LETTER TO JMG

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 cases[9] 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 D2S338[2] 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.

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.

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.bmjjournals.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 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: *RDC1, RAMP1, ILKAP, MIP-T3, ASB1, 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]

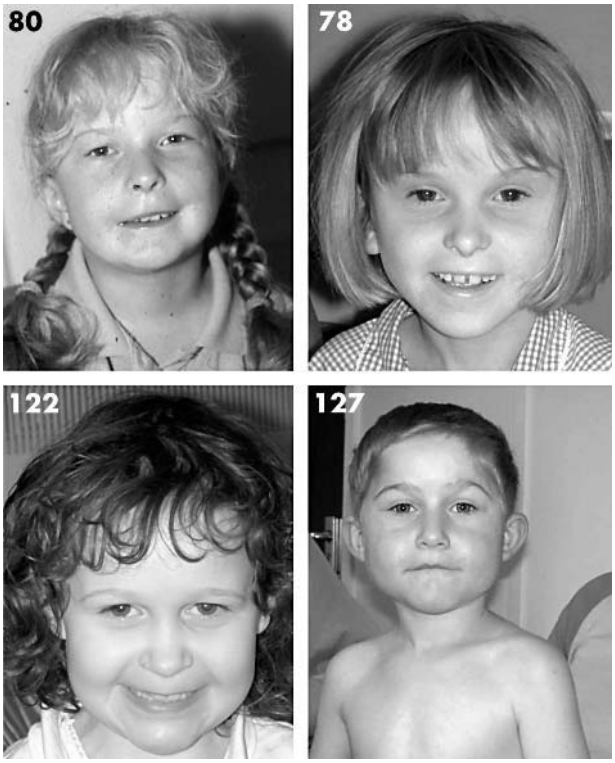

Figure 1 Photographs of four patients with 2q37 deletion illustrate the typical facial appearance in this syndrome.

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 origin[42–45] 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-CCCACTGCCCCAATAGCTC	95/100	55°C
rs11165 (*TWIST2*)	TTACTTTCACGCCGCTATTCT	ACGTCTTTATTTTTCCTGGGTG	T/A SNP	55°C
AC114788CA*	GTTTCTTACTGGGATGCTGAGATATGGAC	FAM-CAAATCCACTTGTTGTCTGGTG	260–290	62.4°C
AC017028CA*	HEX-TCAAAGTGCGCTGAGAGTGG	GTTTCTTGTGGACAGATGTGGAAGTAGC	90–120	62.4°C
AC062017TG	GCAAAGGTTCATACAGATACCGA	HEX-CTGTCAAAGGAAAAAGGGAAGC	160–180	55°C
AC093802CA	GTTTCACCAACTCAAATGCTAATCCA	HEX-CAACATCAGTGTAACCATAAAACA	170–190	52°C
AC093802TTAT	FAM-TCACTCATCTTTGCCTGGATAG	TTCATATTTACACGTAGAAGACGG	230–250†	55°C
AC013469CA*	GTTTCTTATCCTATGGAACACCTCTCCC	HEX-AATTCATCTGACCAAGCATGTG	230–250	62.4°C
AC124862CA	GACGCATCACTCTACCTAAAAAAA	HEX-CAATGCAGGTCTAAATGACCAG	100–120	55°C
AC005237CA*	FAM-ATCAGCTACTGTCAATTCATTCG	GTTTCACCCCTACTCCCAGAAGTCC	80–120	62.4°C
AC005104CA*	GTTTCTTATACATGCACACACGACCACA	TET-GAACAAAGAACTGGACCCTCAG	115–149	62.4°C
AC093642CA*	GTTTCTTGCAGTTAATCTTGACACATCA	FAM-GGGAACAAAAAGAAGGCATGTA	150–170	62.4°C
AC131097CA*	FAM-GTTAAGGGGCTGGACGGG	GTTTCTTAGTCTCCTCGCTCGTGGC	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 *et al*[16])
76	46,XX,del(2)(q37.1)	F	18 years	+	+	B, L		−	−	−	Obesity, lymphoedema of legs	Power *et al*[4]
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	−	I	−	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	−	Hydrocephalus	
8493	46,XX,invdup(2)(q33q37)	F	7 years	+	+	S, Cl	H, Ag, M	−	GA	PDA, PAD	Myopia, arachnodactyly	Bonaglia *et al*[26]
63	46,XX,invdup(2)(q36.2q37.3)	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 *et al*[16])
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 *et al*[2])
106	46,XX,del(2)(q37.3)	F	15 months	Mild	Mild	−		−	−	AS, VSD		
127	46,XY,del(2)(q37.3)	M	5 years	+	+	B	H, Ob	−	−	−	Inguinal hernias, recurrent infections	
128	46,XX,del(2)(q37.3)	F	11 years	+	+	B		−	−	−	Obesity, inguinal hernia, squint	
389	46,XX,del(2)(q37.3)	F	22 years	Mild	Mild	B		−	−	−		
419/622*	t(2;8)(q37.3;q24.3)	N/A	N/A	+	++	B	H, Ag, M	+	+	−	Hernias, recurrent infections	Bijlsma *et al*[7]
10780	46,XX,del(2)(q37.3)	F	12 years	+	+	B, Cr		−	GM	−	Squint, short stature, obesity	KW (Wilson *et al*[2])
122	46,XX,del(2)(q37.3)	F	6 years	+	+	B	SCD	−	−	−	Joint laxity, 2–3 toe syndactyly	
53	46,XY,r(2)(p25.3q37.3)	M	5 months	−	−	Cl		+	Ab	−	Microcephaly	

