

Molecular analysis of 20 patients with 2q37.3 monosomy: definition of minimum deletion intervals for key phenotypes

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Terminal deletions of the long arm of chromosome 2 (2q37) have been recorded in the literature for more than a decade and an associated syndrome first became apparent when nine patients were reported with an Albright hereditary osteodystrophy (AHO)-like metacarpal/metatarsal shortening (brachymetaphalangism).^{1,2} This is also known as brachydactyly-mental retardation syndrome (BDMR, MIM 600430). To date, some 60 or so cases of 2q37 deletion or monosomy resulting from unbalanced translocations have been reported. Significant variability in clinical presentation is apparent, but almost all patients have some degree of mental retardation and facial dysmorphism. Brachymetaphalangism has been reported in approximately 50% of cases.^{1–15} Congenital heart anomalies are present in around 20% of patients with 2q37 monosomy,^{16–22} compared to 1% of the general population. These are predominantly atrial or ventricular septal defects, but more complex problems have been reported.^{17,22} Additionally, there are two reports of tetralogy of Fallot with monosomy 2q37 resulting from unbalanced translocations,^{23,24} but both cases were also trisomic for 17q25 and it is not clear which imbalance was causative. Other phenotypes repeatedly associated with 2q37 deletions include Wilms tumor and urogenital anomalies,^{6,17,19} epilepsy,^{1,2,7–9,14,16,20,25–27} eczema,^{2,5–7,16,28,29} and autism or repetitive, hyperkinetic behaviour.^{1,2,5,7,10,11,15,16,19,25,26,28–32} Situs abnormalities have been reported in two cases⁹ and holoprosencephaly in one infant.³³

Most 2q37 rearrangements reported to date have been only minimally characterised by conventional cytogenetics or subtelomeric fluorescent in situ hybridisation (FISH). A small number have been subjected to more detailed analysis using multiple FISH clones or microsatellite markers,^{2,10,15,26} but the ability to assign breakpoints and make genotype–phenotype correlations has been limited. We therefore sought to conduct detailed molecular analyses of a panel of 2q37 deletion patients, focusing on the critical interval distal to D2S338² and including assessment of individual gene dosage by multiplex amplifiable probe hybridisation (MAPH).³⁴ We define minimal deletion intervals for all of the major phenotypes associated with 2q37 monosomy.

METHODS

This study has been approved by the Leicestershire ethics committee. Seven patients have been described previously.^{2,4,7,16,26} Thirteen additional patients with known 2q37 rearrangements were ascertained through clinical genetics departments in the UK and clinical details are provided as supplementary online information at <http://jmg.bmjournals.com/supplemental/>. Informed consent was obtained from parents or guardians. The patient panel comprised 16 deletions, two inverted duplication/deletions, one ring chromosome and one unbalanced translocation. The ring chromosome (patient 53) has virtually no loss of 2p

Key points

- We have conducted detailed dosimetric analysis in 20 patients with monosomy 2q37.
- No common breakpoints were found, indicating that 2q37 rearrangements are likely not mediated by duplicated low copy repeats.
- The minimum deleted region in patients with characteristic facial dysmorphism and Albright hereditary osteodystrophy (AHO)-like brachymetaphalangism has been narrowed to approximately 3 Mb.
- For the first time, preliminary assignments of critical intervals for other features of the syndrome have now been made. All such intervals share a 1.5 Mb overlap.
- However, considerable clinical variability was apparent and no clear genotype–phenotype correlations could be drawn that would help predict clinical prognosis in a newly-diagnosed young proband.

material, being heterozygous for microsatellite D2S2584, ~160 kb from the telomere, and retaining the 2p subtelomeric FISH probe 2052f6. The phenotype is therefore presumed to be due solely to the 2q37 deletion.

