REVIEW ARTICLE

Mendelian cytogenetics. Chromosome rearrangements associated with mendelian disorders

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The first successful mapping of a mendelian disorder by chromosome rearrangements was that of the Duchenne muscular dystrophy locus to Xp21.¹⁻⁵ Since then, chromosome aberrations which delete, truncate, or otherwise rearrange and mutate specific genes have not only helped in the mapping of other disease loci,⁶ but have turned out to be key elements for the rapid isolation of disease genes by positional cloning strategies.⁷ Accordingly, a listing of the clinical disorders in which associated chromosome rearrangements have been described forms a part of the Human Gene Mapping Workshops.⁶ Although the early success led to a proposal for systematic cytogenetic analysis of subjects with mendelian disorders,⁸ this has rarely been done. A common feeling is that, as mutations, these rearrangements are rare exceptions. The aim of the present review is to document that they may be rare, but are not exceptions, and to focus on factors which may influence their occurrence and facilitate their detection.

Contiguous gene syndromes in relation to mendelian genetics

Genetic disorders are usually classified into mendelian, chromosomal, and multifactorial categories. Mendelism involves transmission patterns of traits which traditionally are thought to be determined by single genes. The mere fact that a chromosome rearrangement may lead to the development of a mendelian disorder suggests that this distinction between mendelian and chromosome disorders may be arbitrary.⁹ This is illustrated by Miller-Dieker syndrome (MDCR), lissencephaly with a characteristic facial appearance, that was originally listed as an autosomal recessive condition owing to the presence of familial cases with two or more affected sibs.⁹ All familial cases analysed have so far been shown to be associated with unbalanced segregation of familial translocations or inversions, leading to segmental aneuploidy (deletion) of a distal segment of 17p.¹⁰⁻¹² Thus, MDCR not associated with a chromosome abnormality is probably best explained as an autosomal dominant condition where all mutations are de novo.

MDCR also illustrates a mutational mechanism that may eventually explain a sub-

stantial part of the heterogeneity and overlap in syndromology: contiguous gene syndromes where microscopic or submicroscopic deletions (or duplications) involve an array of closely positioned genes.^{13,14} A purpose of the molecular characterisation of contiguous gene syndromes is to identify individual genes responsible for specific components of the phenotypic complex. This is probably best illustrated by the molecular studies of deletions and translocations involving 11p13 associated with various combinations of Wilms's tumour, aniridia, genitourinary malformations, and mental retardation (WAGR complex).¹⁵ The resulting isolation of candidate genes for Wilms's tumour (WT1)^{16,17} and aniridia (AN2, PAX6)^{18,19} now provides a means for molecular studies and delineation of monogenic conditions within 11p13.²⁰⁻²⁴ Similarly, the dissection of the phenotype in MDCR has begun with the demonstration of submicroscopic deletions in cases with isolated lissencephaly.^{25,26}

Any visible chromosome imbalance almost invariably represents a contiguous gene disorder, but few chromosomal syndromes include features of sufficient specificity to permit a correlation with a recognised mendelian disorder. This includes many of the classical chromosome disorders,²⁷ as well as newly recognised ones.²⁸ Although these chromosome aberrations may not have immediate implications for known mendelian traits, future molecular dissection of these disorders may change this.

Chromosome rearrangements in relation to autosomal dominant, autosomal recessive, and X linked disease

Specific chromosome rearrangements have predominantly been described in autosomal dominant (AD) and in X linked conditions. Of the 625 chromosomally mapped loci associated with genetic disorders, 54 (8.6%) are X linked.²⁹ However, more than one third of the approximately 70 mendelian disorders associated with a specific chromosome rearrangement are X linked⁶ (figure). This excess can be explained by almost routine application of cytogenetic analysis in two particular groups of

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Localisation of mendelian disorders where chromosome rearrangements have been described. For explanation of symbols, see Appendix.

patients: females affected with X linked diseases, suggesting X;autosome translocations, and males suffering from two or more X linked disorders, suggesting a contiguous gene syndrome. Since there are no a priori reasons to believe that chromosome rearrangements should be less frequent in AD than in X linked disorders, the underrepresentation in AD disorders is probably because of ascertainment bias.

The cytogenetic data in autosomal recessive (AR) disorders are so scanty that reliable statements regarding their frequency cannot be made. In only one AR disorder (Zellweger syndrome) has more than one chromosome rearrangement been described, a de novo deletion and a de novo inversion.^{30 31} A specific

chromosome mutation will only show an AR locus if the other allele happens to be mutated (unmasking of heterozygosity),³² and this will be a rare occurrence as the gene frequencies for even the most common AR disorders do not exceed 1/25 to 1/50. Owing to the number of recessive traits, and the relatively high frequency of familial translocations and inversions in man,³³ some of these breakpoints may affect recessive loci. Thus, several murine balanced translocations are lethal in the homozygous state.³⁴ The risk of unmasking of heterozygosity by a transmissible chromosome rearrangement will increase with the number of individuals that receive the rearrangement. In addition, familial translocations may predispose to the formation of uniparental

Table 1 Chromosome rearrangements in deletion viable regions.