*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, obsessional; 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.

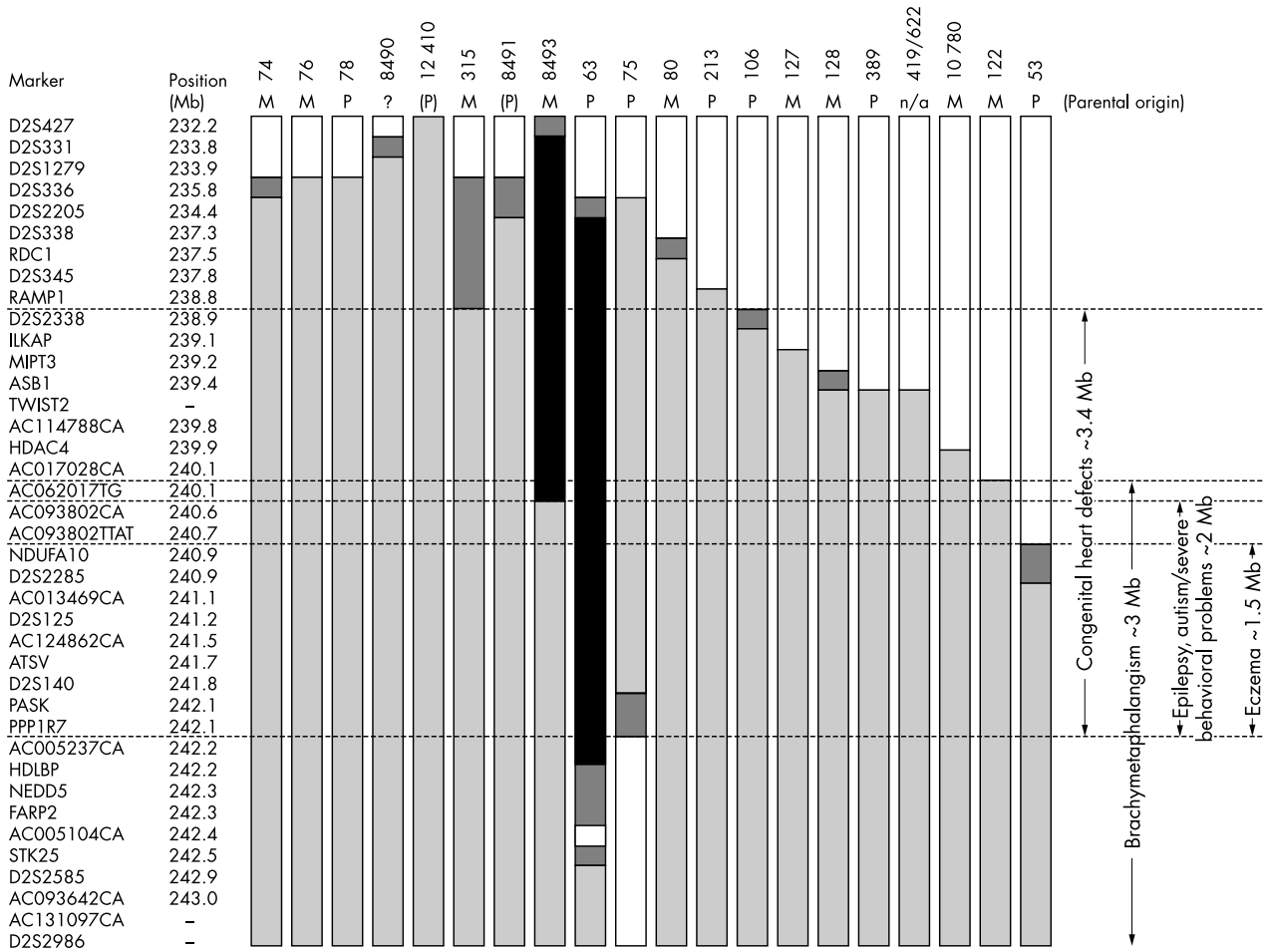

Figure 2 Results and definition of minimal deletion intervals. Positions of markers are those from Ensembl genome assembly release 17.33.1 M, maternal; P, paternal; (P), assumed paternal origin, as patient and mother had one allele in common for every microsatellite tested but paternal sample was not 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 46–50] 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, *GPC1, 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 autism[32] 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.bmjjournals.com/supplemental/

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Clinical descriptions of previously unpublished patients

Patient 78 was first seen in the genetics clinic at age 15 months, with mild to moderate developmental delay. Karyotype was 46,XX,del(2)(q37.1). Investigation of a heart murmur had revealed an ASD and PDA. Length, weight and head circumference were all just below the 50th centile. She was dysmorphic with brachycephaly, frontal bossing, upslanting palpebral fissures, fine hair, round face and small nose. Generalized eczema was present from birth and has remained moderate to severe. Hands and feet appeared normal; no metacarpal or metatarsal shortening was noted. There was generalized joint laxity and hypotonia. She walked alone aged 3 years 10 months. A congenital lung abnormality was queried due to recurrent respiratory infections. By 7 years 5 months, her height and weight had fallen to 2nd and 0.4-2nd centile respectively. Developmentally she was said to be like a 3 year old, with controlling and attention-seeking behaviour and conversation confined to 2-3 word statements.

Patient 8490 is the first child of a healthy unrelated couple with no family history of note. She was born by emergency LSCS for failure to progress and fetal distress following a pregnancy in which the baby had been considered small for dates although had a birth weight of 8lb3oz close to term. There were no immediate neonatal concerns but following an episode of cyanosis the baby was transferred briefly to the special care baby unit. She was hypotonic, had an umbilical hernia (later repaired), excess nuchal skin and feeding difficulties from birth for which she required tube feeding overnight for over 3 months. At 2 months of age she was readmitted having had seizures following her first immunisations which were treated with phenytoin and carbamazepine. She failed to thrive in infancy and was prone to recurrent chest infections. Her early developmental progress was mildly delayed, she walked independently at 23 months of age. At 2 years of age all of her growth parameters lay below 3rd centile and she had no speech. When reviewed aged 6 years she was talking in short sentences but her speech was repetitive and often unclear. She was clumsy with poor coordination and had developed a kyphoscoliosis. She had an episode of sudden hair loss