DNA was extracted from peripheral blood leukocytes or buccal cells using standard methods. MAPH was conducted essentially as described,^{34,35} except that probes were cloned into pCR2.1-TOPO using the TOPO-TA cloning kit (Invitrogen, Paisley, UK) and the sequence of the blocking primers was modified accordingly. Probes were designed to the following 2q37 genes: *RDCL1*, *RAMP1*, *ILKAP*, *MIP-T3*, *ASBI*, *TWIST2*, *HDAC4*, *NDUFA10*, *HDLBP*, *ATSV*, *GP3ST*, *PASK*, *PPP1R7*, *FARP2*, *STK25*, *NEDD5*, *DTYMK*, and to unique sequence adjacent to the polymorphic markers D2S125, D2S140, D2S2585 (2qTEL44), D2S2985 (2qTEL37) and D2S2986 (2qTEL47). Details of probe sequences are available on request. Probes were organised into two multiplex sets for patient analysis and were first tested on DNA from a patient with a large deletion and normal controls to verify their quantitative performance. Results for selected genes were also verified by realtime quantitative PCR (data not shown).

In some cases it was not possible to perform MAPH, as only small quantities of DNA were available from buccal swab samples. We therefore designed 11 new microsatellite markers, spanning the region from immediately proximal to *HDAC4* (BAC AC114788) to the telomere, by in silico

Abbreviations: AHO, Albright hereditary osteodystrophy; BDMR, brachydactyly-mental retardation syndrome; FISH, fluorescent in situ hybridisation; MAPH, multiplex amplifiable probe hybridisation; OR, olfactory receptor

screening of publicly-available BAC sequence using the Tandem Repeats Finder program.³⁶ Primer sequences and annealing temperatures are shown in table 1. All new markers proved to be polymorphic. Existing microsatellite markers from the Genethon and Marshfield genetic maps were analysed using primers available from the public genome databases. Singleplex reactions were conducted for 40 cycles using HotStar PCR mastermix (Qiagen, Crawley, UK) supplemented with 1× Q-solution. Multiplex reactions utilised the Multiplex PCR Mastermix (Qiagen, Crawley, UK) supplemented with 0.5× Q-solution, also for 40 cycles following the manufacturer's recommended thermocycle profile. All microsatellites were labelled with 6-FAM, HEX, or TET fluorophores and analysed on an ABI377 12 cm genotyping gel.

RESULTS

Clinical characteristics

Clinical features for all cases are summarised in table 2. Consistent with the literature, all except the very youngest patient had mild or moderate developmental delay and some degree of facial dysmorphism. Consent for publication of facial photographs was given in four cases (fig 1) and a further five were published previously (patients 75, 76, 10780, 419 and 622).^{2 4 7 16} Common features include round face with flattened nasal bridge, frontal bossing, deep-set eyes, up-slanting palpebral fissures, anteverted nares, and thin upper lip. In contrast, the facial dysmorphism in patient 63 was markedly different (see online supplementary information), consistent with her duplication for much of 2q37 and only a very small telomeric deletion (see molecular results below). AHO-like brachymetaphalangism was observed in 11 (55%) of our patients, autism or repetitive, hyperkinetic behaviours in seven (35%), non-febrile seizures also in seven (35%), eczema in five (25%), and heart abnormalities in four (20%). These frequencies are in keeping with those in the wider literature, with the exception of epilepsy, which has been reported in about one-quarter of patients overall. Frequencies for brachymetaphalangism and autism may be underestimates, since some patients, both in this series and the wider literature, are too young to manifest these phenotypes, while eczema might be overlooked unless severe. There was a marked excess of females in our series, but this is much less apparent in the literature as a whole.