Disorder (locus symbol)	Chromosomal localisation	Type of rearrangement	
		Deletions (No)	Locus specific type
AGS	20p11.23–12.1	Multiple ^{178b 179a}	
AHC	Xp21	Multiple ^{72 180a}	
AIC	Xp22.3	Multiple ^{70 181a}	t(X;3)(p22;q12) ^{182a}
AIED	Xp21	1 ^{180a}	
ANCR	15q11–12	Multiple(mat) ^{65–68a,d 122a 183a}	inv(15)(p11q13)mat ^{68 69b}
AN2/PAX6	11p13	Multiple ^{52a,d 54d}	t(4;11)(q22;p13) ^{60b} t(11;22)(p13;q12.2) ^{58b} t(5;11)(q13.1;p13) ^{59b} t(5;11)(q11;p13) ^{284ax} t(8;12)(p11;p13) ^{184b} t(3;8)(p21;p11) ^{185b} t(5;10)(q22;?) ^c
ANK1	8p11.1	3 ^{187a 188a 186c?}	
APC	5q22	5 ^{189a 191a 190b 183d}	
AZF	Yq11	Multiple ^{193–196a}	
BPES	3q23	4 ^{199a 172d}	t(3;11)(q21;q23) ^{198b} t(3;4)(q23;p15.2) ^{200a} t(3;8)(q23;p21.1) ^{197a}
CDPX1	Xp22.3	Multiple ⁷⁰	
CRS1	7p21	Multiple ^{207 208a}	
CYBB	Xp21	Multiple ^{72 209 210a,b}	
DFN3	Xq21	Multiple ^{37 211}	
DGCR1	22q11	Multiple ^{213–217a,d}	t(2;22)(q14.1;q11.1) ^{212b}
DGCR2	10p13	7 ^{214a,d 218a}	
DMD/BMD	Xp21	Multiple ^{71 72a,b}	Multiple ^{219a}
GCPS	7p13	3 ^{163a 164a}	t(3;7)(p21.1;p13) ^{160b} t(6;7)(q27;p13) ^{161b} t(6;7)(q12;p13) ¹⁶²
GK	Xp21	Multiple ^{71 72a,b}	
HLD	4q12		t(4;5)(q21;p15.3) ^{231b} t(4;6)(q21;p24) ^{232b}
HMRD	16p13.3	4 ^{88a,d}	
HPE2	2p21	4 ^{233a}	
HPE3	7q35	Multiple ^{234 236 237a,d}	t(7;9)(q36;q34) ^{235b}
HPE4	18p	Multiple ^{234 238a,d}	
HSCR	13q33.1	3 ^{239–241a}	
KAL1	Xp22.3	Multiple ^{70a}	
LGCR	8q24.11	Multiple ^{127 244 245 248a,d}	t(2;8)(q33;q24.1) ¹²⁷ t(4;8)(p15.3;q24.1) ¹²⁷ t(8;11)(q24.11;p15.5) ²⁴⁶ inv(8)(q11.23q21.1) ^{247b}
LYP	Xq25	1 ^{73b}	
MBS	13q12.2	1 ^{249a}	t(1;13)(p34;q13) ^{250b}
MDCR	17p13	Multiple ^{10–12 25 26a,d}	
MRX2	Xp22.3	Multiple ⁷⁰	
NF2	22q12.2?		t(4;22)(q12;q12.2) ^{254b}
OA1	Xp22.3	Multiple ²⁷⁰	
PBT	4q12–13	3 ^{257 259 260a}	t(4;15)(q12q21;q11) ^{258ax}
PWCR	15q11–12	Multiple(pat) ^{48–51a,d}	1 X;A translocation (see ref 61) ^a 5 autosomal translocations ^{61b} inv(15)(p13q13)pat ⁶⁴ Multiple ⁴¹ t(5;7;9)(q11.2q34;q21.2q31.3;q22.1) ^{266a} t(7;9)(q11.21;p12) ^{263b}
RB1	13q14	Multiple ^{38–44a,b,c?,d}	
SHFD1	7q11.2–21.3	7 ^{264 265a}	
SRY	Yp12	Multiple ^{70a 267 268a}	
SS	Xp22.3	Multiple ^{70a}	
STS	Xp22.3	Multiple ^{70a}	
TCD	Xq21	Multiple ^{37 174b 271a,b}	t(X;7)(q21.2;p14) ^{272a} t(X;13)(q21.2;p12) ^{274a} t(X;3)(q28;q21) ^{275a} t(X;10)(q28;q11.2) ^{275a} dir ins(8)(q24.11q13.3q21.13) ^{281b}
TKC	Xq28		
TRP1	8q24.11	5 ^{276–280a,c}	
VCFS	22q11.2	Multiple ^{282 283a,d}	
VWS	1q32–41	1 ^{285a}	
WS1	2q35		inv(2)(q35q37.3) ^{287a}
WT1	11p13	Multiple ^{52a,b,d}	
ZWS	7q11.23	1 ^{30a}	inv(7)(p12q11.23) ^{31a}

See Appendix for explanation of locus symbols. a=de novo aberration. b=familial transmission. c=evidence of germline mosaicism. d=unbalanced familial reciprocal translocation/inversion. e=Meera-Khan, personal communication. x=visibly unbalanced translocation.

disomy, whereby AR mutations can be reduced to homozygosity.³⁵ The occasional occurrence of an inherited balanced translocation or inversion would therefore not be unexpected in AR disorders.³⁶

The effect of chromosome localisation on types and frequencies of chromosome rearrangements

Exact determination of frequencies of chromosome rearrangements in mendelian disorders can only be made by systematic studies of specific mendelian disorders. This has only been done in a few disorders, retinoblastoma (RB1) being the classical one. The results from RB1 may not necessarily be valid for other

disorders, and one factor that will influence the frequency of chromosome rearrangements in a specific disorder is the chromosomal localisation of the corresponding gene.

Visible deletions among liveborns are absent or extremely rare for several regions of the human genome (figure),²⁷ probably because they are incompatible with fetal survival.³⁷ Whereas deletions are the most frequent type of rearrangement in those disorders which map to the 'deletion viable' regions (table 1, figure), visible deletions do not occur in liveborns affected with mendelian disorders mapping to the 'deletion non-viable' regions (table 2). The division of the genome into a deletion viable and non-viable part may have consequences not only for the type and fre-

Table 2 Chromosome rearrangements in deletion non-viable* regions.

Disorder (locus symbol)	Chromosomal localisation	Type of rearrangement	
		Miscellaneous	Locus specific type
BWS	11p15.4–15.5	del(11)(p11p13) ^{203a†} del(11)(p11p13) ^{205a†} multiple dup(11p)pat ^{103 202d}	t(9;11)(p11.11p15.5)mat ^{103b†} t(4;11)(p15.2;p15.4)mat ^{103b} t(11;22)(p15.5;q12)mat ^{204b} t(11;16)(p15.5;q12)mat ^{103b} t(11;12)(p15.5;q13.1)mat ^{103b} inv(11)(p11.2p15)mat ^{103b} inv(11)(p15.4q22.3)mat ^{103b} 46,XX,t(1;17)(q42.1;q25) ^{95a} 46,XX,inv(17)(q12q25) ^{96a} 46,XY,t(2;17)(q35;q23–24) ^{97a} 46,XY,t(7;17)(q34;q25) ^{95a} 46,XY,t(13;17)(q31;q25) ^{95a} t(X;9)(q13.1;p24) ^{225 228a} t(X;12)(q13.1;q24.2) ^{227a} t(X;1)(q13.1;p36.33) ^{224a} t(X;1)(q27;q23) ^{229a} t(X;8)(q13;p21.2) ^{118b} t(X;5)(q27;q31) ^{243a} t(X;15)(p11;q11) or (q11;p11) ^{142a} t(X;9)(p11;q34) ^{143a} t(X;17)(p11;p11.2) ^{145a} t(X;9)(p11;q33.2) ^{145a} t(X;13)(p11.21;q12.3) ^{144a} t(X;10)(p11;q22) ^{146a} t(X;4)(q21;q28) ⁹ t(X;5)(p11.2;q35.2) ^{147a} 45,X/46,Xr(X) ^{141a} t(X;2)(q13.3;q32.2) ^{117a} t(X;1)(q13.3;q21) ^{8a} ins(X)(p11.4q13.3q21.2)mat ^{106b} t(X;10)(p11;p14) ^{253a} inv(X)(p11.4q22) ^{254b} t(1;17)(p34.3;q11.2) ^{92b} t(17;22)(q11.2;q11.2) ^{93b}
CMPD1	17q24.3–25.1		
CMPD1/ SRA1	17q24.3–25.1		
EDA	Xq13.1		
F9 FGDY IDS IP1	Xq27 Xq13 Xq28 Xp11		
MNK	Xq13.3		
NDP	Xp11		
NF1	17q11.2		
OCRL	Xq26.1?	+ ?r(17)(cen-q12), del(17)(cen-q12) ⁹¹	t(X;3)(q25;q27) ^{256a} t(X;20)(q26.1;q11.2) ^{257a} t(2;16)(p13.3;p13.3) ^{84a} t(7;16)(q34;p13.3) ^{85a} t(16;22)(p13.3;?) inv(16)(p13.3;q13) ^{86a} inv(16)(p13.3q13) [†]
RSTS	16p13.3		

See Appendix for explanation of locus symbols. * Including regions with only 1–3 reports of viable deletions. † Breakpoints not at established 11p15.4–5 loci. ‡ Personal observation. § J Beck, personal communication. || Cited in ref 87.

quency of rearrangements in mendelian disorders, but also for selection of strategies for their detection.

