinoblastoma/MR	Retinoblastoma is an embryonic tumor of the eye; variability in patients with interstitial deletions at 13q14, have been seen and may include retinoblastoma tumor as well as mental retardation, reintoblastoma without mental retardation, and no retinoblastoma	180200	RBI	13q14.2	Variable size	80% have a detectable deletion	Cowell et al <sup>164,165</sup>
Rubinstein–Taybi	Mental retardation, broad thumbs and toes, and facial abnormalities	180849	CREBBP	16p13.3	25% of patients have a deletion encompassing the CREBBP gene	11% have a detectable deletion	Petrij et al <sup>166,167</sup>
Smith–Magenis	Broad flat midface with brachycephaly, broad nasal bridge, brachydactyly, speech delay, and hoarse, deep voice; other common features include decreased or absent deep tendon reflexes, pes planus or pes cavus, decreased sensitivity to pain, and decreased leg muscle mass, suggestive of peripheral neuropathy; self-destructive behaviors, primarily onychotillomania and polyembolokolomania, and significant symptoms of sleep disturbance have been observed	182290	RAI1	17p11.2	3.7 Mb deletion mediated by LCRs	90%–99% have a detectable deletion	Seranski et al <sup>168–171</sup>

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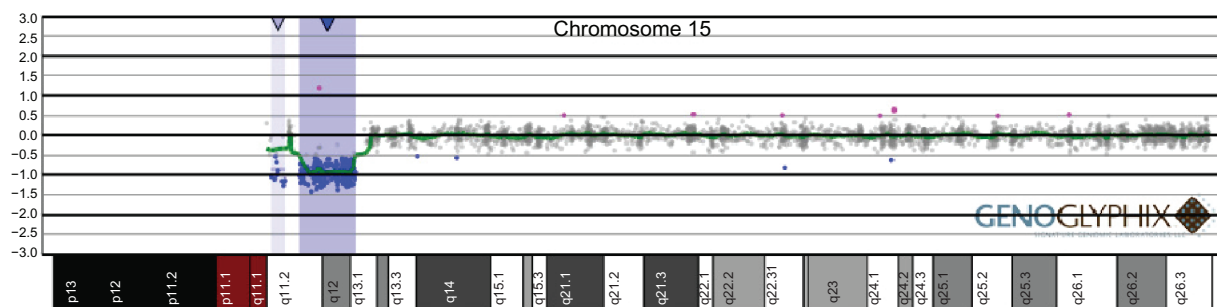


Table 1 (Continued)

Microdeletion/ microduplication syndrome	Common features	OMIM#	Gene/locus	Location	Size of aberration	Detection rate for deletion/duplication by microarray	References
Sotos	Excessively rapid growth, acromegalic features, and a nonprogressive cerebral disorder with mental retardation; high-arched palate and prominent jaw has been noted; bone age is advanced in most	117550	NSDI	5q35.3	Some cases are 2 Mb in size mediated by LCRs; however, there are some variable size deletions.	10%–40% have a detectable deletion depending upon ethnicity	Kurotaki et al <sup>150,172–174</sup>
Steroid sulfatase deficiency	Steroid sulfatase deficiency causes an X-linked form of ichthyosis, and has a variable presentation characterized by dry, scaly skin, sparse hair and conical teeth in affected males	308100	STS	Xp22.31	interstitial deletions of the STS gene	80%–90% have a detectable deletion	Ballabio et al <sup>175–178</sup>
Trichorhinophalangeal Type I	Dysmorphic features include sparse scalp hair, a bulbous tip of the nose, a long flat philtrum, a thin upper vermillion border and protruding ears; skeletal abnormalities include cone-shaped epiphyses at the phalanges, hip malformations, and short stature	190350	TRPS1	8q23.3	interstitial deletions of TRPS1 gene	<20% have a detectable deletion	Momeni et al <sup>179,180</sup>
WAGR	Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation	194072	PAX6 WT1	11p13	Contiguous gene deletion of PAX6 and WT1	~66% have a detectable deletion	Crolla et al <sup>181</sup>
Williams–Beuren	Supravalvular aortic stenosis, multiple peripheral pulmonary arterial stenoses, elfin face, mental and statural deficiency, characteristic dental malformation, and infantile hypercalcemia	194050	ELN	7q11.23	1.5 Mb	>95% have a detectable deletion	Nickerson et al <sup>152,182</sup>
Wilms tumor Type I	Wilms tumor I is part of a contiguous gene deletion syndrome, WAGR. Wilms tumor is one of the most common solid tumors of childhood, occurring in 1 in 10,000 children and accounting for 8% of childhood cancers	194070	WT1	11p13	25 bp, only detectable by FISH when part of the contiguous gene deletion, WAGR	Rare deletions unless associated with contiguous gene syndrome	Royer-Pokora et al <sup>183</sup>
Wolf–Hirschhorn	Severe growth retardation and mental defect, microcephaly, “Greek helmet” facies, and closure defects, including cleft lip or palate, coloboma of the eye, and cardiac septal defects	194190	Multiple	4p16.3	Terminal and interstitial deletions of 4p with a critical region of 750 kb	95% have a detectable deletion	van Buggenhout et al <sup>184–186</sup>
X-linked heterotaxy	Randomization of the placement of visceral organs, including the heart, lungs, liver, spleen, and stomach; the organs are oriented randomly with respect to the left-right axis and with respect to one another	306955	ZIC3	Xq26.3		Deletions detectable by FISH/array CGH are rare	Ferrero et al <sup>187,188</sup>

