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ARTICLE

The 2q37-deletion syndrome: an update of the clinical spectrum including overweight, brachydactyly and behavioural features in 14 new patients

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The 2q37 locus is one of the most commonly deleted subtelomeric regions. Such a deletion has been identified in >100 patients by telomeric fluorescence *in situ* hybridization (FISH) analysis and, less frequently, by array-based comparative genomic hybridization (array-CGH). A recognizable '2q37-deletion syndrome' or Albright's hereditary osteodystrophy-like syndrome has been previously described. To better map the deletion and further refine this deletional syndrome, we formed a collaboration with the Association of French Language Cytogeneticists to collect 14 new intellectually deficient patients with a distal or interstitial 2q37 deletion characterized by FISH and array-CGH. Patients exhibited facial dysmorphism (13/14) and brachydactyly (10/14), associated with behavioural problems, autism or autism spectrum disorders of varying severity and overweight or obesity. The deletions in these 14 new patients measured from 2.6 to 8.8 Mb. Although the major role of *HDAC4* has been demonstrated, the phenotypic involvement of several other genes in the deleted regions is unknown. We further refined the genotype–phenotype correlation for the 2q37 deletion. To do this, we examined the smallest overlapping deleted region for candidate genes for skeletal malformations (facial dysmorphism and brachydactyly), overweight, behavioural problems and seizures, using clinical data, a review of the literature, and the Manteia database. Among the candidate genes identified, we focus on the roles of *PRLH*, *PER2, TWIST2, CAPN10, KIF1A, FARP2*, *D2HGDH* and *PDCD1*.
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Keywords: 2q37-deletion syndrome; genotype–phenotype correlation; intellectual disability; overweight; brachydactyly; AHO-like syndrome

INTRODUCTION

Deletions of the distal 2q37 region involve the last cytogenetic band on the long arm of chromosome 2, which is divided into three sub-bands: 2q37.1, 2q37.2 and 2q37.3. The last sub-band notably contains a small subtelomeric region, 2qtel, which displays non-deleterious polymorphic deletions or duplications. 2q37 Deletions have been described in >115 patients in the literature, associated clinically with intellectual deficiency, brachydactyly, obesity and short stature, ie, the so-called Albright's hereditary osteodystrophy-like (AHO-like) syndrome (OMIM: brachydactyly-mental retardation syndrome no. 600430; http://omim.org/). A precise mapping of the deleted regions is not often available, as most published cases have been characterized by conventional cytogenetics, subtelomeric fluorescence *in situ* hybridization (FISH) or microsatellite markers, and array-based comparative genomic hybridization (array-CGH) has only been used in a few studies.[1–10]

At least 197 genes are located in the 2q37 region (230.7–243.2 Mb; Hg19; NCBI map viewer http://www.ncbi.nlm.nih.gov/mapview/). Of these, 11 have been reported as being potentially related to the 2q37-deletion phenotype so far,[5,10–17] but the phenotypic implications of

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most of them remain unknown. Among the candidate genes with a known phenotype, *HDAC4* has notably been established as being responsible for brachymetaphalangy and intellectual disability.[10] *HDAC4* (MIM 605314) is a class II histone deacetylase that functions as a corepressor for DNA-binding transcription factors. It is a member of a group of enzymes that catalyses the removal of the acetyl group from lysine residues in histones and nonhistone proteins, resulting in the repression of transcription. They are ubiquitously expressed and have a role in transcriptional regulation, cell cycle progression and developmental events. *HDAC4* is critical for proper skeletogenesis and chondrogenesis as well as neuronal survival.[10]

To obtain optimal genotype–phenotype correlations for other candidate genes, a collaborative study was initiated within the telomere network of the Association des Cytogénéticiens de Langue Française (Association of French Language Cytogeneticists, ACLF), enabling us to investigate 14 patients with a 2q37 deletion. The proximal breakpoint of the deletions, the parental origin of the deleted allele and the presence of the 2qtel polymorphism were analysed. The genotype–phenotype correlation analysis was then focused on some of the clinical features often associated with the 2q37 deletion, such as facial dysmorphism, brachydactyly, obesity, intellectual disability, seizures and behavioural disorders of the autistic spectrum (ASD). We used the data mining tool Manteia (http://manteia.igbmc.fr/), and notably the rodent database (Mouse Genome Informatics (MGI), to optimize the search for candidate genes in a region of nearly 9 Mb corresponding to our longest deletion (P1) from 2q37.1 to the telomere. This tool enabled us to propose a map of genes of interest for the main clinical features.

MATERIALS AND METHODS

Population

A collaborative study was set up to collect patients from seven centres for genetics (2002–2011). Informed consent was obtained for all patients tested. We recruited 14 patients (6 males and 8 females) with a known 2q37 deletion. Their ages ranged from 4 to 39 years. In total, 12 patients had terminal deletions, including 9 with purely distal deletions (P1–4, P6, P7, P10, P11 and P13) and 3 with a deletion due to translocation (P8, P9 and P12). One patient had an interstitial 2q37.2 deletion (P5) and one patient had a 2q37 del/dup rearrangement (P14).

Methods

All samples were obtained and analysis performed with the required consent from patients or their parents.

Karyotyping

Conventional cytogenetic analyses were performed on peripheral blood lymphocytes using the 550-band and/or 850-band level, including GTG and RHG banding for family members.

Fluorescence *in situ* hybridization

Academic and commercial probes were used. Among them RP11-341N2, GS-1011O17 and RP11-789L24 were used for diagnosis and to test the 2qtel polymorphism in parents and probes RP11-574K22 (P10), RP11-35I12 (P4) and RP11-332L11 (P4) for 2q37-deletion mapping. DNA for noncommercial probes was extracted from BAC and PAC colonies (N Carter, Sanger institute, Cambridge, UK), amplified with the illustra TempliPhi amplification kit (GE Healthcare, Piscataway, NJ, USA) and labelled with Cyanine3-dCTP or Biotin-dNTP using a nick translation method (BioNickTM DNA Labeling System, Invitrogen, Carlsbad, CA, USA). Hybridizations with commercial subtelomeric probes were performed according to the manufacturers' recommendations. Deletions were detected or confirmed by FISH in all 14 cases.