DISORDERS MAPPING TO REGIONS WHERE DELETIONS ARE VIABLE

Retinoblastoma, Wilms's tumour, and aniridia

The early detection of cases with deletion of a D group (No 13) chromosome in association with retinoblastoma (RB1)^{38–40} led to extensive cytogenetic screening of large series of patients.^{41–44} Consequently visible deletions have been found in 2 to 4% of all patients with RB1 when examined by metaphase technique, and in 4 to 8% of patients when examined by high resolution techniques. Reciprocal translocations have been detected in approximately 1% of patients in several independent surveys using both metaphase and prometaphase resolution, corresponding to 10% of the detected rearrangements. Thus, between 5 and 10% of all cases with RB1 have a visible chromosome mutation.

Larger systematic cytogenetic studies have not been reported in association with Wilms's tumour (WT1)/aniridia, so a direct comparison with the individual traits included in the Wilms's tumour/aniridia/genitourinary malformation/mental retardation (WAGR) complex cannot be made. However, in three large series of Wilms's tumour patients, altogether comprising 1335 cases,^{45–47} aniridia was

observed in 23 cases (1.7%). Furthermore, 1/3 of aniridia cases are sporadic and, of these, 1/3 develop Wilms's tumour.⁴⁸ A visible deletion of 11p13 was seen in all 18 cases with combined WT1/aniridia in three high resolution cytogenetic surveys,^{47 49 50} supporting the fact that most subjects with this combination have a visible deletion. All evidence supports a single map position for aniridia at 11p13.⁵¹ If so, 1/3 × 1/3 (10%) of independent cases with aniridia may have a visible deletion. Since both traits are easily recognised, this is in line with the large number of cases with the WAGR complex and deletions of 11p13 that have been reported.⁵² As expected for contiguous gene syndromes, visible deletions and more complex rearrangements within 11p13 may not affect both loci.^{50 53 54} The limited distance between WT1 and the candidate aniridia loci (700 to 1000 kb)^{18 55} explains why a few persons with Wilms's tumour and aniridia have deletions below the limit of microscopic resolution.^{55 56} Balanced chromosome rearrangements involving 11p13 have not been reported in association with Wilms's tumour, but one translocation with a breakpoint within the region has been seen in association with Potter syndrome,⁵⁷ and three reciprocal translocations have been reported in familial aniridia.^{58–60} Taken together, the data are compatible with a frequency of chromosome rearrangements in all independent cases with WT1, aniridia, and WT1/aniridia in the same

range as observed in RB1 (2 to 10%), with deletions being by far the most frequent type of mutation.

Disorders associated with imprinting:

Prader-Willi and Angelman syndromes

Repeated observations of rearrangements involving chromosome 15 in patients with Prader-Willi syndrome (PWCR) led to numerous systematic studies.⁶¹⁻⁶³ As a result, 60% of patients have been found to carry detectable chromosome 15 rearrangements, mostly deletions within 15q11-13 (table 1). The cytogenetic spectrum of 300 PWCR subjects with a chromosome 15 abnormality included 182 interstitial deletions, 34 unbalanced reciprocal translocations, 14 Robertsonian translocations, 16 small marker chromosomes, and four duplications,⁶¹⁻⁶³ plus six balanced translocations and one pericentric inversion.⁶¹ The inversion was inherited from an unaffected father.⁶⁴ Assuming that 60% of PWCR cases have a cytogenetic defect, the frequency of apparently balanced rearrangements thus appears to be close to that of RB1 ($7 \times 60/300 = 1.4\%$). However, it should be emphasised that balanced rearrangements were not reported among 358 PWCR patients studied in larger chromosome surveys in the period 1981 to 1991.⁶¹⁻⁶³

Cytogenetic deletion of 15q11-13 is also observed in 50 to 60% of subjects with Angelman syndrome (ANCR).⁶⁵⁻⁶⁸ Among the fewer than 100 cases with ANCR that have been studied so far, one apparently balanced rearrangement has been reported, a maternally inherited inversion with a breakpoint within 15q13,⁶⁸ which was associated with a de novo submicroscopic deletion in the affected child.⁶⁹

The frequency of visible deletions in RB1, PWCR, and ANCR thus varies considerably (~5 to 60%), whereas the frequency of apparently balanced cytogenetic rearrangements may be within the same order of magnitude (~1%).

X linked disorders

On the X chromosome, the male deletion viable regions involve Xp22.3, Xp21, Xq21, and Xq25 (figure).^{37 70-74} Owing to the excellent morbid anatomy of the X chromosome,²⁹ these deletions are associated with recognisable mendelian traits, either as single gene disorders⁷³ or as part of contiguous gene syndromes.^{37 70-72} In a survey of five males with DMD and additional clinical signs suggesting a contiguous gene disorder, visible deletions were detected in all five cases.⁷¹ Bivariate flow karyotyping of 10 visible deletions within Xp21 associated with contiguous gene syndromes has provided a size estimate of these deletions in the range 4 to 14 Mb.⁷²

The frequency of visible deletions in patients with single gene disorders mapping to Xp21 appears to be lower than observed in many autosomal disorders. In a systematic survey of 165 males with Duchenne or Becker muscular dystrophy only, no chromosome re-

arrangements were observed.⁷⁵ This may be somewhat surprising since submicroscopic deletions are extremely common in DMD, and since intragenic deletions in the 2.4 Mb DMD locus might potentially reach the lower limit of microscopic resolution.

Disease associated deletions involving the distal part of Xp22.3 are seen in both males and females, in males associated with recessive traits and in females with dominant traits.⁷⁰ Most other X chromosome deletions are preferentially inactivated in female carriers, either without phenotypic effects or associated with Turner symptoms, including gonadal dysgenesis or secondary amenorrhoea/premature menopause.⁷⁶ However, deletion of the region Xq27 may result in preferential activity of the deleted X chromosome,⁷⁷ and it has been suggested that this might be because of deletion of a locus which is involved in the normal X inactivation process.⁷⁸ If so, visible or submicroscopic deletions of Xq27 should be considered, along with X;autosome translocations, in females affected with disorders mapping to this region.

DISORDERS MAPPING TO REGIONS WHERE DELETIONS ARE NON-VIABLE

In contrast to deletions, breakpoints associated with constitutional autosome translocations detected in an unbiased way in large series of prenatal diagnoses⁷⁹ (figure), as well as in reported X;autosome translocations,^{80 81} are distributed all over the genome. Hence, the presence of disease specific translocations would not be expected to be influenced by the chromosomal localisation of a disorder to the same extent as deletions. One modification of this is that the G-C rich chromosomal reverse (R) bands contain many more genes than the A-T rich G bands.^{82 83} Therefore, disease specific breakpoints in translocations and inversions should predominantly be located in R bands, which is indeed the case (figure).

If RB1 is the prototype of a clearly recognised disease localised within a chromosomal region where gross deletion is compatible with fetal survival, Rubinstein-Taybi syndrome (RSTS), von Recklinghausen neurofibromatosis (NF1), and, to some extent, campomelic dysplasia (CMPD1) exemplify disorders mapping to regions where deletions do not or only rarely occur.