**Abbreviations:** BWS, Beckwith-Wiedemann syndrome; LCR, low-copy repeat; AHC, adrenal hypoplasia congenita; GKD, glycerol kinase deficiency; DMD, Duchenne muscular dystrophy; WAGR, Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation; DGS/VCFs, DiGeorge/velocardiofacial syndrome; CGH, comparative genomic hybridization.





**Figure 1** Identification by oligonucleotide microarray-based comparative genomic hybridization (aCGH) of a single-copy loss of the *SNRPN/UBE3A* locus at 15q12, deletion of which is found in individuals with Prader–Willi/Angelman syndrome. Probes are ordered on the x axis according to physical mapping positions, with the most proximal chromosome 15 q-arm clones on the left and the most distal chromosome 15 q-arm clones on the right.

Telomeric DNA consists of tandem repeats of simple G-rich sequences that show remarkable conservation throughout eukaryotic evolution. All human chromosomes terminate with approximately 2–20 kb of the simple tandem repeat (TTAGGG)<sub>n</sub>.<sup>20</sup> Proximal to this telomeric repeat tract is a structurally complex region of subtelomeric DNA that can extend several hundred kb from the end of most chromosomes and has been shown to be highly polymorphic.<sup>21–24</sup> Present on all but the short arms of acrocentric chromosomes 13–15 and 21–22, the unique subtelomeric regions have elicited study because they are relatively gene-rich<sup>25,26</sup> and are prone to rearrangement by a number of mechanisms.<sup>27,28</sup> Thus, rearrangements of the subtelomeric regions have been suggested to represent a high proportion of abnormalities in individuals with idiopathic mental retardation and, because they are gene-rich, to result in more significant clinical consequences than similarly sized imbalances elsewhere in the genome.<sup>17,25,29</sup>

Several clinically well recognized genetic disorders are associated with terminal deletions, including deletion of distal 5p associated with cri du chat syndrome<sup>4</sup> and distal deletion of 4p associated with Wolf–Hirschhorn syndrome.<sup>5,30</sup> Deletion of the distal band of the short arm of chromosome 1 (monosomy 1p36) is the most common terminal deletion syndrome, occurring in about 1 in 5000 newborns.<sup>7–9</sup>

The development of sets of FISH probes for the simultaneous interrogation of all the unique human subtelomeres<sup>29,31,32</sup> has allowed for the detection of submicroscopic chromosomal abnormalities in patients with idiopathic mental retardation but without features suggestive of a particular syndrome. The largest study of subtelomeric abnormalities to date examined 11,688 cases with subtelomere FISH and detected pathogenic abnormalities in 2.6%.<sup>33</sup> Visible deletions of every telomeric band have been identified.<sup>17</sup> Some of these abnormalities have been identified in a sufficiently large number of patients that the abnormality can be conclusively linked to the phenotype,

which could in turn be delineated by comparison of clinical features among affected individuals.<sup>34,35</sup> Other subtelomeric abnormalities have been identified in only one or a few patients and cannot be considered syndromic until a consistent collection of clinical features is delineated.