Array-CGH

Genomic DNA samples were extracted from peripheral blood using the QIAamp DNA Blood Midi kit (Qiagen, Valencia, CA, USA). Array-CGH was performed in all patients using the Agilent 60 k (one patient) or 180 k (nine patients) oligoarrays (Human Genome CGH Microarray Kit, Agilent Technologies, Santa Clara, CA, USA) or a BlueGnome (Cambridge, UK) BAC/PAC microarray (four patients). Random primer labelling and hybridization were carried out with sex-matched reference DNA according to the manufacturer's recommendations. Images were acquired using an Agilent or Axon scanner (Axon, Molecular Devices, Sunnyvale, CA, USA). Data were processed with Genepix 6.0 (Axon), BlueFuse (BlueGnome) or Feature Extraction (v9.5.3.1) software (Agilent Technologies), and results were analysed with the CGH Analytics software (v3.5.14; Agilent Technologies) using the ADM2 algorithm and a three-point filter.

Quantitative PCR

Quantitative PCR was performed in three patients (P8, P9 and P14) to clarify the position of the proximal breakpoint. Primers for the *COL6A3* and *HDAC4* genes were designed and tested using standard procedures (Eurogentec, Seraing, Belgium) on a LightCycler 480 Real-Time PCR System (Roche Diagnostics, Basel, Switzerland).

Genotyping

DNA genotyping of family members was performed by PCR amplification using standard procedures, with a panel of five sequence-tagged site microsatellite primers specific to chromosome 2 (region 2q37.3): D2S125, D2S2985, D2S2988, D2S2986 and D2S2585 (Eurogentec).

Data-mining software manteia

Manteia is a database integrating different kinds of data generated from human and animal models within a single framework, for *in silico* data mining. The system permits all experimental results and annotations from animal models to be linked to the human genome, making it possible to take advantage of data not available for humans to look for candidate genes responsible for genetic disorders. To highlight genes from the 2q37 deletion that could be responsible for each clinical feature observed in patients, we used Manteia to select those known to lead to obesity, abnormal behaviour or bone abnormalities in humans or mice. The MGI mouse data set were used because it contains numerous annotations including those from knockout experiments to provide genotype–phenotype correlations not available for humans.

RESULTS

Clinical characteristics

The clinical features of the patients are summarized in Tables 1 and 2.

The skeletal phenotype in the 2q37-deletion syndrome is well known and characteristic. In this series, 13/14 patients had a specific facial dysmorphism and 10/14 displayed brachydactyly type E (brachymetacarpy and/or brachymetatarsy). The facial dysmorphism was remarkable for frontal bossing (5/13), uncombable hair with a low frontal hairline (6/13), thin eyelids (10/13), thin palpebral fissures (8/13), a small nose with a V-shaped tip (11/13), protruding cheekbones (5/13), a small mouth with thin lips (12/13), smooth philtrum (11/13), low-set ears (8/13) and a large chin (7/13; Figure 1). Bilateral AHO-like brachydactyly was present in 10/14 patients and detected as early as 4 years of age. Brachymetacarpy was present in 9/13 patients, always present and more severe in the fourth digital ray. The fifth digital ray was also shortened in four patients, and both the third and fourth digital rays in one patient. Brachymetatarsy was present in 6/11 patients. The fourth and fifth digital rays were most often shortened compared with the second and third digital rays. Broad halluces and asymmetrical legs were present in six and two patients, respectively, (Figure 1, Tables 1 and 2). Three patients

Table 1 Clinical features of patients with purely distal 2q37 deletions

Patient	*P1*	*P2*	*P3*	*P4*	*P6*	*P7*	*P10*	*P11*	*P13*	*Total cases (pure)*
2q37 Deletion size[a] (Mb)	8.8	8.6	8.5	8.2	6.5	5.2	4.2	4.1	3.5	
Cytogenetic localization	del(2)(q37.1)	del(2)(q37.1)	del(2)(q37.1)	del(2)(q37.1)	del(2)(q37.2)	del(2)(q37.3)	del(2)(q37.3)	del(2)(q37.3)	del(2)(q37.3)	
Parental origin of deleted allele	Pat	NA	Pat	Pat	NA	Mat	Pat	Mat	NA	4 Pat/2 mat
Sex	F	F	F	F	F	M	F	F	M	2 M/7 F
Age at evaluation (years)	39	18	17	9	4	17	9	11	14	
Global developmental delay	Moderate	Moderate	Moderate, language conserved	Severe, language absent	Moderate	Moderate	Moderate	Moderate, language absent	Mild, dyscalculia	9/9
Hypotonia	–	–	Axial	Axial	Axial	–	–	–	–	3/9
Autistic spectrum disorders	NA	–	NA	Stereotypies, refusal to make eye contact	Echolalia	Physical touch repulsion	Echolalia, bright lights attraction	Whistling and rocking stereotypies	–	5/7
Other behavioural problems	NA	Strangeness, restlessness	NA	Frustration intolerance, self-biting	Enuresis, frustration intolerance, AD	Ag, opposition, coprophagy, polyphagy	–	–	Voluble, talkative, very friendly, AD	5/7
Growth parameters										
IUGR	+	NA	–	–	–	+	+	–	–	3/8
Short stature (< −2 SD)	–	+	–	–	–	–	–	+	–	2/9
Thinness *vs* obesity/overweight										
BMI-for-age[b]	Obesity 36 (> +2 SD)	Overweight 26.4 (+1.5 SD)	Overweight 26.6 (+1.5 SD)	Overweight 19.5 (+1.5 SD)	Overweight 17 (+1SD)	Suspected overweight	–	Severe thinness 12.8 (< −3 SD)	Obesity 29.8 (> +2 SD)	Overweight or obesity 6/8
Skeletal abnormalities										
Brachydactyly (hand/foot rays)	4, 5/NA	4/4	4/3, 4, 5	3, 4, 5/3, 4, 5	NA/4, 5	4, 5/NA	–	4/NA	–	7/9
Broad hallux	–	+	–	+	+	–	–	–	–	3/9
Joint hypermobility	–	–	–	+	–	–	–	–	–	1/9
Asymmetrical limbs	–	–	–	–	–	–	–	+	–	1/9
Facial dysmorphism										
Low and uncombable frontal set hair	+	+	+	+	–	+	–	–	+	6/9
Frontal bossing	–	–	–	+	–	–	+	–	–	2/9
Thin and arched eyebrows	+	+	+	+	+	+	+	+	+	9/9
Narrow palpebral fissures	+	+	+	+	+	+	+	–	+	8/9
V-shaped appearence of nasal tip	+	+	+	+	+	–	+	+	+	8/9
Hypoplastic alae nasi	–	–	–	+	+	+	+	+	–	5/9