Rubinstein-Taybi syndrome, von Recklinghausen neurofibromatosis, and campomelic dysplasia

A locus for RSTS has been assigned to 16p13.3 after the identification of several independent chromosome rearrangements with breakpoints within this region.⁸⁴⁻⁸⁷ Apart from small distal deletions associated with the haemoglobin H/mental retardation syndrome,⁸⁸ viable visible deletions of 16p13 have not been described at all.^{27 85 87} This, together with the detection of submicroscopic deletions in 25% of RSTS subjects with normal karyotypes,⁸⁷ indicates that it is not deletions as such that do

not occur or that are not compatible with the RSTS phenotype, but rather the size of the deletions.

Both RB1 and WT1 are tumour suppressor loci.⁸⁹ However, it is unlikely that this feature in itself is associated with the high frequency of visible deletions seen in these disorders. Neurofibromatosis type 1 (NF1) also involves a tumour suppressor gene that maps to 17q11.2.⁶ The largest deletion which has so far been described in a patient with NF1 was 380 kb in size,⁹⁰ well below the limit of microscopic resolution. This is in line with the general absence of reported constitutive deletions of this part of chromosome 17 (figure).²⁷ In the only published case with a visible deletion of the proximal part of 17q, the deleted segment was still present in most of the cells as a small ring chromosome.⁹¹ In contrast, and by analogy with the findings in RSTS, reciprocal translocations have been described in NF1 (table 2).^{92,93}

In campomelic dysplasia (CMPD1), chromosome analysis has been performed in a number of cases because of the frequent association with 46,XY sex reversal (SRA1).⁹⁴ Four de novo reciprocal translocations and one inversion, all involving 17q24-25, provide compelling evidence for the localisation of both CMPD1 and SRA1 to this region.⁹⁵⁻⁹⁷ Only a few viable deletions involving the distal part of 17q have been reported.⁹⁸⁻¹⁰⁰ Thus, CMPD1 may illustrate a disorder mapping to a region where viable deletions do occur, but only rarely. Although CMPD1/SRA1 has been suggested to be a contiguous gene syndrome,^{95,101} visible deletions have not been reported in patients with CMPD1/SRA1. Thus, the observed pattern of chromosome rearrangements in CMPD1 resembles the pattern in disorders mapping to regions where deletions do not occur at all.

Disorders associated with imprinting:

Beckwith-Wiedemann syndrome

Genetic imprinting of one or more loci within 11p15 has been implicated in the aetiology of Beckwith-Wiedemann syndrome.^{102,103} As in Prader-Willi syndrome,^{61,104} several different types of chromosome rearrangements have been encountered in BWS, including balanced rearrangements with breakpoints in the critical region of 11p15, exclusively of maternal origin, and duplications of the distal part of 11p15, exclusively of paternal origin (table 2). It has been suggested that the duplications lead to excess expression of a paternally imprinted growth promoting gene within the region, such as insulin growth factor 2 (IGF2), whereas the balanced translocations might affect a maternally imprinted regulator within the region.¹⁰³ Viable deletions involving the distal part of 11p15 have not been described,²⁷ so it is not likely that such deletions will be seen in association with BWS either.

X linked disorders

Menkes disease illustrates an X linked disorder which maps to an R band region (Xq13.3)

where visible deletions have not been described in males.^{105,106} In a continuing cytogenetic survey of more than 200 unrelated males with Menkes disease, not a single case with a visible deletion has been detected.¹⁰⁷

Although the proven X linked contiguous gene syndromes map to those regions where cytogenetic deletions are viable, X linked contiguous gene syndromes located within most R band regions would be expected to be more numerous, considering the high gene density of R bands. However, these disorders will probably be associated with either submicroscopic rearrangements¹⁰⁸ or with 'balanced' rearrangements which will lead to limited loss of material. The same argument applies to autosomal contiguous gene syndromes mapping to deletion non-viable regions.

So far, few mendelian disorders have been associated with visible duplications.^{103,109} In general, duplications are better tolerated than deletions,²⁷ so a smaller part of the genome will be duplication non-viable. However, it is reasonable to assume that for disorders associated with duplication of genetic material, the chromosomal localisation may also influence the occurrence of visible chromosome mutations.

The effect of the parental origin of de novo chromosome rearrangements

De novo chromosome rearrangements are predominantly of paternal origin, including all X;autosome translocations examined so far.^{95,110-116} This skewed parental origin has several implications for the detection of structural rearrangements in mendelian disorders.

DE NOVO REARRANGEMENTS OF THE X CHROMOSOME

As most chromosome rearrangements are paternal in origin, those involving the X must occur predominantly in females, where the phenotypic effect will be influenced by the X inactivation pattern. In balanced X;autosome translocations, where the translocation X is as a rule the active one,^{80,81} truncation of a disease gene will lead to affected status in the female carrier. This mechanism is a main contributor to the disproportionately large number of X linked disorders where structural rearrangements have been described (figure). Since affected females with normal chromosomes are less likely to be reported, the actual frequency of X;autosome translocations in affected females is unknown. The best estimate may come from Menkes disease (MNK), where diagnosis, including that of females, has been centralised to a few centres in the world. So far, two of six known MNK females are translocation carriers (J Beck, personal communication).^{107,117}

Males will only inherit an X;autosome translocation if the translocation does not lead to gonadal dysgenesis, a frequent finding in females with breakpoints on the X chromosome.⁷⁶ In addition, an associated mendelian disorder in the mother will have to be suffi-

ciently mild to allow reproduction. As a consequence, X;autosome translocations are in general rare in males.^{80 118} This, together with the presumed male non-viability of deletions involving the major part of the X chromosome (figure), led to the suggestion that intrachromosomal rearrangements, such as inversions and shifts, will be likely types of cytogenetic rearrangements in males affected with most X linked disorders.¹⁰⁷ These rearrangements are probably very rare.^{119–121}

DISORDERS WHERE GENOMIC IMPRINTING IS INVOLVED

As discussed previously, deletions involving almost the same region of 15q11–13 are frequently observed in both PWCR and ANCR. However, the deletion is always of paternal origin in PWCR^{61–63} and always of maternal origin in ANCR.¹²² Although the proportion of affected subjects carrying a cytogenetically visible deletion is the same in the two disorders, two significant aetiological factors support a higher frequency of PWCR than ANCR: (1) the large excess of maternal non-disjunction¹²³ that may predispose to subsequent uniparental maternal disomy, as observed in PWCR,^{124 125} and (2) the presumed higher frequency of de novo rearrangements (deletions) of paternal origin which will also lead to PWCR.

In Beckwith-Wiedemann syndrome, all balanced rearrangements involving the distal part of 11p15 have been found to be inherited from the mother, similar to a preponderance of maternal transmission of BWS in non-cytogenetic familial cases.^{103 126} Together with the predominantly paternal origin of de novo rearrangements, this implies that few if any de novo balanced rearrangements will be observed in subjects affected with BWS. In contrast, the mother may frequently carry the balanced rearrangement as a de novo rearrangement of paternal origin, or may have inherited the rearrangement from her father.