Molecular characteristics

Molecular results are summarised in fig 2. Parental samples were available in 16 of the 19 non-familial cases. All 16 were shown to be de novo rearrangements, none showed co-existence with the known 2q subtelomeric polymorphism.^{37 38}



Figure 1 Photographs of four patients with 2q37 deletion illustrate the typical facial appearance in this syndrome.

and approximately equal proportions of paternally and maternally-derived rearrangements were observed. A similar lack of bias in parental origin is seen in Williams-Beuren, DiGeorge, and 18p- syndromes,³⁹⁻⁴¹ whereas Sotos, Wolf-Hirschhorn, Cri-du-chat, and 18q- syndromes are predominantly paternal in origin⁴²⁻⁴⁵ and 1p36 deletions show a slight maternal bias.⁴⁶

As suggested by the original cytogenetic analyses, all patients were found to have terminal deletions with the exception of patient 75 (AW, Fisher *et al*¹⁶), who showed an interstitial deletion with the distal breakpoint localised between D2S140 (deleted) and AC005237CA (retained). Microsatellite analysis in patient 63 showed that the inverted duplication detected cytogenetically was accompanied by a previously undetected small terminal deletion. The duplicated and deleted regions were apparently separated by a small region of normal gene dosage, as judged by relative

Table 1 Primer sequences for SNPs and microsatellites

Marker	Forward primer	Reverse primer	Size (bp)	Annealing temperature
rs3086056 (HES6)	GTTCACTCTGGCTCACCTCAAT	HEX-CCCACTGCCCAATAGCTC	95/100	55°C
rs111165 (TWIST2)	TTACTTTTACGCGCTATTCT	ACGCTTTTATTTTCTCTGGGTG	T/A SNP	55°C
AC114788CA*	GTTTCTACTGGGATGCTGAGATGGAC	FAM-CAATCCACTTGTGTCTGGTG	260-290	62.4°C
AC017028CA*	HEX-TCAAAGTGCCTGAGAGTGG	GTTTCTGTGGACAGATGTGGAAGTAGC	90-120	62.4°C
AC062017TG	GCAAAGGTTACATACAGATACCGA	HEX-CTGTCAAAGGAAAAAGGGGAAGC	160-180	55°C
AC093802CA	GTTTACCAACTCAAATGCTAATCCA	HEX-CAATCAGTGTAACCATAAAACA	170-190	52°C
AC093802TAT	FAM-TCACTCATCTTTCCTGGATAG	TTCATATTTACAGTAGAAGACGG	230-250†	55°C
AC013469CA*	GTTTCTATCTATGGAACACCTCTCCC	HEX-AATTCATCTGACCAAGCATGTG	230-250	62.4°C
AC124862CA	GACGCATCACTCTACCTAAAAAAA	HEX-CAATGCAGGTCTAAATGACCAG	100-120	55°C
AC005237CA*	FAM-ATCAGCTACTGTCAATTCATTG	GTTTCACTTCTCTCCGAGAAGTCC	80-120	62.4°C
AC005104CA*	GTTTCTTATACATGCACACACGACCACA	TET-GAACAAAGAAGTGGACCCTCAG	115-149	62.4°C
AC093642CA*	GTTTCTGCAAGTAACTTGCACACATCA	FAM-GGGAACAAAAAGAAGGCATGTA	150-170	62.4°C
AC131097CA*	FAM-GTTAAGGGGCTGGACGGG	GTTTCTAGTCTCTCGCTCGTGGC	200-220	62.4°C

*These markers were amplified as one multiplex PCR, as described in Methods; †fragment is ~520 bp in length and was digested with *Hpa*II prior to analysis on ABI377.