Table 1 (Continued)

Patient	*P1*	*P2*	*P3*	*P4*	*P6*	*P7*	*P10*	*P11*	*P13*	*Total cases (pure)*
Smooth philtrum	+	+	+	+	−	+	+	+	+	8/9
Thin upper lip	+	+	+	+	+	+	+	−	+	8/9
Broad and square chin	+	+	+	+	−	+	−	−	+	6/9
Full cheeks	+	+	+	−	−	−	−	−	+	4/9
Deep-set ears	NA	+	+	−	+	+	+	−	+	6/8
Other	Lower limbs lymphoedema, thrombopenia, hyperthyroidism			Ectopic kidney	Constipation, febrile seizures	Stretch marks	Clubfeet, sacral dimples, scoliosis, long and thin fingers, DSP	Seizures, urinary reflux, umbilical H, APA, cleft palate, Felty'ssyndrome, DBD	Astigmatism, anaemia, haematoma	

Abbreviations: AD, attention deficit; Ag, aggressiveness. APA, abnormal placement of anus; BMI, body mass index; DBD, diffuse bone demineralization; DSP, decreased sensibility to pain; F, female; Felty's syndrome, neutropenia, large spleen and juvenile chronic arthritis; H, hernia; IUGR, intrauterine growth retardation; NA, not available; M, male; Mat, maternal; Pat, paternal.
[a]Minimal deleted region.
[b]WHO reference curves 2007.

displayed short stature, <2 SD below the mean (P2, P8 and P11). Four patients had normal growth and stature (P9, P10, P12 and P14).

The body weight of the patients was evaluated and three categories defined: normal, overweight (a body mass index (BMI), higher than 1 SD above the mean) and obesity (BMI>2 SD), according to BMI-for-age reference curves (WHO 2007). Five patients >4 years of age were overweight (P2, P3, P4, P6 and P8), and three patients >7 years of age were obese (P1, P5 and P13). For patient P7, the BMI was not available but clinical abdominal adiposity was described with a suspicion of overweight. One patient (P11) displayed delayed growth, with both BMI and height <3 SD below the mean.

Some patients had a past history of hypotonia (5/14). All patients had global developmental delays or mild to severe intellectual deficiencies according to their age. A lack of language acquisition was noted in two patients (9 years and 11 years). In total, 10 of 12 patients (not available for 2 patients) displayed abnormal behaviour, 7 displayed ASDs (7/12) and 4 displayed attention deficit or hyperactivity disorder (4/12). Seizures were present in 3/14 patients.

Malformations were also observed in 6 patients, including hernias (3/14), cryptorchidism (2/14), clubfeet (2/14) and cleft palate (1/14).

Deletion mapping

Among the 14 patients, 13 (P1–4, P6–14) had distal 2q37 deletions ranging from 2.6 to 8.8 Mb. The largest encompassed 120 genes. The proximal breakpoints (Hg19) were distributed among the three subbands, 2q37.1, 2q37.2 and 2q37.3 (Table 3). Nine patients had purely distal deletions (P1–4, P6–7, P10–11 and P13). Three patients had a 2q37 deletion derived from translocations: der(2)t(2;6)(q37.3;p25.3) for P8, der(2)t(2;3)(q37.3;q29) for P9 and der(2)t(2;21)(q37.3;qter) for P12. P5 had an interstitial 2q37.2 deletion of 1.1 Mb and P14 a der(2)dup(2)(q37.2q37.3)del(2)(q37.3) rearrangement. The results of the mapping are summarized in Figure 2 and Table 3.

Parental analysis

We performed segregation analysis to correlate the phenotype with the origin of the 2q37-deleted chromosome (paternal or maternal) and to explore the hypothesis that the 2qtel polymorphism could be a predisposing deletion in the parents.

Both parental samples for genotyping were available in nine families. Microsatellite markers ascertained a paternal origin of the 2q37 deletion in five patients and a maternal origin in four patients. We used FISH to search for the 2qtel polymorphism in eight families, and detected it in the three normal fathers of P2, P3, and P8. P2's mother was deceased. In the family of P3, the 2q37 deletion was of paternal origin and the father had a 2qtel polymorphism, but we could not ascertain if this polymorphic chromosome was transmitted. In the family of P8, the 2q37 deletion was of maternal origin. According to data from the fathers of P2, P3, and P8 and 14 other normal subjects (data not shown), the length of the so-called polymorphism or polymorphic 2qtel deletion was <500 kb. Therefore, among the parents tested, none had the same deletion as their child.

Genotype–phenotype correlation

We classified the pathological clinical features observed in the patients into three main groups: 'skeleton' for facial dysmorphism/brachydactyly, 'weight' for overweight/obesity and 'behaviour' for ASD/behavioural problems. To clarify the role of each of the deleted genes in the three groups, we listed candidate genes for these clinical features in

Table 2 Clinical features of patients with interstitial or associated distal 2q37 deletions.