A similar sex dependent transmission pattern might be possible in balanced rearrangements associated with ANCR⁶⁹ and PWCR,^{61 64} where the phenotypic effect of truncation or deletion⁶⁹ will be influenced by the parental origin of the inherited rearrangement.⁶⁸ Thus, apparently balanced rearrangements in PWCR should be of paternal origin,⁶⁴ and of maternal origin in ANCR.⁶⁹

It has now become an almost routine pro-

cedure to search for the parental origin of chromosome rearrangements. Owing to the excess of de novo rearrangements of paternal origin, demonstration of a maternal origin of de novo rearrangements in a specific disorder will be much more significant with respect to a possible involvement of genomic imprinting¹²² than demonstration of a paternal origin.⁹⁵

Mutational aspects with relevance for positional cloning

ARE BREAKPOINTS IN BALANCED REARRANGEMENTS LOCUS SPECIFIC?

Although the majority of reciprocal translocations and inversions included in tables 1 and 2 are balanced at the cytogenetic level, a few of these have been shown to be associated with large submicroscopic deletions.^{127 128} If this were a general feature, the assumption that these rearrangements involve single breaks within the target locus would be erroneous.⁹³ However, of 23 apparently balanced rearrangements studied at the gene level,^{129–138} 22 had breakpoints within the candidate gene locus (table 3). The assumed locus specificity of breakpoints in cytogenetically balanced rearrangements in mendelian disorders therefore seems justified, even though these rearrangements may not be truly conserved at the sequence level, since small deletions from a few bp to < 30 kb have been noted (table 3).

LOCALISATION OF BREAKPOINTS OUTSIDE THE SPECIFIC TARGET

Six unrelated reciprocal translocations have been reported in retinoblastoma patients,⁴¹ along with 14 specific reciprocal and eight insertional translocations. The odds therefore seem to favour a rearrangement as being disease specific. However, they also illustrate that the coincidental occurrence of a rearrangement is not uncommon. Further studies of the family, linkage studies in other families, search for similar published reports, and comparison with the clinical features associated with deletions or duplications of the regions involved are needed when considering the significance of a detected rearrangement.

Even if a structural chromosome mutation turns out to be the aetiological factor, some mutational mechanisms have been documented or suggested which may limit the utility of both balanced and unbalanced rearrangements for positional cloning, or at least provide

Table 3 Molecular details of assumed locus specific rearrangements.

Disorder (locus symbol)	No of studied rearrangements	No which truncate the specific locus	No with sequenced/estimated deletion	Size of deletion
DMD	11	11 ^{129–132}	2	71/72 bp ¹²⁹ 5 kb ¹³²
GCPS	3	2 ¹⁶⁶		
MNK	2	2 ^{138 251 252}		
NF1	1	1 ¹³⁵		
RB1	4	4 ^{133 134}	1	< 30 kb ¹³⁴
TCD	1	1 ¹³⁶		
WS1	1	1 ¹³⁷		
Total	23	22		

conflicting data as to the disease or locus specificity.

Spreading of X inactivation in X;autosome translocations

Although the majority of X;autosome translocations associated with mendelian disorders have involved the X linked locus, it would be logical to assume that the autosomal breakpoint would occasionally represent the target. Most of the documented cases have been X;13 translocations associated with RB1.^{41 139} At the cytogenetic level, 13q14 harbouring the RB1 locus seemed to be intact in all cases. The suggested mechanism for the development of RB1 in these cases is spreading of X inactivation into the autosomal segment including the RB1 locus.¹³⁹ Inactivation of a putative locus at 9q32–34 by spreading of X inactivation has also been suggested in two X;autosome translocation carrying girls with incontinentia pigmenti or hypomelanosis of Ito.¹⁴⁰

The paradox of incontinentia pigmenti (IP1 and IP2)

At least seven, possibly eight,⁹ X chromosome rearrangements have been detected in sporadic cases of IP, with most of the breakpoints within Xp11.^{141–147} IP is considered an X linked dominant disorder, which is lethal in males, and which only occurs in females as a result of the functional mosaicism associated with random lyonisation. The paradoxes of IP are as follows. (1) The locus for familial IP has been assigned to Xq28 by linkage analysis and not to Xp11.^{148 149} Therefore, two loci associated with IP (IP1 and IP2) have been invoked. (2) It has been suggested that two, maybe three, of the translocation carriers^{143 145} did not have IP but hypomelanosis of Ito (HI).^{140 150} HI has been considered the 'negative' of IP because the abnormal hypopigmented skin areas are distributed in the same pattern. The disorder may be a clinical manifestation of mosaicism or chimerism, as evidenced by the frequent association with chromosomal mosaicism involving a variety of different chromosomes.^{150 151} (3) Several different X chromosome breakpoints have been detected in the chromosomal rearrangements associated with IP.^{152–154} The distance between two distinct regions of breakpoints within Xp11, one close to the centromere and one more distal, is at least 2.5 Mb,¹⁵⁴ suggesting that if IP1 exists, the locus must be extremely large, or several loci within Xp11 may be involved. (4) Of two of the translocations stated to be associated with HI, one maps to the distal region and one to the proximal region in Xp11.¹⁵⁴

Considering the similar distribution of skin defects in IP and HI, the defect in these sporadic cases with IP may also involve somatic mosaicism, perhaps associated with X inactivation. One of the rearrangements involved a r(X),¹⁴¹ so dynamic mosaicism associated with ring chromosome instability might even be involved,¹⁵⁵ in which case the gene(s) responsible for the pigmentary abnormalities might

be situated anywhere on the X chromosome (for example, IP2 in Xq28). One implication of this would be that positional cloning of a putative IP1 locus defined by X chromosome breakpoints¹⁵⁴ may be impossible.

Unmasking of mutations by rearrangement induced non-random X inactivation

If the normal X chromosome contains a mutated locus, non-random X inactivation of a structurally abnormal X chromosome may incidentally lead to clinically affected status of a female.¹⁵⁶ The erroneous conclusion that the disease locus is regionally defined by the breakpoints of the rearrangement may be avoided by careful X inactivation studies. The possibility exists that this mechanism may be involved in IP1. It is uncertain whether a similar mechanism might be involved in two X;autosome translocations with different breakpoints on Xp in Rett syndrome,^{157 158} a disorder in which X linkage has been suggested by almost exclusive involvement of girls, but where linkage analysis seems to have excluded the X chromosome.¹⁵⁹

Localisation of breakpoints close to but outside the open reading frame

The locus for Greig cephalopolysyndactyly (GCPS) has been pinpointed to 7p13 by three balanced familial translocations,^{160–162} by deletions,^{163 164} and by linkage studies.¹⁶⁵ By the candidate gene approach,⁷ two of the three familial translocations were found to interrupt a zinc finger gene GLI3 located within 7p13.¹⁶⁶ However, the breakpoint in the third translocation occurred about 10 kb downstream of the 3' end of GLI3. It was speculated that as a result a *cis* acting element was brought into the region of GLI3, thereby deregulating its expression.¹⁶⁶

Dynamic mosaicism associated with ring chromosomes

Carriers of ring chromosomes harbouring tumour suppressor genes may be at increased risk of developing chromosome specific types of tumours, for example, r(13) carriers may develop RB1, r(11) carriers WT1, r(22) carriers meningioma, etc.¹⁵⁵ Conversely, the development of a specific type of tumour in a ring carrier may suggest that a tumour suppressor locus is located somewhere on that chromosome. Apart from the primary deletion associated with the formation of the ring, ring chromosomes are predisposed to secondary somatic rearrangements initiated by sister chromatid exchanges. The result may be fragmentation, gain or loss of ring material, including complete monosomy (dynamic mosaicism). A comparison between the localisation of the primary breakpoints and the likely tumour suppressor loci involved suggests that the secondary instability may be the most important factor predisposing to the development of tumours.¹⁵⁵ Thus, unlike conventional constitutional deletions which can be used for the

generation of disease related deletion maps, correlations between the primary ring associated deletions and phenotypic features should be regarded with caution.