Table 2 Clinical characteristics of patients

ID	Karyotype	Sex	Age	Facial dysmorphism	Developmental delay	Skeletal anomalies	Behaviour	Eczema	Seizures	Congenital heart anomalies	Other	Previous reference
74	46,XX,del(2)(q37.1)	F	20 months	+	+	—	—	—	—	—	Hypotonia, lumbar lordosis	LM (Fisher <i>et al</i> ^{1,6})
76	46,XX,del(2)(q37.1)	F	18 years	+	+	B, L	—	—	—	—	Obesity, lymphoedema of legs	Power <i>et al</i> ⁶
78	46,XX,del(2)(q37.1)	F	7 years	+	+	—	CAS	—	—	ASD, PDA	Recurrent infections	
8490	46,XX,del(2)(q37.2)	F	10 years	+	+	B, S	R	++	—	—	Umbilical hernia	
12410	46,XY,del(2)(q37.1)	M	32 years	+	++	Os	+	—	GM	—	Oedema and ulceration of legs	
315	46,XY,del(2)(q37.1)	M	4 years	+	+	—	H	—	—	—	Myopia	
8491	46,XX,del(2)(q37.3)	F	16 years	+	+	B, D, P	—	—	F	PDA, PAD	Hydrocephalus	Bonaglia <i>et al</i> ^{2,6}
8493	46,XX,invdup(2)(p33q37)	F	7 years	+	+	S, Cl	H, Ag, M	—	GA	—	Myopia, arachnoidactyly	
63	46,XX,invdup(2)(p36.2q37.3)	F	9 years	+	+	Cl	—	—	F	—	Squint, glaucoma, recurrent infections	
75	46,XX,del(2)(q37.2)	F	10 years	+	+	—	Aut	+	GM	ASD, CA	Neonatal hypercalcaemia	AW (Fisher <i>et al</i> ^{1,6})
80	46,XX,del(2)(q37.3)	F	9 years	+	+	B, Cl	Ag	—	Ab	—	2–3 toe syndactyly, joint laxity, squint, horseshoe kidney	
213	46,XX,del(2)(q37.3)	F	15 years	+	+	B, D, L, S	—	+	—	—	Joint laxity, myopia, squint	RA (Wilson <i>et al</i> ²)
106	46,XX,del(2)(q37.3)	F	15 months	Mild	Mild	—	—	—	—	AS, VSD	Inguinal hernias, recurrent infections	
127	46,XY,del(2)(q37.3)	M	5 years	+	+	B	H, Ob	—	—	—	Obesity, inguinal hernia, squint	
128	46,XX,del(2)(q37.3)	F	11 years	+	+	B	—	—	—	—	Hernias, recurrent infections	Bijlsma <i>et al</i> ⁷
389	46,XX,del(2)(q37.3)	F	22 years	Mild	Mild	B	—	—	—	—	Squint, short stature, obesity	KW (Wilson <i>et al</i> ²)
419/622*	46,XX,del(2)(q37.3)	N/A	N/A	+	++	B	H, Ag, M	+	+	—	Joint laxity, 2–3 toe syndactyly	
10780	46,XX,del(2)(q37.3)	F	12 years	+	+	B, Cr	—	—	GM	—	Microcephaly	
122	46,XX,del(2)(q37.3)	F	6 years	+	+	B	—	—	—	—		
53	46,XY,r(1)(p25.3q37.3)	M	5 months	—	—	Cl	—	+	Ab	—		

*Familial translocation—data represent a composite for all family members with an unbalanced der(2) karyotype.

Ab, absences; Ag, aggression; AS, atrial stenosis; ASD, atrial septal defect; Aut, autism; B, brachymetaphalangism; CA, coarctation of the aorta; CAS, controlling, attention-seeking; Cl, fifth finger clinodactyly; Cr, craniosynostosis; D, bilateral dislocation of the hips; F, febrile; GA, generalised atonic; GM, grand mal; H, hyperkinesia; I, post-immunisations; L, abnormalities of the long bones; M, self-mutilating; Ob, obesity; Os, osteoporosis; P, Perthes disease of the hip; PAD, pulmonary artery dilatation with left ventricular hypertrophy; PDA, patent ductus arteriosus; R, routine bound; S, scoliosis; SCD, receptive language and social communication disorders; VSD, ventricular septal defect.