Patient	*P8*[a]	*P9*[a]	*P12*[a]	*P14*[a]	*Total cases (associated)*	*P5 (interstitial)*
2q37 Deletion size[b] (Mb)	5	4.8	3.9	2.6		1.1
Cytogenetic localization	der(2)t(2;6)(q37.3;p25.3)	der(2)t(2;3)(q37.3;q29)	der(2)t(2;21)(q37.3;qter)	der(2)dup(2)(q37.2q37.3) del(2)(q37.3)		del(2)(q37.2q37.2)
Parental origin of deleted allele	Mat	NA	Pat	Mat	1Pat/2Mat	NA
Sex	M	M	F	M	3 M/1 F	M
Age at evaluation	7 years 10 months	16 years	16 years 1/2	7 years 10 months		7 years 10 months
Global developmental delay	Moderate	Mild	Moderate	Mild	4/4	Mild
Hypotonia	Axial	Distal muscular weakness	−	−	2/4	−
Autistic spectrum disorders	Stereotypies, light obsession	−	Obsessive disorders	−	2/4	−
Other behavioural problems	Ag, frustration intolerance, AD, sleeping difficulties	ADHD, sleeping difficulties	NA	−	2/3	−
Growth parameters						
IUGR	−	−	+	−	1/4	−
Short stature (< −2 SD)	+	−	−	−	1/4	−
Thinness vs obesity/overweight	Overweight	−	−	−	Overweight 1/4	Obesity
BMI-for-age[c]	18.3 (+1.5 SD)					20.7 (> +2 SD)
Skeletal abnormalities						
Brachydactyly (hand/foot rays)	3, 4/4	3, 4, 5/2, 3, 4, 5	4/4, 5	−	3/4	−
Broad hallux	+	+	−	+	3/4	−
Joint hypermobility	−	+	−	+	2/4	−
Asymmetrical limbs	−	+	−	−	1/4	−
Facial dysmorphism						
Low and uncombable frontal hair	−	−	−	−	0/4	−
Frontal bossing	+	+	−	+	3/4	−
Thin and arched eyebrows	+	−	−	−	1/4	−
Narrow palpebral fissures	−	−	−	−	0/4	−
V-shaped appearence of nasal tip	+	+	+	−	3/4	−
Hypoplastic alae nasi	−	−	−	−	0/4	−
Smooth philtrum	+	+	−	+	3/4	−
Thin upper lip	+	+	+	+	4/4	−
Broad and square chin	−	−	+	−	1/4	−
Full cheeks	+	−	−	−	1/4	−
Deep-set ears	+	+	−	−	2/4	−
Other	Cryptorchidism, inguinal H, pyloric stenosis, WSN, congenital torticollis, clubfoot, oculomotor dyspraxia	Abnormal teeth enamel, umbilical H	Seizures	Cryptorchidism, left megaureter, long fingers, livedo		Retrocerebellar cyst

Abbreviations: AD, attention deficit; ADHD, attention deficit hyperactivity disorder; Ag, aggressiveness; BMI, body mass index; F, female; H, hernia; IUGR, intrauterine growth retardation; M, male; Mat, maternal; NA, not available; Pat, paternal; WSN, wide-spaced nipples.

[a]Non-isolated 2q37 deletion.

[b]Minimal deleted region.

[c]WHO reference curves 2007.

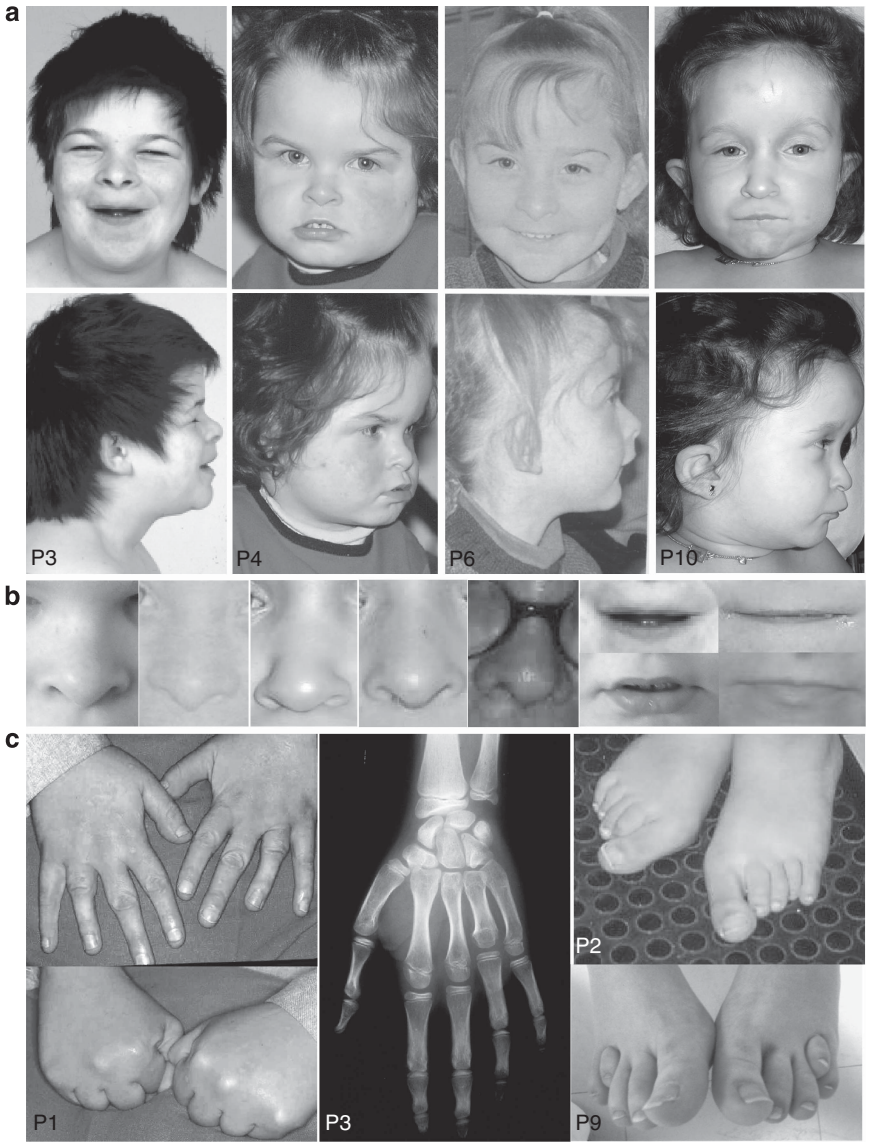

Figure 1 (**a**) Photographs of patients P3, P4, P6, and P10 at 17, 2, 4 and 4.5 years of age, respectively. (**b**) Photographs of the nose showing the V-shape of the nasal tip; photographs of the mouth showing the thin upper lip and smooth philtrum. (**c**) Photographs and X-rays of the hands and feet of patients P1, P3, P2 and P9, showing brachydactyly type E affecting the fourth digital ray (P1, P2 and P3) and second, third, fourth and fifth digital rays (P9).

the 14 patients and in the literature and used the Manteia database to compare them to genes from the homologous region of the mouse genome associated with a similar phenotype (Figure 3). To find genes related to skeletal abnormalities, we searched the database using the terms 'skeletal phenotype', 'abnormal axial skeleton morphology' and 'craniofacial phenotype'. We also included the terms 'brachydactyly' and 'abnormal paw/hand/foot morphology', however, no candidates related to these terms could be found. We searched for obesity-related genes using the term 'increased body weight' in the phenotype data set. For abnormal behaviour, we looked for genes related to 'abnormal social interaction', 'abnormal behaviour' or 'seizure' phenotypes. Two genes, *PER2* (MIM 603426) and *HDAC4*,[10] were found to be involved in all three groups. However, in this cohort, some patients without brachydactyly displayed an *HDAC4* deletion, and this discrepancy needs to be explored. Thereby, to correlate the candidate genes of the Literature and Manteia with the phenotypes of our patients, we established three maps named 'skeleton', 'weight' and 'behaviour' (Figure 4).