and her hair, which had previously been thick and dark, regrew sparse blonde and wispy with patchy alopecia. By 10 years of age she had developed autommune thyroiditis and Raynaud's phenomenon. She was having increasing difficulties with her balance and walking. She has some problems with urinary continence although this is improving. She is intermittently constipated and has recurrent rectal prolapse. She is mildly asthmatic and has been seizure free since the age of 2 years. On examination she is dysmorphic with a flat nasal bridge, epicanthic folds, upslanting palpebral fissures and a high palate. She has wiry hair and patchy alopecia. There is a mild kyphoscoliosis, short distal phalanges of the first fingers, shortening of the 3rd to 5th metacarpals bilaterally (confirmed radiologically) and broad toes. She is very routine bound but mixes well. Her karyotype is 46,XX,del(2)(q37.2).

Patient 12410 was ascertained to have a cytogenetic abnormality, 46,XY,del(2)(q37.1), at the age of 32 years. Maternal karyotype was normal, but his father had died of a myocardial infarction. The patient's early motor milestones were normal but severe delay in speech and intellectual development necessitated special education and later institutionalized care. Seizures commenced aged 25 years, initially of grand mal type but subsequently partial with myoclonic jerks, and his behaviour is sometimes difficult. Since age 27, he has sustained ten fractures involving the lower limbs caused by minor trauma and a dislocated hip. X-ray revealed generalized osteoporosis that may result from relative inactivity or long-term anticonvulsant medication. On examination at the age of 32, height, weight and head circumference were on the 3rd, 90th and 75th centiles respectively, with central obesity. Speech was limited with marked echolalia. He was brachycephalic with low anterior and posterior hair lines. Dysmorphic features included short, upslanting palpebral fissures, strabismus and high arched eyebrows. The philtrum was flat and the upper lip thin. There was mild prognathism and the ears were long, with a poorly developed tragus, thickened lobes and mild posterior rotation. His hands were small, with tapering fingers and thumb, and bilateral single transverse palmar creases. Examination of the lower limbs revealed genu valgum, small flat feet, pitting oedema of the lower limbs and ulcerative skin lesions.