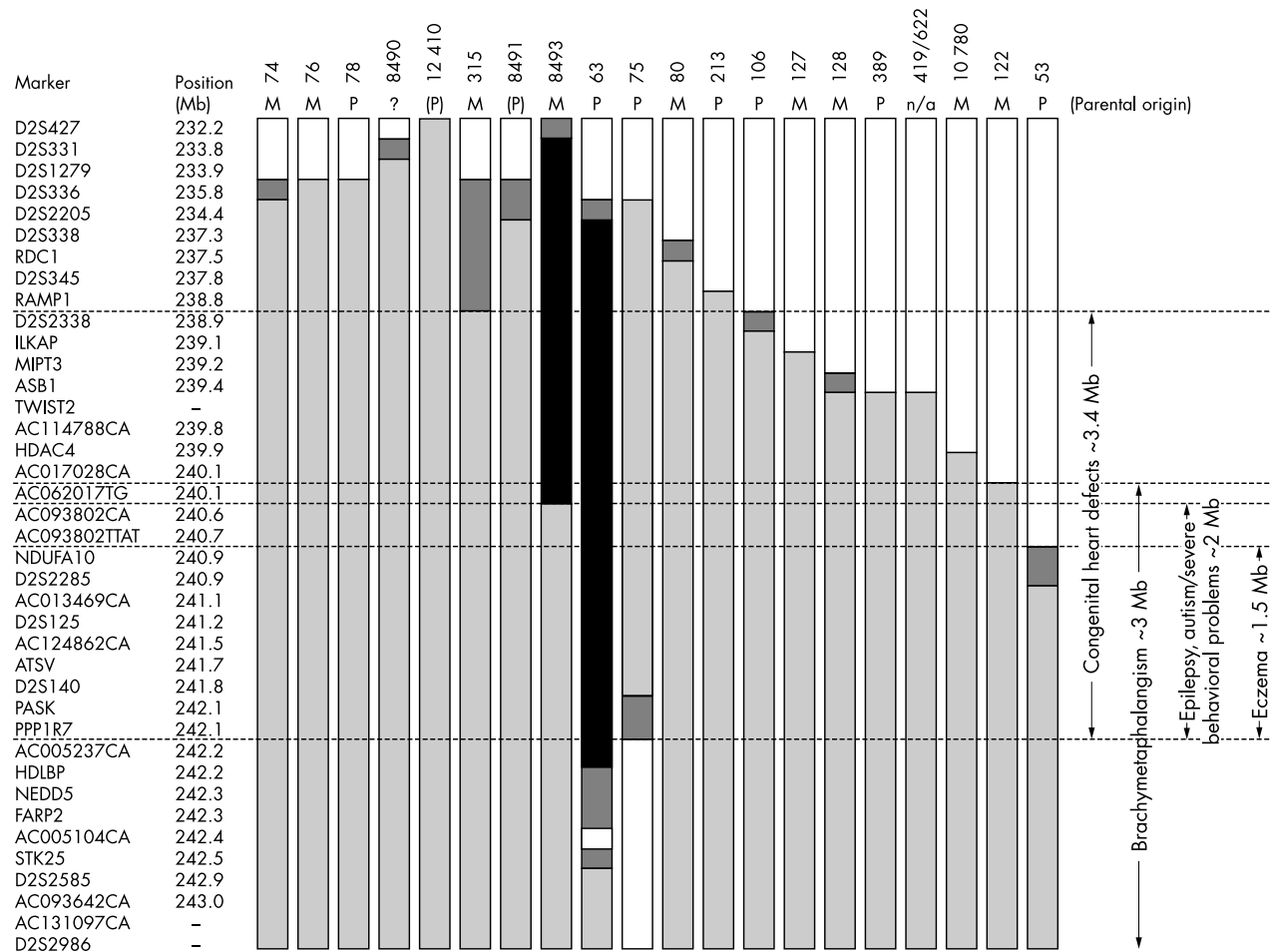


Figure 2 Results and definition of minimal deletion intervals. Positions of markers are those from Ensembl genome assembly release 17.33.1 M, maternal; P, paternal; (P), assumed paternal origin, as patient and mother had one allele in common for every microsatellite tested but paternal sample was not available; n/a, not applicable to familial translocation; white shading, normal dosage; black shading, duplicated; grey shading, deleted; hatched shading, uninformative or not tested.

peak heights of the microsatellites. This has not yet been verified by alternative methods, but would be in keeping with the mechanism proposed by Bonaglia *et al*²⁶ for the causation of inverted duplications.