DISCUSSION

Mapping

Subtelomeric deletions associated with developmental delays account for 2.5% of the aetiology of learning disabilities. In the largest study of the kind, in which the telomeres of 11 688 individuals were investigated, the 2qtel subtelomeric deletion was a frequently encountered variation, observed in seven patients as a pure deletion.[18] In the study by Ravnan *et al*, near half of the phenotypically altered patients had terminal 2q deletions, but it was not explicitly indicated whether the 2q deletion was a deleterious del 2q37 or only the common polymorphism. Indeed, the first subtelomeric FISH probes used encompassed the polymorphic loci.[19] In the literature, >115 patients with 2q37 deletions were described between 1983 and

Table 3 2q37 Deletion mapping results and associated CNVs obtained by array-CGH (Hg 19)

Patient	*2q Cytoband*	*End of last probe still present (bp)*	*Start of first deleted probe (bp)*	*Minimal size (Mb)*	*Associated CNV*	*Comments*
P1	q37.1q37.3	234 394 188	234 429 660	8.77	No	
P2	q37.1q37.3	234 436 218	234 605 832	8.59	No	
P3	q37.1q37.3	234 655 746	234 670 367	8.53	No	
P4	q37.1q37.3	235 022 777	235 036 825	8.16	No	
P6	q37.2q37.3	236 665 772	236 716 581	6.48	dup(10)(p21.1p21.1) 197 kb chr10:26 797 312–26 993 952 bp	Encompasses the 12 last exons of APBB1IP not involved in the clinical features of the patients (P1-14)
P7	q37.3	237 985 224	238 000 056	5.2	No	
P10	q37.3	238 798 998	238 996 422	4.2	No	
P11	q37.3	239 084 078	239 105 871	4.09	del(4)(q22.1q22.1) 142 kb chr4:92 550 144–92 692 347 bp	Encompasses a partial part of FAM190A (intron)
P13	q37.3	239 636 287	239 665 010	3.53	dup(7)(q36.2q36.2) 285 kb chr7:153 332 127–153 617 280 bp	Encompasses the first exon of DPP6 (polymorphic region)
P8	q37.3	237 554 113	238 258 614	4.94	dup(6)(p25.3) 1.21 Mb chr6:145 997–1 356 756 bp	6p25 Duplication associated with low birth weight, mental retardation, obesity, facial dysmorphism and seizures[40]
P9	q37.3	238 410 947	238 440 095	4.76	dup(3)(q29) 1.87 Mb chr3:195 932 835–197 803 820 bp	3q29 Duplication syndrome associated with mental retardation, microcephaly, obesity and facial dysmorphism (OMIM no. 611936)
P12	q37.3	239 275 210	239 307 975	3.89	dup(21)(qter)	Absence of variation on chromosome 21 with array-CGH
P14	q37.3	240 548 464	240 575 606	2.62	dup(2)(q37.2q37.3) 3.51 Mb chr2:237 038 297–240 548 464 bp	No reported patient with pure and similar 2q37 duplication and described phenotype (DECIPHER and literature)
P5 interstitial	q37.2	Maximal deleted region 235 670 886–236 827 204	Minimal deleted region 235 744 424–236 817 126	1.07	No	DECIPHER patient 251750 with similar interstitial deletion (autism and developmental delay)

Abbreviations: CGH, comparative genomic hybridization; CNV, copy number variation.

2012. Among them, 74 had pure 2q37 deletions (71 distal and 3 interstitial), and 41 showed associated rearrangements (37 reciprocal translocations and 4 inv/dup deletions)[1–10,13–17,20–33] (Table 4). A precise mapping of the deletions, however, was carried out in only a few studies (27/115 patients).[1–10,13,14,24,25,30,32] The patients with purely distal deletions (seven females, three males) included in the DECIPHER database (http://decipher.sanger.ac.uk/) had various deletion sizes ranging from 3 to 9.9 Mb. Unfortunately, clinical features were only mentioned for 2 of the 10 patients. However, clinical data were included for four females with rearranged distal deletions ranging in size from 1.59 to 5.78 Mb. In our series, we proceeded to carefully map the deletions of all patients, and observed the typical 2q phenotype regardless of the size of the deletion, which ranged from 8.8 Mb (P1) to 2.6 Mb (P14).

Parental analysis

In accordance with the report by Ravnan *et al*[18] showing that the majority of chromosomal terminal deletions were *de novo* (48/60 familial studies), we confirmed in our series that, strictly speaking, no patient had inherited the 2q37 deletion from his/her parents. The 2q polymorphism is a common condition in the population (5%).[34] Indeed, three parents (out of eight families tested) had the 2q polymorphism. Moreover, considering the possible role of the 2q polymorphism as a predisposing factor for the largest distal 2q deletion, the family of P8 illustrates the opposite trend. Indeed, the deleted 2q37 region was of maternal origin whereas the 2q polymorphism was found in the father. Parental origin did not seem to interfere in the phenotype, as an analysis of the ratio of paternal (five) to maternal (four) origin showed no bias.