Because the distal G-negative bands of the unique chromosome arms are gene-rich,<sup>25</sup> deletion or retention of this region may have profound clinical consequences in individuals with telomeric imbalances. Thus, accurate delineation of the nature of the imbalance, either terminal or interstitial, is crucial for diagnosis and prognosis. Recent large-scale prospective studies using microarrays show interstitial deletions are two to three times more frequent than terminal imbalances.<sup>36,37</sup> Recently, Ballif et al<sup>38</sup> characterized 169 cases with subtelomeric abnormalities identified by microarray analysis. Of these 169 cases, 42 had interstitial deletions. In addition, six (3.5%) individuals had complex rearrangements that showed deletions with duplications or additional deletions. The identification of complex rearrangements suggests chromosome abnormalities are often more complex than what was once thought.

## Recurrent abnormalities mediated by underlying genomic architecture

Many recurrent chromosomal abnormalities are caused by nonallelic homologous recombination (NAHR) mediated by flanking segmental duplications.<sup>39–42</sup> In NAHR, improper crossing-over between nonallelic, directly repeated, homologous segments (such as low-copy repeats) between sister chromatids (intrachromosomal) or between homologous chromosomes (interchromosomal) produces two reciprocal products, ie, a tandem or direct duplication and a deletion.

Such recurrent syndromes are termed “genomic disorders” and usually meet several criteria, ie, the rearrangement has breakpoints in flanking segmental duplications, the rearrangement is almost always de novo in affected individuals and is rarely seen in controls, and patients with the same

rearrangement have similar, consistent phenotypes.<sup>40,41</sup> The underlying genomic architecture in each of the genomic disorders identified to date is similar, ie, a stretch of unique sequence (50 kb–10 Mb) flanked by large (>10 kb), highly homologous (>95%) segmental duplications that provide the substrate for NAHR.

NAHR has been implicated in the recurrent rearrangements in Charcot–Marie–Tooth disease,<sup>43</sup> hereditary neuropathy with liability to pressure palsies,<sup>44</sup> and Prader–Willi,<sup>45</sup> Angelman,<sup>46</sup> Smith–Magenis,<sup>47</sup> DiGeorge/velocardiofacial (DGS/VCFS),<sup>48</sup> Williams–Beuren,<sup>49</sup> and Sotos<sup>50</sup> syndromes (see Table 1). Almost invariably, the abnormalities identified in individuals with the same genomic disorder are of identical size. For example, the common deletion in 7q11.23 found in Williams syndrome is about 1.6 Mb in size<sup>51</sup> and is present in greater than 90% of patients.<sup>52,53</sup> The common Smith–Magenis syndrome deletion within 17p11.2 is approximately 5 Mb<sup>47,54</sup> and is found in the majority of patients.<sup>47,55</sup> Approximately 90% of individuals with DGS/VCFS have an approximately 3 Mb deletion at 22q11.2, and most of the remainder have an alternate distal deletion breakpoint, resulting in a smaller 1.5 Mb deletion, and both deletions are mediated by closely related low copy repeats in the region.<sup>56</sup> Atypical breakpoints have been reported for other recurrent rearrangements mediated by segmental duplications. For example, some of the rarer rearrangements of 17p11.2 associated with Smith–Magenis syndrome do not have breakpoints flanked by the typical paired segmental duplications, and are not associated with known genomic architectural features,<sup>57</sup> and some of the breakpoints in the recently identified 16p11.2p12.2 microdeletion syndrome are not flanked by segmental duplications.<sup>16</sup>