Breakpoint mapping and minimum deletion intervals

Since we wished to focus on the critical interval for AHO-like phenotype, distal to D2S338, breakpoints in the larger deletions were not characterised in detail. Breakpoints in the nine smallest terminal deletions, the translocation, and one duplication/deletion all localised within a 3.8 Mb region bounded by D2S338 proximally and AC013469CA distally. Two of these breakpoints, patients 10780 and 122, were precisely localised to non-overlapping intervals of 169 and 33.8 kb, respectively, within the *HDAC4* gene. Taken as a whole, these data define the most distal breakpoints so far characterised for both interstitial and terminal 2q37 deletions.

We then attempted to define the minimal deleted interval for each of the major features of the syndrome (fig 2). Due to the apparent reduced penetrance, this was done on an inclusion-only basis, that is, the absence of a clinical characteristic was not used as a criterion for excluding that genomic region. The critical interval for the AHO-like brachymetaphalangism extends from *HDAC4* to the telomere, a region of approximately 3 Mb, as defined by patients 10780 and 122. These patients also both show the characteristic

facial dysmorphism. The interstitial nature of the deletion in patient 75, who clinically showed an atrial septal defect, eczema, epilepsy, and autism,¹⁶ potentially excludes a number of the most telomeric 2q genes as candidates for these phenotypes. Thus, the minimum deleted region amongst our patients with autistic or hyperkinetic behaviour and/or epilepsy is ~2.1 Mb between *HDAC4* and AC005237CA. An overlapping 1.5 Mb region is deleted in patients with eczema, while *RAMP1* and AC005237CA bound a ~3.4 Mb region common to patients with cardiac septal defects (fig 2).

DISCUSSION

Genotype–phenotype correlations have been instructive in a number of other deletion syndromes to define discrete clinical subgroups, leading to more accurate prognostication and identification of candidate genes for specific phenotypes.^{44–50} In conducting this detailed analysis of 20 patients with 2q37 rearrangements, our aims were threefold: (a) to refine the minimal deleted region for the AHO-like brachymetaphalangism; (b) to determine whether genotype–phenotype correlations could be drawn for other features of the syndrome; and (c) to precisely map the breakpoints as possible clues to the rearrangement mechanism.

Brachymetaphalangism

The critical interval for the AHO-like brachymetaphalangism is unequivocally assigned to the 3 Mb region from *HDAC4* to

the telomere. This represents a refinement of approximately 2 Mb compared to the previous minimum interval.¹⁵ It has previously been suggested that much of this interval could be excluded due to arachnodactyly in patient 8493.²⁶ However, the duplicated region in this patient extends just proximal of the Indian hedgehog gene (*IHH*). Mutations of *IHH* are now known to cause brachydactyly type A.⁵¹ Therefore, duplication of the gene might result in the reverse phenotype, unusually long fingers, which would account for the arachnodactyly phenotype in this patient and would likely override any subtle abnormality due to the terminal 2q deletion. Three genes previously proposed as candidates for the brachymetaphalangism phenotype, *GPCI*, *HDLBP*, and *STK25*,^{10 12 52} are localised within the 3 Mb minimal region and remain candidates. Conversely, *TWIST2*, which we considered a candidate gene on the basis of its proposed role in regulating osteoblast development,⁵³ is not deleted in patient 10780 and can therefore be excluded. Brachymetaphalangism is partially penetrant and is present in approximately half of the patients deleted for this minimum region. Some patients show additional, more serious, skeletal abnormalities but, due to the small number characterised to date, it is unclear whether these represent pleiotropic effects of the same underlying gene.