Dynamic mosaicism may not be limited to the development of tumours, but should also be considered as a possible mechanism in the development of other disorders in ring carriers. One possible association is Russell-Silver syndrome which shares many clinical features with ring chromosome 15 deficiencies.¹⁶⁷

Conclusions

The present review has primarily been concerned with those rearrangements which can be expected to be encountered in a majority of mendelian disorders. Thus, the fragile site at Xq27 associated with the most common form of X linked mental retardation has not been discussed since it is so far the only fragile site known to be associated with a specific clinical entity.

Although deletions occur less frequently than reciprocal translocations in newborn screening series,³³ any deletion of visible size will have a big chance of involving part or all of a gene. This may explain why viable deletions are the most frequent type of cytogenetic mutation in mendelian disorders. In contrast, a single breakpoint or a submicroscopic deletion associated with a translocation or inversion has to be more precisely located in order to involve a specific locus.

The majority of visible deletions associated with mendelian disorders has been observed in sporadic cases (tables 1 and 2). A few exceptions have been reported, which may be explained by the presence of mosaicism in a parental carrier, or a less severe phenotype associated with small deletions within certain regions, such as 13q14 associated with RB1.⁴¹ In most other situations, the assumption that chromosomal deletions are reproductive lethal mutations is probably true. However, familial occurrence of deletions associated with mendelian disorders can be expected in two conditions: deletions involving the male deletion viable regions of the X chromosome, and familial translocations, especially insertional translocations.^{41 54 168-172}

Apart from insertional translocations, other rare types of familial and sporadic rearrangements have been identified in association with mendelian disorders, in part during chromosomal surveys.^{91 106} As mentioned previously, intrachromosomal rearrangements, including shifts, may be the expected type of chromosome mutation in males affected with the majority of X linked diseases.¹⁰⁷ Whether this apparent accumulation of otherwise rare types of rearrangement may reflect ascertainment which are different from those usually encountered in cytogenetics (prenatal diagnosis, MCA/MR, spontaneous abortions, etc) is at present unknown.

Without valid data derived from systematic cytogenetic surveys in the majority of disorders, the best estimate of a basic frequency

of chromosome rearrangements in an autosomal dominant disorder is approximately 1%, corresponding to the frequency of balanced translocations and inversions observed in RB1 (and maybe in PWR and ANCR). If, in addition, visible deletions within the specific chromosome region are viable, this figure will be considerably higher.

The data favour that cytogenetic rearrangements will be present in a small, but not insignificant, fraction of subjects affected with many mapped and unmapped mendelian disorders. The detection of a chromosome mutation will have obvious counselling implications in the individual family. Considering the impact even a single specific rearrangement may have for gene mapping and cloning, a more systematic effort to detect these rearrangements should be pursued. In terms of value for rapid molecular isolation of the locus of interest, rearrangements involving locus specific breaks (for example, balanced translocations and inversions) will in general be the most valuable ones. Although the presence of additional congenital anomalies, other unexpected diseases, spontaneous abortions, stillbirths, etc, may suggest the involvement of a chromosome mutation in a patient or within a family, subjects with balanced rearrangements may not suffer from additional disorders.¹⁰⁷ Furthermore, translocations and inversions may be both familial and de novo mutations (tables 1 and 2). Therefore, some of the most valuable mutations in terms of positional cloning may only be detected by systematic analysis.

If a reciprocal translocation is detected in a disorder that has not been mapped previously, the odds will favour a breakpoint within an R band being the specific one. In some cases this may ease subsequent attempts to confirm the specificity of new translocations, for example, by linkage mapping. Furthermore, for large scale screening programmes, high resolution chromosome analysis may be too cumbersome and time consuming. Screening strategies can be devised which in part will alleviate this. In disorders with a known chromosomal localisation, complete karyotyping by high resolution technique may not be needed. In disorders mapping to regions where deletions are unlikely to be viable, normal good quality metaphase technique may be sufficient to detect the single break rearrangements that can be expected. In addition, the deletion map shown in the figure may provide a basis for tentative exclusion mapping of mainly autosomal dominant disorders, where repeated chromosome analysis has failed to identify rearrangements. Such disorders might be expected to map within the deletion non-viable or less viable part of the genome. This was the case with two of the most recently mapped disorders, RSTS^{85 87} and CMPD1.⁹⁵

Linkage mapping will be greatly eased by the rapidly increasing numbers of highly polymorphic microsatellites which can be analysed by the PCR technique.¹⁷³ In this context a continuous registration and clinical follow up of subjects with known chromosome re-

arrangements will become increasingly important. Whenever a disease has been mapped to a specific chromosome region, rapid reinvestigation of subjects carrying chromosome rearrangements within that region for key clinical features may provide essential mapping and clinical data. This approach was used successfully to detect choroideraemia¹⁷⁴ in a patient with a previously reported Xq21 deletion,¹⁷⁵ and to show reduced nerve conduction velocity in a patient with a large visible duplication encompassing the CMT1A locus on 17p.¹⁰⁹

The rapid construction of complete YAC and cosmid contigs^{176,177} will greatly facilitate future mapping and isolation of specific disease breakpoints/genes, for example, in combination with in situ hybridisation techniques. The detection of rearrangements associated with mendelian diseases will therefore remain an important challenge for the clinical cytogeneticist. Many cytogenetic laboratories may be discouraged from systematic studies by the rarity of mendelian disorders and by the expectation of a relatively low frequency of associated cytogenetic rearrangements. As has been shown so convincingly in other fields of human genome mapping, concerted action would be the logical way to ensure a systematic detection of these highly valuable mutations in man.