Gait was rigid, unsteady and wide based, requiring assistance. General examination was otherwise normal.

Patient 315 is a four-year-old boy born to unrelated parents at 42 weeks gestation weighing 3.6kg. He had an Apgar of 5 at 1 minute and 6 at 8 minutes and, although requiring no resuscitation, was initially irritable and floppy. He has one younger male sibling who is well and there is no contributory family history of note. Early milestones were normal but he presented at two years of age with delay in walking, poor speech and hyperactivity. Initial investigation revealed no underlying cause for developmental delay but subsequently an abnormal karyotype was found, 46,XY,del(2)(q37.1). Parental chromosomes were normal. On examination at 4 years, height and weight were on the 10th centile but head circumference was below the 3rd centile. He was mildly dysmorphic with short upslanting palpebral fissures and high arched eyebrows. The nose was short and upturned and the philtrum flat and long with a thin upper lip. The ears were simple and cupped with thickened outer helices. The hands revealed a left sided single transverse palmar crease with tapering fingers. He had genu valgum with poorly developed calf musculature. General examination revealed no other abnormality. The patient had little speech and showed echolalia. He is moderately myopic and has good hearing. He engaged in little social interaction but manipulated toys well. He had a wide based, flat-footed gait.

Patient 8491 was born following a normal pregnancy between 34-37 weeks gestation weighing 2.08kg. She required intubation for about 5 minutes and subsequently went to special care. She had micrognathia and required nasogastric top-up feeds. There is a history of bilateral congenital hip dislocation, Perthes disease of the right hip, hydrocephalus requiring a VP shunt, fits at age 2¼ mainly associated with fever and marked excess delta activity on EEG. All motor and language skills have been delayed and she attends a special school, but is sociable and not aggressive. On examination, she was small with weight on the 25th centile and head circumference between the 25th and 50th. She had a round face

and short neck, mid-face hypoplasia with a low nasal bridge and mandibular prognathism. Her left ear appeared rather simple and cupped. She has a mild pectus excavatum and quite a pronounced lumber lordosis. She had short 4th and 5th metacarpals on the right hand and 3rd, 4th and 5th on the left with knuckle dimples and short distal phalanges, particularly of the thumb. In the feet, she had first ray hypoplasia with short 2nd to 5th metatarsals and distal phalanges. There was no cutaneous ossification or abnormal pigmentation. Initial cytogenetic analysis was normal, but a 2q37.3 deletion was subsequently detected by subtelomeric FISH analysis and was just discernible on G-banded karyotype.

Patient 63 is a female born weighing 6lb 6oz at 41 weeks gestation. She had a small head from birth and required tube feeding for 2 days. At 9 months she was nearly sitting alone and starting to reach out. She walked at 23 months. Length, weight and head circumference were all around 3rd centile. Dysmorphic features included trigonocephaly, a high forehead, wide lower face, hooded eyes, bilateral ptosis, flat nasal bridge, anteverted nares, wide mouth, small ears and clinodactyly of the 5th fingers. Cytogenetic analysis showed an inverted duplication of the long arm of chromosome 2, karyotype 46,XX,inv dup(2)(q36.2q37.3). Renal and cardiac echo were normal. There is a history of squint, unilateral glaucoma that required goniotomy, recurrent chest infections, meningitis at age five and also two febrile convulsions by this age, but no other seizures. At 9 years she remained small, was able to read and was fond of puzzles and computers but was still not continent at night. There was mild camptodactyly of the little fingers but no clinical evidence of metacarpal or metatarsal shortening.

Patient 80 was born prematurely at 34 weeks weighing 2.44kg and had severe hyaline membrane disease and pneumothorax. On examination at 11 months, there was mild hypotonia, facial dysmorphism and bilateral single palmar creases. Head circumference was on the 50th centile, weight on the 10th centile and length on the 50th centile. Chromosome analysis revealed a 2q37 deletion, karyotype 46,XX,del(2)(q37.3). At 2 years, head

circumference had fallen to the 10th centile. At 8 years, the patient had one fit, accompanied by repeated absences at school. EEG was normal. A horseshoe kidney was discovered on scan following a urinary tract infection. She also required a squint operation. On examination at 9 years there was frontal bossing, upslanting palpebral fissures, narrow pinched nose with hypoplastic alae, slightly small ears, mild little finger clinodactyly, short tapering fingers, possible shortening of 4th and 5th metacarpals, shortening of 4th and 5th metatarsals and mild proximal 2-3 toe syndactyly. She has moderate to severe delay, uses short sentences and attends a school for the learning disabled. She is shy with a short attention span and has behavioural problems with aggression.