Additional clinical features

Several other features of 2q37 deletions, such as congenital heart anomalies, eczema, autism, and epilepsy, have potentially greater morbidity and thus are clinically more significant. We therefore sought to make genotype-phenotype correlations and investigate whether these are discrete features of a contiguous gene deletion syndrome or pleiotropic effects of haplo-insufficiency for a single gene. Minimum intervals, ranging from 1.5 to 3.4 Mb, could be defined for each of these features. However, these phenotypes are less specific than brachymetaphalangism and, being more common in the general population, phenocopies will also exist. Thus, our assignment of critical intervals for these phenotypes, which is based on a small number of patients, should be regarded as preliminary and requires verification in a larger panel of patients. Some additional support for an autism susceptibility locus at 2q37.3 is already available from a small terminal deletion in a patient with isolated autism³² and from a weak suggestion of linkage in one genome scan.⁵⁴ As presently defined, all minimum intervals share a 1.5 Mb region of overlap. Thus it remains to be determined whether the 2q37 deletion phenotype represents a contiguous gene deletion syndrome and it is possible that developmental abnormalities of several organ systems might result from haplo-insufficiency of a single gene.

Genotype-phenotype correlations

Amongst this panel of 2q37 deletion patients, we found no clear relationship between clinical features and the size or position of the monosomic region. Patients with very similar deletion breakpoints showed markedly different phenotypes, for example 10780 and 122, or 127 and 389. The same is true in translocation families, where individuals with identical 2q37 deletions have been reported with discordant phenotypes.^{12 14} This represents a significant challenge in predicting phenotype for this deletion, since the likely clinical outcome in a young proband cannot be determined from the deletion breakpoints. Variable expressivity is common in deletion syndromes and may be due to reduced penetrance of the haplo-insufficient genes, epigenetic factors, modifying effects of other genes, as recently proposed for *VEGF* and cardiovascular defects in DiGeorge (del22q11) syndrome,⁵⁵ or multigenic inheritance.⁵⁶ An additional factor might be recessive phenotypes that are only uncovered in a minority of deletion patients.

Mechanism of rearrangement

Elucidating chromosomal breakpoints can provide clues as to the underlying mechanism of rearrangement. Several interstitial deletion syndromes, including Williams-Beuren (7q), Smith-Magenis (17p) and DiGeorge (22q), show clustered breakpoints and are commonly mediated by low copy repeat sequences and inversion polymorphisms.⁵⁷⁻⁵⁹ Clusters of olfactory receptor (OR) genes have also been implicated in recurrent rearrangements involving chromosomes 4p and 8p.^{60 61} OR-like genes have also been mapped to 2q37.3, but they do not co-localise with the deletion breakpoints in our patients. Furthermore, a recent study suggests that duplicated segments are not involved in mediating the majority of terminal deletions and translocations.⁶² Our data, which show a lack of identical breakpoint locations, support this finding.

Summary

This detailed analysis of 20 patients with 2q37.3 monosomy has, for the first time, allowed minimal deletion intervals to be defined for all the major phenotypes of the syndrome. However, there is striking phenotypic variability and it is clear that the size and extent of the deleted region cannot be used as a predictor of the likely phenotype in the patient. As increasing numbers of small deletions are detected by more widespread use of subtelomeric FISH, this presents a challenge for clinicians in trying to determine the likely prognosis for a young proband. Ultimately, therefore, the real challenge is to identify not only the gene(s) on 2q37 responsible for the phenotypes in these patients, but also the modifiers, be they genetic, epigenetic, or environmental, that contribute to the phenotypic variability between patients with similar breakpoints. Only then can we begin to give more precise prognostic information to the parents of a child newly-diagnosed with a 2q37.3 deletion.

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An appendix showing clinical descriptions of previously unpublished patients is available online at <http://jmg.bmjournals.com/supplemental/>

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