Nonallelic homologous recombination predicts that reciprocal duplications of low copy repeat-mediated deletions should occur with equal frequency.<sup>40</sup> However, duplications have been reported more rarely than expected.<sup>58–62</sup> One explanation is that individuals with duplications usually have milder phenotypes that may not lead to clinical investigation than individuals with deletions.<sup>59,61–66</sup> Furthermore, duplications involving segments smaller than 1.5 Mb may be routinely missed, even by FISH of interphase nuclei.<sup>67</sup> However, recent large population studies of individuals tested by microarray analysis have shown that the frequency of reciprocal duplications is higher than in previous studies with other cytogenetic technologies.<sup>68–71</sup> Duplications of the common Rett syndrome gene *MECP2* have been identified in males with developmental delay,<sup>72</sup> and the reciprocal duplications of microdeletion syndromes, such as 3q29

microdeletion syndrome,<sup>73</sup> Williams–Beuren syndrome,<sup>74</sup> and the 22q11.21 microdeletion syndrome,<sup>59</sup> have been identified by microarray testing. The clinical significance of some of these reciprocal duplications is not known. For example, only two individuals had de novo microduplications of 3q29, whereas the remaining cases were inherited from a carrier parent. Thus, the clinical significance of these duplications is unclear, and any phenotype may be modulated by an as yet unidentified genetic modifier.

Several new syndromes, including 8p23 duplication<sup>75</sup> and 16p12.1 microdeletion,<sup>76</sup> can be transmitted from parent to child. The study of 16p12.1 microdeletions presents an interesting case study of the previously underappreciated complexity of genetic disorder pathogenesis. Recurrent microdeletions of 16p12.1 have been identified in individuals referred for genetic testing for idiopathic mental retardation and congenital anomalies, and appear to be enriched in such individuals compared with clinically normal controls.<sup>76</sup> Almost all the 16p12.1 microdeletions identified have been inherited from a carrier parent. Carrier parents for the 16p12.1 microdeletion are more likely to exhibit learning disability, bipolar disorder or depression, and seizures than noncarrier parents. The presence of varying degrees of learning disability in the adult family members suggests that some transmitted abnormalities are pathologic and have an underappreciated contribution to the phenotype.<sup>76</sup>

## Deletions of varying size may elucidate causative genes for syndromes

Because many chromosomal alterations are large and encompass numerous genes, the ascertainment of individuals with overlapping deletions and varying clinical features may allow researchers to narrow the region in which to search for candidate genes. For example, varying-sized deletions at Xp21 comprise a contiguous gene syndrome that encompasses seven disorders, ie, adrenal hypoplasia congenita, glycerol kinase, Duchenne muscular dystrophy, McLeod phenotype, chronic granulomatous disease, retinitis pigmentosa, and ornithine transcarbamylase deficiency. The first recognized patient with an Xp21 contiguous gene deletion was diagnosed with Duchenne muscular dystrophy associated with chronic granulomatous disease, retinitis pigmentosa, and McLeod phenotype.<sup>77</sup> Molecular studies of subsequent individuals with varying-sized deletions at Xp21 and varying phenotypes allowed for the construction of a disease gene map and the identification of causative genes for each of these disorders.<sup>78–81</sup>

Such an approach also allowed researchers to delineate the critical regions of trichorhinophalangeal syndrome type 1 and trichorhinophalangeal syndrome type 2, also known as Langer-Giedion syndrome. Langer-Giedion syndrome combines the features of trichorhinophalangeal syndrome type 1 and multiple exostoses type 1. The cytogenetic basis of Langer-Giedion syndrome was unknown until high-resolution banding identified interstitial deletions in the long arm of chromosome 8 in patients with this syndrome,<sup>82,83</sup> and the location of the deletion was subsequently determined to be 8q24.1.<sup>84,85</sup> Mapping of the deletion breakpoints in a cohort of Langer-Giedion syndrome patients showed that 75% have cytogenetically detectable deletions of 8q24.1.<sup>86</sup> The identification of an individual with trichorhinophalangeal syndrome Type 1 but not exostoses and with a partial microdeletion of 8q23<sup>87</sup> suggested that Langer-Giedion syndrome was caused by deletion of two or more genes, disruption of one of which results in trichorhinophalangeal syndrome Type 1 and disruption of the other of which results in multiple exostoses. Buhler et al<sup>88</sup> concluded that the Langer-Giedion syndrome is due to a deletion extending from 8q24.11 to 8q24.13, whereas trichorhinophalangeal syndrome Type 1 is caused by an even smaller deleted segment, namely, 8q24.12. Thus, it was determined that Langer-Giedion syndrome, which combines features of trichorhinophalangeal syndrome Type 1 and multiple exostoses, is a contiguous gene syndrome caused by haploinsufficiency of both *TRPS1* and *EXT1*.<sup>89</sup>