Patient 106 is a female born at 38 weeks weighing 5lb 6oz, after a pregnancy complicated by severe vomiting. Early feeding was difficult, with a brief period of tube feeding. A heart murmur was noted and follow-up identified aortic stenosis and a ventricular septal defect. On examination at 3 months the head circumference was on the 50th centile, while weight and height were on the 10th centile. Karyotype was 46,XX,del(2)(q37.3). At 16 months, she was cruising and pulling to stand and spoke more than 6 words. There was possible mild motor delay, small hands and feet, possible asymmetry in the length of the legs, plagiocephaly, frontal bossing, but otherwise no dysmorphism.

Patient 127 is a male born by Ventouse delivery after a normal pregnancy. He was slow in feeding, which persisted through much of the first year. He underwent bilateral inguinal hernia operations as a baby and walked at 2 years. There is a history of recurrent respiratory infections. At age five, he is described as always active, noisy, with a short attention span and obsessional behavior. He is behind at school. On examination he had thick blond hair, prominent philtrum, prominent cheeks, thin lips, high palate, small chin, short 4th and 5th metacarpals and short thumbs. Height was just below the 9th centile and weight 9-25th centile. Cytogenetic analysis revealed a 46,XY,del(2)(q37.3) karyotype. An abdominal scan to exclude situs inversus was normal.

Patient 128 was born at 38 weeks gestation, weighing under 5lb. She was hypotonic in the newborn period. At 3 months she had an operation for a lump in the groin, possibly an inguinal hernia. Subsequently she underwent a squint correction operation. Weight gain was noted from age 4, associated with increased appetite. Aged 11, she had learning difficulties and a short temper. She attends a special school, has simple reading skills and uses a computer. Height was on the 25th centile, weight 98th centile, head circumference 55cm. She had truncal obesity, a round face, narrow palpebral fissues, prominent cheeks and anteverted nose, but no eczema. There is shortening of the 3rd, 4th and 5th metacarpals, confirmed on X-ray, together with cone epiphysis of the little finger middle phalanx and shortening of distal phalanx of thumb. The 3rd, 4th and 5th toes are proximally placed, with very short 4th metatarsals. The heart is clinically normal. Testing for Prader-Willi syndrome was normal. Karyotype was determined to be 46,XX,del(2)(q37.3) with deletion of subtelomeric FISH probe 210e4.

Patient 389 was ascertained at the age of 22 years. She has mild learning difficulties but attended mainstream school with additional help. Her height was on the 25th centile, with normal weight for height and she does not have an AHO-like body habitus. She has upslanting palpebral fissures and epicanthic folds, but is not otherwise facially dysmorphic. She has short 4th and 5th metacarpals, slightly short toes and short terminal phalanges of the thumbs and great toes. Serum calcium and phosphate levels were normal. Her karyotype is 46,XX,del(2)(q37.3), confirmed by deletion of FISH probe D2S90.

Patient 122 was seen in the genetics clinic aged 6 years 7 months. She was born at term weighing 7lb, fed well and gained weight rapidly. She crawled at 11 months and walked at 18 months. Speech was delayed, with only 5 words at 18 months then improved rapidly to sentences by 2 years. At age 6, she is one year behind at school and was recently thought to have receptive language and social communication disorders. Original chromosome

analysis was normal but on repeat analysis, a subtelomeric 2q deletion was identified by FISH, 46,XX,del(2)(q37.3). On examination, she had a round face with full cheeks and slight downward slant to palpebral fissures. Head circumference was 51.7cm (50^{th}-75^{th} centile), height 9^{th} centile and weight 50^{th} centile. There was generalized joint laxity and reduced muscle tone. The liver edge was palpable. Slight shortening of 5^{th} metacarpals was noted bilaterally with shortening of 4^{th} and 5^{th} metatarsals and mild 2-3 toe syndactyly.

Patient 53 was born at 37 weeks weighing 2.1 kg. He was slow to feed initially and was noted to have a small head at 3 months. At 7 months he was smiling, sitting alone briefly and starting to reach out. He had eczema and absences but normal EEG. Length and weight were below the 0.4 centile but growth was parallel to the centile line. On examination there was a slight upslant to palpebral fissures and clinodactyly of the 5^{th} fingers. No other dysmorphic features were noted. Cytogenetic analysis revealed a ring chromosome 2, karyotype 46,XY,r(2)(p25.3q37.3). There is virtually no loss of 2p material and the phenotype is therefore presumed to be due solely to the 2q37 deletion.