Phenotype–genotype correlation

The 2q37 deletion or 2q subtelomeric microdeletion is a condition that overlaps a recognizable '2q37-deletion syndrome' with an AHO-like phenotype. Table 4 shows similarities between the literature and this study for clinical findings, such as developmental delays, abnormal behaviour, brachydactyly type E and dysmorphic features, but discrepancies can be noted with respect to weight, as discussed in a later paragraph. There was no obvious difference in phenotype

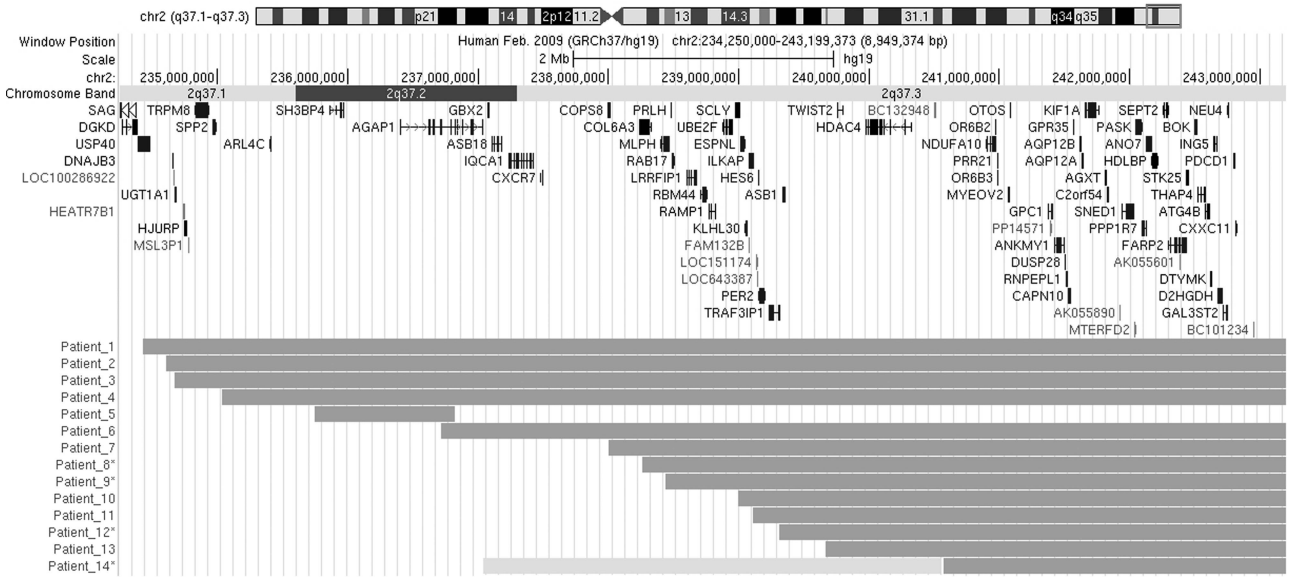

Figure 2 Map of 2q37 deletions in the 14 patients (dark grey) and of the duplicated region in P14 (light grey), with the included genes (UCSC genome browser: http://genome.ucsc.edu/cgi-bin/hgGateway).

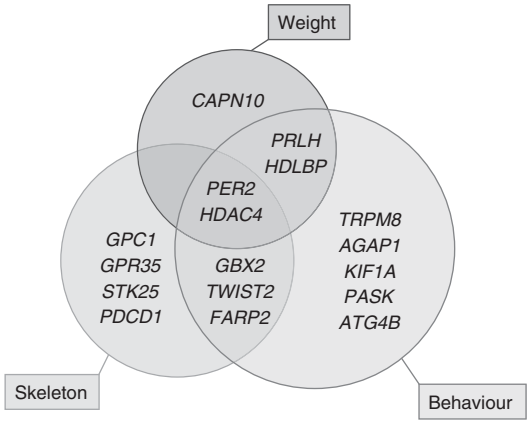

Figure 3 Graphical representation of candidate genes reported in the literature and deduced from the Manteia database for the three groups of features (skeleton, behaviour and weight).

between global (pure and associated) and pure 2q37 deletions. A sex ratio bias observed in the literature (65 females/44 males for global 2q37 deletions and 42 females/26 males for pure deletions) was confirmed in this study (8 females/5 males and 7 females/2 males, respectively; Table 4). Previously reported malformations were rare in this study and might have been coincidental, as they were more frequent when the 2q37 deletion was associated with another chromosomal imbalance (P8, P9, and P14; Tables 1 and 2). The cardiac malformation previously reported in 20% of patients[12] was absent in the 14 patients of our cohort.

Skeleton

Among the 66 patients reviewed by Casas *et al*,[23] 23% had a short stature (<2 SD below the mean), as did 3 patients in this study (21%; Tables 1 and 2). Morphological dysmorphisms like brachydactyly type E and facial features were the most easily recognizable symptoms of 2q37 syndrome. Facial dysmorphism was present in all patients except patient P5, which could be explained by the interstitial deletion (Figure 1). The characteristic dysmorphic facial features have been previously described in detail (see for review Falk and Casas[12]) and include the shape of the nose, the appearance of the philtrum, arched eyebrows, a prominent forehead, a small mouth with thin lips and sparse hair. In our cohort, the most frequent features were the V-shaped appearance of the nasal tip, thin arched eyebrows, thin palpebral fissures, a thin upper lip with a smooth philtrum, low set ears, a large chin and hair set low on the forehead. The oldest patient (P1: 39 years) still displayed these characteristic and easily recognizable features. Candidate genes for facial dysmorphism shared by all patients and located between 240.6 Mb (P14 breakpoint) and 242.7 Mb at 500 kb from the telomeric region (Hg19) were identified as *GPC1*,[15,16] *GPR35*,[14] *FARP2*, *STK25*[11] and *PDC1*.

Brachydactyly has been previously described in about half of all patients.[12,20,23] In our series, 10 of 14 patients had brachydactyly type E. The 'skeleton' map (Figure 4) is consistent with Figure 3 and shows that all patients with brachydactyly had deletions of the same 'skeleton' candidate genes such as *PER2*, T*WIST2*, *HDAC4*,[10] *GPC1*,[15,16] *GPR35*,[14] *FARP2*, *STK25*[11] and *PDC1*. *HDAC4* remains the major candidate, as reported by Williams *et al*,[10] but curiously, patients P10 and P13, who did not show brachydactyly, still had deletions of *HDAC4*. This could be the result of variable expressivity or an incomplete penetrance of haploinsufficiency. As a matter of fact, P13 and P10 had other skeletal disorders, such as facial dysmorphism, as well as clubfeet, sacral dimples and scoliosis in P10. The gene *TWIST2* (MIM 607556) is involved in various skeletal malformations such as short limbs, abnormal vertebrae and altered craniofacial morphology in humans and rodents (OMIM, Manteia). *FARP2* has been described in abnormal bone trabecular morphology related to abnormal osteoclast function (Manteia). Knockout mice for the *PDCD1* gene display large spleens, lupus-like proliferative arthritis[35] (Manteia), and abnormal myelopoiesis and leukopoiesis. This