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- AGS Alagille syndrome**
- AHC Adrenal hypoplasia, congenital**¹⁷²
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- AIC Aicardi syndrome**⁷⁰
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- AIED Åland island eye disease**¹⁸⁰
- ANCR Angelman syndrome (happy puppet)**^{65-69 122}
- 183 Williams CA, Zori RT, Stone JW, et al. Maternal origin of 15q11-13 deletions in Angelman syndrome suggests a role for genomic imprinting. *Am J Med Genet* 1990;35:350-3.
- AN2 Aniridia 2**^{15 18 24 45-60 128 168-170}
- ANK1 Spherocytosis type II (ankyrin defect)**
- 184 Kimberling WJ, Fulbeck T, Dixon L, Lubs HA. Localization of spherocytosis to chromosome 8 or 12 and report of a family with spherocytosis and a reciprocal translocation. *Am J Hum Genet* 1975;27:586-94.
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- APC Adenomatous polyposis coli, incl Gardner syndrome**⁷¹
- 189 Herrera L, Kakati S, Gibas L, Pietrzak E, Sandberg AA. Gardner syndrome in a man with an interstitial deletion of 5q. *Am J Med Genet* 1986;25:473-6.
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- AZF Azoospermia**
- 193 Anderson M, Page DC, Pettay D, et al. Y;autosome translocations and mosaicism in the aetiology of 45,X maleness: assignment of fertility factor to distal Yq11. *Hum Genet* 1988;79:2-7.
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- BPES Blepharophimosis, ptosis, epicanthus inversus syndrome**¹⁷²
- 197 De Almeida JCC, Llerena JC Jr, Neto JBG. Another example favouring the location of BPES at 3q2. *J Med Genet* 1993;30:86.
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- BWS Beckwith-Wiedemann syndrome**^{102 103 126}
- 202 Brown KW, Gardner A, Williams JC, et al. Paternal origin of 11p15 duplications in the Beckwith-Wiedemann syndrome. *Cancer Genet Cytogenet* 1992;58:55-70.
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- CDPX1 Chondrodysplasia punctata 1**⁷⁰
- 206 Ballabio A, Carozzo R, Gil A, et al. Molecular characterization of human X/Y translocations suggests their aetiology through aberrant exchange between homologous sequences on Xq and Yq. *Ann Hum Genet* 1989;53:9-14.
- CMPD1/SRA1 Campomelic dysplasia/sex reversal, autosomal 1**^{94-97 101}
- CMT1A Charcot-Marie-Tooth neuropathy 1**¹⁰⁹
- CRS1 Craniosynostosis, syndromic 1**
- 207 Motegi T, Ohuchi M, Ohtaki C, et al. A craniosynostosis in a boy with a del(7)(p15.3p21.3): assignment by deletion mapping of the critical segment for craniosynostosis to the mid-portion of 7p21. *Hum Genet* 1985;71:160-2.
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- CYBB Chronic granulomatous disease**
- 209 Royer-Pokora B, Kunkel LM, Monaco AP, et al. Cloning of the gene for an inherited human disorder—chronic granulomatous disease—on the basis of its chromosomal location. *Nature* 1986;322:32-8.
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- DFN3 Deafness, conductive, with fixed stapes**²⁷¹
- 211 Reardon W, Roberts S, Phelps PD, et al. Phenotypic evidence for a common pathogenesis in X-linked deafness pedigrees and in Xq13-q21 deletion related deafness. *Am J Med Genet* 1992;44:513-17.
- DGCR1 DiGeorge syndrome 1**
- 212 Augusseau S, Jouk S, Jalbert P, Prieur M. DiGeorge syndrome and 22q11 rearrangements. *Hum Genet* 1986;74:206.
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Appendix This appendix contains references not mentioned in the text, listed alphabetically according to locus, including references to rearrangements included in tables 1 and 2, and some selected key references. Locus specific cross references to the text are included.

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- 217 Wilson DI, Cross IE, Goodship JA, et al. A prospective cytogenetic study of 36 cases of DiGeorge syndrome. *Am J Hum Genet* 1992;51:957-63.
- DGCR2 DiGeorge syndrome 2**²¹⁴
- 218 Monaco G, Ciccimarra F, Pignata C, Garofalo S. T cell immunodeficiency in a patient with 10p deletion syndrome. *J Pediatr* 1989;115:330.
- DMD/BMD Duchenne and Becker muscular dystrophy**^{219-221, 225-115-116 129-132}
- 219 Boyd Y, Buckle V, Holt S, et al. Muscular dystrophy in girls with X;autosomal translocations. *J Med Genet* 1986;23:484-90.
- 220 Boyd Y, Buckle VJ. Cytogenetic heterogeneity of translocations associated with Duchenne muscular dystrophy. *Clin Genet* 1986;29:108-15.
- 221 Boyd Y, Cockburn D, Holt S, et al. Mapping of 12 translocation breakpoints in the Xp21 region with respect to the locus for Duchenne muscular dystrophy. *Cytogenet Cell Genet* 1988;48:28-34.
- 222 Monaco AP, Neve RL, Coletti-Feener C, et al. Isolation of candidate cDNA for portions of the Duchenne muscular dystrophy gene. *Nature* 1986;323:646-50.
- 223 Ray PN, Belfall B, Duff C, et al. Cloning of the breakpoint of an X;21 translocation associated with Duchenne muscular dystrophy. *Nature* 1985;318:672-5.
- EDA Ectodermal dysplasia, anhidrotic (hypohidrotic)**
- 224 Limon J, Filipiuk J, Nedoszytko B, et al. X-linked anhidrotic ectodermal dysplasia and de novo t(X;1) in a female. *Hum Genet* 1991;87:338-40.
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- F9 Haemophilia B (coagulation factor IX deficiency)**
- 229 Vianna-Morgante AM, Batista DAS, Levisky RB, Zatz M. X;autosomal translocations in females with X-linked recessive diseases. *7th Int Congr Hum Genet (Berlin)* 1987;1:97.
- FGDY Aarskog syndrome**¹¹⁸
- GCPS Greig cephalopolysyndactyly**¹⁶⁰⁻¹⁶⁶
- GFDH Goltz focal dermal hypoplasia**⁷⁰
- GK Glycerol kinase deficiency**^{71,72}
- 230 Walker AP, Muscatelli F, Monaco AP. Isolation of the human glycerol kinase gene by positional cloning. *Hum Mol Genet* 1993;2:107-14.
- HLD Huntington-like disease**
- 231 Froster-Iskenius UG, Hayden MR, Wang HS, et al. A family with Huntington disease and reciprocal translocation 4;5. *Am J Hum Genet* 1986;38:759-67.
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- HMRD Haemoglobin H disease/mental retardation (deletion type)**⁸⁸
- HPE2 Holoprosencephaly 2**
- 233 Hecht BKM, Hecht F, Münke M. Forebrain cleavage gene causing holoprosencephaly: deletion mapping to chromosome band 2p21. *Am J Med Genet* 1991;40:130.
- HPE3 Holoprosencephaly 3**
- 234 Münke M. Clinical, cytogenetic, and molecular approaches to the genetic heterogeneity of holoprosencephaly. *Am J Med Genet* 1989;34:237-45.
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- HPE4 Holoprosencephaly 4**
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- HSCR Hirschsprung disease**
- 239 Bottani A, Xie Y, Binkert F, Schinzel A. A case of Hirschsprung disease with a chromosome 13 microdeletion, del(13)(q32.3q33.2): potential mapping of one disease locus. *Hum Genet* 1991;87:748-50.
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- IDS Hunter disease (iduronate-2-sulphatase deficiency)**
- 242 le Guern E, Couillin P, Oberlé I, Ravise N, Boue J. More precise localization of the gene for Hunter syndrome. *Genomics* 1990;7:358-62.
- 243 Mossman J, Blunt S, Stephen R, Jones EE, Pembrey M. Hunter's disease in a girl: association with X;5 chromosomal translocation disrupting the Hunter gene. *Arch Dis Child* 1986;58:911-15.
- IP1 Incontinentia pigmenti**¹⁴⁰⁻¹⁵⁴
- KAL1 Kallmann syndrome 1**⁷⁰
- LGCR Langer-Giedion syndrome**¹²⁷
- 244 Bühler EM, Bühler UK, Beutler C, Fessler R. A final word on the tricho-rhino-phalangeal syndromes. *Clin Genet* 1987;31:273-5.
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- LYP Lymphoproliferative syndrome, X linked**⁷³
- MBS Moebius syndrome**
- 249 Slee JJ, Smart RD, Viljoen DL. Deletion of chromosome 13 in Moebius syndrome. *J Med Genet* 1991;28:413-14.
- 250 Ziter FA, Wiser WC, Robinson A. Three generation pedigree of a Moebius syndrome variant with chromosome translocation. *Arch Neurol* 1977;34:437-42.
- MDCR Miller-Dieker syndrome**^{10-12 25 26}
- MNK Menkes disease**¹⁰⁵⁻¹⁰⁷
- 251 Mercer JFB, Livingstone J, Hall B, et al. Isolation of a partial candidate gene for Menkes disease by positional cloning. *Nature Genet* 1993;3:20-5.
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- MRX2 Mental retardation, X linked**⁷⁰
- NDP Norrie disease**¹⁰⁸
- 253 Ohba N, Yamashita T. Primary vitreoretinal dysplasia resembling Norrie's disease in a female: association with X autosomal chromosomal translocation. *Br J Ophthalmol* 1986;70:64-71.
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- NF1 Neurofibromatosis 1 (von Recklinghausen)**^{90-93 135}
- NF2 Neurofibromatosis 2 (central, bilateral acoustic neurinoma)**
- 255 Arai E, Ikeuchi T, Karasawa S, et al. Constitutional translocation t(4;22)(q12;q12.2) associated with neurofibromatosis type 2. *Am J Med Genet* 1992;44:163-7.
- OA1 Ocular albinism 1 (Nettleship-Falls type)**⁷⁰
- OCRL Oculocerebrorenal syndrome of Lowe**
- 256 Hodgson SV, Heckmatt JZ, Hughes E, Crolla JA, Dubowitz V, Bobrow M. A balanced de novo X/autosomal translocation in a girl with manifestations of Lowe syndrome. *Am J Med Genet* 1986;23:837-47.
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- PAX6 Paired box gene 6 associated with aniridia**^{19 24}
- PBT Piebald trait**
- 258 Yamamoto Y, Nishimoto H, Ikemoto S. Interstitial deletion of the proximal long arm of chromosome 4 associated with father-child incompatibility within the Gc-system. Probable reduced gene dosage effect and partial piebald trait. *Am J Med Genet* 1989;32:520-3.
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- 261 Lacassie Y, Thurmon TF, Tracy MC, Pelias MZ. Piebald trait in a retarded child with interstitial deletion of chromosome 4. *Am J Hum Genet* 1977;29:641-2.
- PWCR Prader-Willi syndrome**^{61-64 104 124 125}
- RB1 Retinoblastoma susceptibility**^{38-44 112 133 134 139}
- RP3 Retinitis pigmentosa 3**
- 262 McDowell C, Burghes AH, Anson-Cartwright S, et al. X-linked retinitis pigmentosa (XLRP): mapping of the gene to Xp21, pulsed field gel electrophoresis (PFGE) of the region and cloning strategies. *Am J Hum Genet* 1990;47:A256(1009).
- RSTS Rubinstein-Taybi syndrome**⁸⁴⁻⁸⁷
- SHFD1 Split hand and foot deformity 1**
- 263 Hasegawa T, Hasegawa Y, Assamura S, et al. EEC syndrome (ectrodactyly, ectodermal dysplasia and cleft lip/palate) with a balanced reciprocal translocation between