## Genotype-first approach to diagnosis

Many of the recently identified syndromes have been identified through a genotype-first approach, rather than a typical phenotype-first approach.<sup>6</sup> In the phenotype-first approach, the astute clinician would gather patients based on clinical presentation. This approach took many years to observe several rare individuals and develop a syndrome. The resulting syndromes had very consistent phenotypes among patients. In contrast, the genotype-first approach identifies patients with the same or overlapping genomic alterations and then describes the phenotypes observed. In this latter approach, the patients often display varying features, and in hindsight would not have been grouped based on clinical presentation alone.

Recently, microarrays designed to interrogate known segmental duplication “hotspots” of the genome have identified several previously unrecognized genomic disorders. Recurrent microdeletions of chromosome 10q22.3q23.3,<sup>90,91</sup> 15q24,<sup>13–15</sup> 16p11.2p12.2,<sup>16</sup> 17q21.31,<sup>10–12</sup>

and 17q23.1q23.2<sup>92</sup> have been identified in such a manner. In all cases, the majority of patients identified met the classical definition of a recurrent genomic disorder. The deletions were flanked by segmental duplications, the deletions were always apparently de novo in origin, and the patients had similar clinical features.<sup>41</sup> However, the clinical features of these syndromes do not usually evoke a diagnostic Gestalt, which demonstrates the utility of the genotype-first approach in the absence of striking clinical features.

The genotype-first approach may also enable the identification of small deletions or duplications that reveal the causative genes for specific clinical features, which can aid diagnosis and prognosis. For example, researchers recently identified what is likely to be the causative gene for features of 2q32q33 microdeletion syndrome.<sup>92</sup> Individuals with the syndrome have severe mental retardation, growth retardation, dysmorphic facial features, thin and sparse hair, feeding difficulties, and cleft or high palate. Although deletions of varying sizes have been reported, the smallest region deleted in all patients contains at least seven genes. One of these genes, *SATB2*, is a DNA-binding protein that regulates how genes are expressed. Deletion of *SATB2* has been suggested to cause the cleft or high palate of individuals with 2q32q33 microdeletion syndrome. The recent study identified three individuals with small deletions of this region, all of which spanned part of *SATB2*. Common clinical features among these individuals included severe developmental delay, behavioral problems, and tooth abnormalities. Interestingly, only one of the individuals had a cleft palate. Because the individuals had a portion of only one gene missing and the presence of many of the features associated with the larger microdeletion syndrome, the study authors suggested deletion of *SATB2* was sufficient to cause several of the clinical features associated with 2q32q33 microdeletion syndrome.<sup>92</sup>

## Summary

Chromosomal disorders are the most frequent cause of mental retardation and developmental disabilities in our population. The phenotypes are often complex, and the result of a gain or loss of multiple, dosage-sensitive genes in the altered segments. The characterization of these complex phenotypes with overlapping deletions has allowed for the identification of genes causing particular features of the syndrome. The use of high-resolution technologies, such as microarrays, has allowed for the identification of new syndromes through a genotype-first approach at an unprecedented frequency never before imagined through the

light microscope. Cytogenetics is no longer in its infancy, and has emerged a “new” genome science that, with the use of new technologies, has established the causes of mental retardation, developmental disabilities, and birth defects in our population.

## Disclosure

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