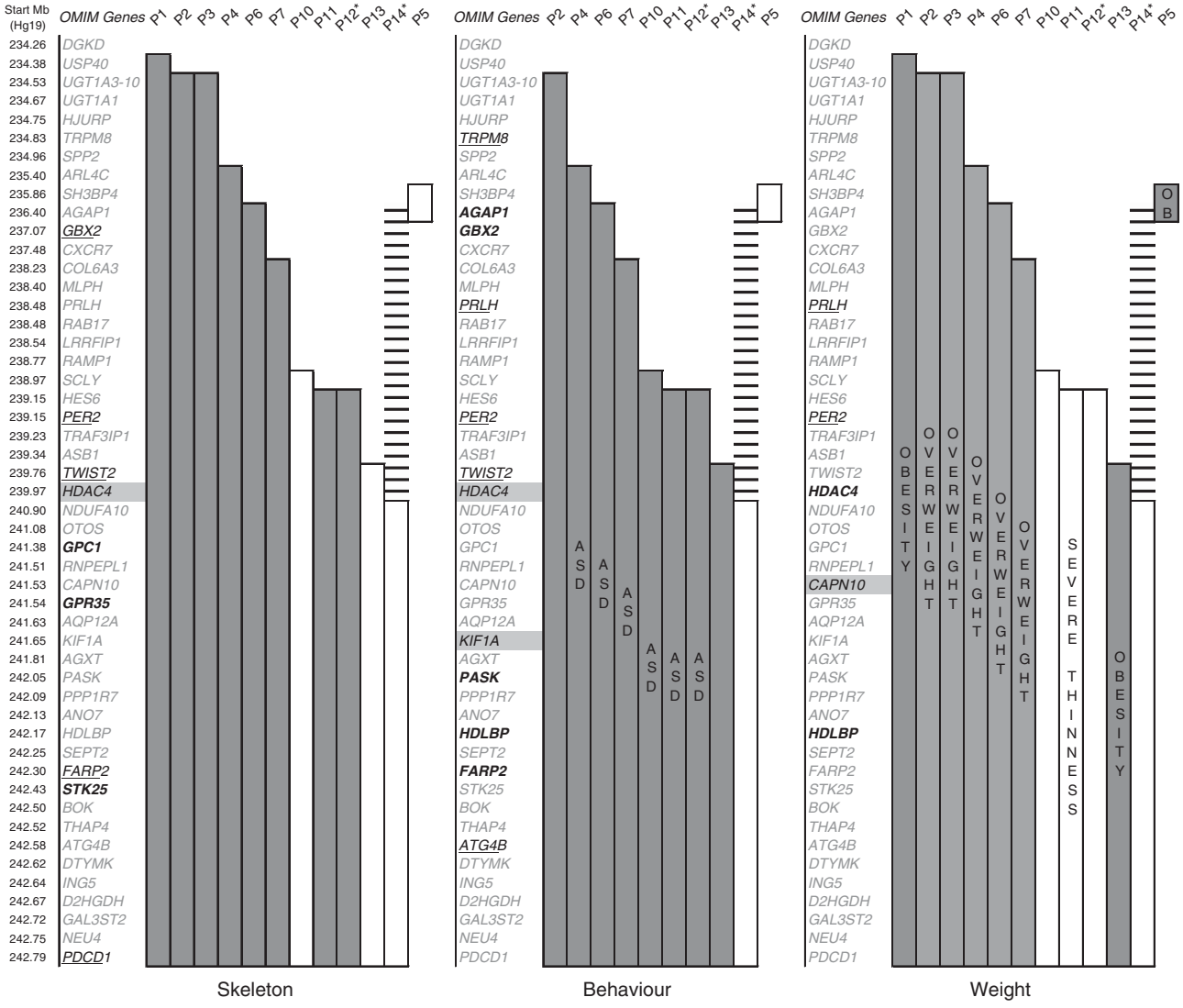

Figure 4 Representation of genotype–phenotype correlations in patients with 2q37 deletions, on three physical maps named 'skeleton', 'behaviour' and 'weight' when documented. Patients P8 and P9 were not included as their associated rearrangements may interfere in the phenotype (see Table 3). First column on the left: location of the genes (Hg 19). On each of the three maps the first column comprises the list of OMIM genes with candidate genes from the literature (bold), from Manteia (underlined) and both (highlighted). The columns represent the deleted genes in the patients; P5 has an interstitial deletion (last column). The columns for patients symptomatic for the concerned features are darkened. The hatched area indicates the duplicated region (P14). *Associated cytogenetic abnormality. OB, obesity.

phenotype is similar to the Felty syndrome (rheumatoid arthritis, splenomegaly and neutropenia) observed in patient P11. A mutation in the second allele of *PDCD1* could explain this severe phenotype.

Weight

Among the 66 patients reviewed by Casas *et al*,[23] >40% showed overweight or obesity, and a tendency toward obesity was found in older patients. In this study, overweight (6/14) was observed more frequently than obesity (3/14), mostly in patients with the largest deletions (>4.8 Mb). The youngest patient, P6 (4 years old), was already overweight. In the literature, three genes are associated with this phenotype: *HDAC4*,[10] *CAPN10*[12] and *HDLBP*.[12] Among them, *CAPN10* is involved in susceptibility to human noninsulin-dependent diabetes mellitus (MIM 605286) and in increased body weight in mice (Manteia). Nevertheless, the 'overweight' map in Figure 4 shows that these three genes were also deleted in normal-weight patients (P10–12). Interestingly, the Manteia candidate gene *PRLH* encoding prolactin-releasing peptide (PrRP) was deleted in most overweight or obese patients (P1–4, P6 and P7) but not in patients with normal weights (P10–12 and P14). Recent research has shown the involvement of PrRP and its receptor in the control of feeding behaviour in invertebrates and vertebrates, and PrRP-deficient mice show hyperphagia.[36,37] The obese patient P5 is deleted for only two genes *SH3BP4* and *AGAP1 (CENTG2)*. A patient with *SH3BP4* deletion, inherited from a normal parent, is reported in the DECIPHER database (ID 254671), and four patients with a deletion interrupting *AGAP1* have been described: 1 in DECIPHER (ID 251750) and three by Wassink *et al*[17] but none of them were obese. Subsequently, P5 patient results may be interesting in narrowing a potential genomic region critical for obesity (*AGAP1*).