- 7q11.21 and 9p12 (or 7p11.2 and 9q12). *Clin Genet* 1991;40:202–6.
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- ²⁶⁶ Sharland M, Patton MA, Hill L. Ectrodactyly of hands and feet in a child with a complex translocation including 7q21.2. *Am J Med Genet* 1991;39:413–14.
- SR Y Testis-determining factor**⁷⁰
- ²⁶⁷ Distèche CM, Casanova M, Saal H, *et al.* Small deletions of the short arm of the Y chromosome in 46,XY females. *Proc Natl Acad Sci USA* 1986;83:7841–4.
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- ²⁶⁹ Sinclair AH, Berta P, Palmer MS, *et al.* A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature* 1990;346:240–4.
- SS Short stature, X linked**⁷⁰
- ²⁷⁰ Ogata T, Matsuo N, Shimizu N. A ring X chromosome, 46,Y,r(X)(p22.3q28), as a cause of extreme short stature in a male. *Am J Med Genet* 1990;35:241–4.
- STS X linked ichthyosis**⁷⁰
- TCD Choroideraemia**^{37 136 174 175}
- ²⁷¹ Cremers FP, Van den Pol DJR, Diergaarde PJ, *et al.* Physical fine mapping of the choroideremia locus using Xq21 deletions associated with complex syndromes. *Genomics* 1989;4:41–6.
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- ²⁷⁴ Siu VM, Gonder JR, Jung JH, Sergovich FR, Flintoff WF. Choroideremia associated with an X-autosomal translocation. *Hum Genet* 1990;84:459–64.
- TKC Torticollis, keloids, cryptorchidism, and renal dysplasia**
- ²⁷⁵ Zuffardi O, Fraccaro M. Gene mapping and serendipity. The locus for torticollis, keloids, cryptorchidism and renal dysplasia (31430, McKusick) is at Xq28, distal to the G6PD locus. *Hum Genet* 1982;62:280–1.
- TRP1 Trichorhinophalangeal syndrome 1**
- ²⁷⁶ Fryns JP, Van den Berghe H. 8q24.12 interstitial deletion in trichorhinophalangeal syndrome type I. *Hum Genet* 1986;74:188–9.
- ²⁷⁷ Goldblatt J, Smart RD. Tricho-rhino-phalangeal syndrome without exostoses, with an interstitial deletion of 8q23. *Clin Genet* 1986;29:434–8.
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- VCFS Velo-cardio-facial syndrome**
- ²⁸² Driscoll DA, Spinner NB, Budarf ML, *et al.* Deletions and microdeletions of 22q11.2 in velo-cardio-facial syndrome. *Am J Med Genet* 1992;44:261–8.
- ²⁸³ Scambler PJ, Kelly D, Lindsay E, *et al.* Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus. *Lancet* 1992;339:1138–9.
- ²⁸⁴ Kelly D, Goldberg R, Wilson D, *et al.* Confirmation that the velo-cardio-facial syndrome is associated with haploinsufficiency of genes at chromosome 22q11. *Am J Med Genet* 1993;45:308–12.
- VWS Van der Woude syndrome 1**
- ²⁸⁵ Bocian M, Walker AP. Lip pits and deletion 1q32–q41. *Am J Med Genet* 1987;26:437–43.
- WAGR see also AN2, WT1**¹⁵
- ²⁸⁶ Puissant H, Azoulay M, Serre JL, Piet LL, Junien C. Molecular analysis of a reciprocal translocation t(5;11)(q11;p13) in a WAGR patient. *Hum Genet* 1988;79:280–2.
- WS1 Wardenburg syndrome 1**¹³⁷
- ²⁸⁷ Ishikiriya S, Tonoki H, Shibuya Y, *et al.* Wardenburg syndrome type I in a child with a de novo inversion (2)(q35q37.3). *Am J Med Genet* 1989;33:505–7.
- WT1 Wilms's tumour susceptibility**^{15–17 20–23 45–49 52–57 128 168–170 286}
- XX Kell blood group precursor (McLeod phenotype)**
- ²⁸⁸ Ho MF, Monaco AP, Blonden LAJ, *et al.* Fine mapping of the McLeod locus (XX) to a 150–380-kb region in Xp21. *Am J Hum Genet* 1992;50:317–30.
- ZWS Zellweger syndrome**^{30 31}