Table 4 Comparison of clinical features in this study and in the literature (when documented), including 112 patients with a distal 2q37 deletion[a]

	Distal 2q37 deletions global: pure and associated		*Distal 2q37 deletions pure only*	
	Literature 112 patients	*Current study 13 patients*	*Literature 71 patients*	*Current study 9 patients*
Average deletion length (Mb)[b]	5.13 (24 Cases)	5.67 (13 Cases)	5.73 (16 Cases)	6.39 (9 Cases)
Sex ratio	44 M/65 F	5 M/8 F	26 M/42 F	2 M/7 F
Dysmorphic features	103/107	13/13	63/67	9/9
	96.3%	100%	94%	100%
Type E brachydactyly	60/78	10/13	38/49	7/9
	76.9%	76.9%	77.6%	77.8%
Obesity or overweight	28/69	7/12	17/44	6/8
	40.6%	58.3%	38.6%	75%
Developmental delay	106/106	13/13	67/67	9/9
	100%	100%	100%	100%
Abnormal behaviour	47/54	10/11	32/38	7/7
	87%	90.9%	84.2%	100%
Autistic spectrum disorders	32/49	7/11	25/39	5/7
	65.3%	63.6%	64.1%	71.4%

Abbreviations: F, female; M, male.
[a]For review see Falk and Casas[12] and Casas *et al*.[23]
[b]When documented.

In Table 4, the discrepancy between pure 2q37 deletions in the literature and in this study (38.6% *vs* 75%) could be explained by the lack of availability of BMI curves for previous reports, and semantic heterogeneity (overweight *vs* obesity). Indeed, the BMI-for-age has to be established to determine weight gain, and these curves were not available for most reported children.

Intellectual deficiency and seizures

Among previously reported patients for whom clinical evaluations were carried out, 100% had either a global developmental delay or hypotonia, and mild to severe mental retardation. In this series, five patients had a history of hypotonia, all patients had intellectual deficiency with mild to severe developmental delays but without major motor deficits, and P10 and P11 showed no language acquisition. Seizures have been previously described in 20–35% of patients with 2q37 deletions[20,38] and were present here in 3 patients: P11 and P12 had generalized seizures and P6 had febrile seizures. The candidate genes for seizures identified using Manteia were *HDAC4* and *D2HGDH*. Both were deleted in P6, P11 and P12. Interestingly, Williams *et al* have described an epileptic patient (2282) with a deletion distal to *HDAC4*, including *D2HGDH*.[10] *D2HGDH* is involved in D-2-hydroxyglutaric aciduria (MIM 600721), a neurometabolic disorder characterized by developmental delays, epilepsy, hypotonia and dysmorphic features.

Behavioural disorders

As shown by Falk and Casas[12], multiple reports have documented a behavioural phenotype overlapping the autistic spectrum. A diagnosis of autism or description of autistic behaviour has been reported in 24–35% of patients.[20,23] Most of the patients in our study had heterogeneous behavioural disorders, with seven in the autistic spectrum, and patients P4 and P11 were reported as being autistic. The 'behaviour' map shows that all affected patients shared a deletion of the following candidate genes: *TWIST2, HDAC4*,[10] *KIF1A*,[15] *PASK*,[5] *HDLBP*,[5] *FARP2*,[5] and *ATG4B*. P14 (del/dup 2q37.3) showed normal behaviour but carried deletions of the same candidate genes, except for *HDAC4* and *TWIST2*. *HDAC4* mutations and deletions have been reported as being associated with self-injurious and aggressive behaviour.[10] However, other genes could be involved, as evoked by the deletion distal to *HDAC4* in the autistic patient referred to above (2282).[10] *TWIST2* has been reported to be involved in knockout mice with dystonic movements.[39] *AGAP1*[13,17] is another candidate gene located in 2q37 and the four patients previously cited with *AGAP1* deletion (ID 251750 and Wassink *et al*[17]) had autistic disorders. Interestingly, P5 had a similar deletion but no behavioural problems. *KIF1A*, highlighted by the literature[15] and Manteia, encodes a motor protein involved in the anterograde transport of synaptic-vesicle precursors along axons, and a mutation in this gene has been reported in a patient with nonsyndromic intellectual disability (MIM 601255). *KIF1A* is also associated with hypoactivity and hyporesponse to tactile stimuli in knockout mice (Manteia).

In data from Manteia, the gene *PER2* was shared by the three phenotypic groups (Figure 3). A single reference in humans has reported a heterozygous mutation in *PER2* in advanced sleep-phase syndrome. Interestingly, *PER2* is a member of the period family of genes, associated in KO mice with abnormal food intake, sleep patterns, social interaction, body weight gain and skeletal development.

CONCLUSION

From these 14 new patients with a 2q37 or subtelomeric deletion, we mapped the smallest region of overlap and the genes responsible for facial dysmorphism, brachydactyly, overweight and behavioural problems. The 2q37 subtelomeric region is a gene-rich region spanning 8.8 Mb for our largest deletion (Figure 2). The 2.6 Mb region of overlap contains >25 OMIM genes. Of these, some, such as *HDAC4*, are known to be implicated in behavioural disorders, autism or intellectual disability. The molecular data from our group of patients added to observations from the literature and the DECIPHER database allowed us to focus on other candidate genes. This deletion is still under-diagnosed, but the presence of brachydactyly

type E and the characteristic facial features could direct clinicians toward this syndrome. However, a few patients with pure deletions did not display the most recognizable features (eg, P10 and P13 missed brachydactyly), or possessed a more severe phenotype (eg, P4 had severe behavioural trouble and P11 displayed Felty's syndrome). This could be explained by variations in genetic background, mutations in the second allele or epigenetic phenomena, such as imprinting, although the sex ratio of the inherited deletion is not in favour of the last hypothesis. The expression of regulatory elements in the deleted region or at distance upstream or downstream may also interfere with the phenotype of the 2q37 subtelomeric microdeletion. The associated copy number variations have been explored in the present patients and no potential modifier emerged (Table 3).[40] Furthermore, genetic, as well as functional, analysis would be useful as deletion of *HDAC4* was reported as resulting in reducing expression of *RAI1*.[10] These studies may provide new insights into the pathogenic role of the haploinsufficient 2q37 genes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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