Telomeric 22q13 deletions resulting from rings, simple deletions, and translocations: cytogenetic, molecular, and clinical analyses of 32 new observations

J J Luciani, P de Mas, D Depetris, C Mignon-Ravix, A Bottani, M Prieur, P Jonveaux, A Philippe, G Bourrouillou, B de Martinville, B Delobel, L Vallee, M-F Croquette, M-G Mattei

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The terminal regions of human chromosomes are known to contain specialised DNA sequences and may be vulnerable to rearrangements causing human genetic diseases and particularly idiopathic mental impairment.^{1,2} During the last decade, there have been several reports of patients who are described as having a 22q13 monosomy resulting from simple terminal deletions.^{1–11} A common phenotype emerged from these reports, including variable learning difficulties with disproportionate verbal delay, generalised hypotonia, normal to accelerated growth, and minor facial dysmorphism.¹⁰ Monosomies for 22q13 have also been reported that result from unbalanced translocation with an acrocentric short arm.^{10–12} The acrocentric short arms only bear ribosomal genes, and their duplication or deletion is not generally thought to be phenotypically significant. Therefore such translocations can be considered as “pure” terminal 22q13 deletions.

A distinct group of 22q13 monosomies has been reported that result from the formation of a ring chromosome which combines loss of some long arm material with loss of part of the short arm, with no clinical consequences. Nevertheless, although ring chromosome 22 has been described in over 50 cases,¹³ it remains uncertain whether the variable phenotype is caused by the loss of a variable amount of chromosomal material or by a cellular mosaicism arising from instability of the ring.

Regardless of the causative rearrangement, very few cases of “pure” 22q13 monosomy have been investigated up to now by detailed molecular studies. In order to characterise this syndrome better, facilitate the diagnosis, and provide targeted health care for affected individuals, we have studied 33 patients (32 new observations) with a pure 22q13 partial monosomy, using molecular and cytogenetic methods.

METHODS

Subjects

Our study involved 33 patients with a “pure” partial 22q13 monosomy, with exclusion of all rearrangements involving loss or gain of euchromatic material from any other chromosome than number 22. There were 17 patients with an r(22) chromosome (cases 1 to 17), one of whom has already been reported (case 2¹⁴). Twelve patients had a simple terminal 22q13 deletion (cases 18 to 29). Four patients had an unbalanced translocation involving an acrocentric short arm (cases 30 to 33) and were considered as “pure” 22q13 monosomies. Among these translocations, one (case 30) resulted from the malsegregation of a balanced paternal translocation and the karyotype was 46,XX,der(22)t(14;22)(p11;q13)pat; two (cases 31 and 33) were de novo translocations involving the 22q13 band and the short arm of an unidentified acrocentric, with the karyotype 46,XX,der(22)t(22;acro)(q13;p11). Case 32 was a de novo tandem

Key points

- This is the most extensive study to date of patients with telomeric 22q13 monosomy, including ring chromosomes, simple 22q13 deletions, and unbalanced translocations with an acrocentric short arm.
- The deletions were shown to be extremely variable in size, extending from 160 kb to 9 Mb, and their parental origin was much more often of paternal (74%) than maternal origin (26%).
- Phenotype-genotype correlations showed no gross phenotypic differences between the 22q13 deletion and the r(22) syndromes for similar sized deletions. Nevertheless, behavioural disorders were a constant feature and increase in severity with age. Although patients with simple 22q13 terminal deletion had a general tendency to overgrowth, the r(22) patients often showed growth failure.
- This is the largest series of patients to have been molecularly characterised and includes the r(22) patient with the smallest deletion described to date. The minimum critical region responsible for the monosomy 22q13 phenotype includes the genes *PROSAP2/SHANK3*, *ACR*, and *RABL2B*, but not *ARSA*.

translocation involving the 22q13 band and the short arm of a chromosome 15, with the karyotype 45,XY,-22,-15,+der(22pter→22q13::15p12→15qter).

Clinical examination of the patients was undertaken using the same criteria for all. The parents were interviewed with a standard questionnaire about their child's development and behaviour, and the resulting data were used to assess the child's disability. For all patients, pregnancy and birth data showed no remarkable events. The age and sex of the patients are reported in table 1, as well as the main clinical signs scored for degree of severity (+, ++, +++).

Procedures

Metaphase spreads from the patients were prepared according to standard procedures and at least 50 metaphases were analysed for each of them, in order to detect any mosaicism. Characterisation of the deleted material was done by fluorescence in situ hybridisation (FISH) using BAC and PAC clones obtained from the Sanger Institute (www.sanger.ac.uk), and cosmid clones from Invitrogen (Invitrogen-Life Technologies, Cergy-Pontoise, France). All these probes, for which the relative order was determined by searching in

Table 1 Main clinical signs of 33 patients with 22q13 partial monosomy

Patients		Age (y)	Sex	Hypotonia	Global development delay	Speech delay	Growth (N,A,D)	Dysplastic ears	Seizures	Behavioural disorders	Size (Mb)
r(22)	1	20	M	+	+	++	D+	-	-	+++	0.16
	2	10	M	-	+	+	N	+	-	++	0.31
	3	14	M	-	+	+++	N	+	-	+++	0.31
	4	26	F	+	+	+	N	+	++	+++	0.9
	5	6	F	+	+	++	N	+	-	++	0.9
	6	16	M	+	+	++	D	+	+	+++	1.6
	7	7	M	+	++	+++	N	-	-	+	1.6
	8	1	F	+	+/-	nd	D	+	-	-	1.72
	9	20	M	-	+	++	N	+	-	+++	2.3
	10	36	F	+	+	+	N	+	-	+++	2.3
	11	9	M	-	+	++	N	+	-	++	2.3
	12	34	F	+	++	+++	N	+	+	+++	3.09
	13	27	M	+	++	+++	N	+	-	+++	3.09
	14	12	F	+	++	+	N	+	-	++	3.09
	15	16	M	+	++	+++	N	+	-	++	5.6
	16	3	F	+	+++	++	D	+	-	+	5.8
	17	3	M	+	++	++	N	+	-	+	5.8
del(22)	18	6	F	-	+/-	++	N	-	-	+	0.16
	19	4	F	+	+	++	N	-	-	++	0.31
	20	16	F	+	+	++	N	-	-	+++	0.31
	21	3	F	++	+++	+	A	+	-	+	5.8
	22	12	F	+	++	+++	N	+	+	++	5.8
	23	14	F	+	+++	+++	A	+	-	++	5.8
	24	3	M	+	+++	++	A	+	-	+	5.85
	25	15	M	+	+++	+++	N	+	+	+/-	7.2
	26	6	F	+	+++	+++	N	+	+	+/-	7.2
	27	6	F	+	+++	+++	N	+	+	+/-	7.2
	28	4	M	+	+++	+++	A	+	-	+	8.9
	29	13	M	++	+++	+++	A	+	-	+/-	8.9
t(22)	30	9	F	+	+	+++	N	+	-	+	0.31
	31	29	F	-	+	++	N	-	-	+++	0.31
	32	8	M	+	+	++	A	+	++	++	3.9
	33	2.5	M	+	++	+	N	+	-	+	5.8

F, female; M, male; nd, not determined; N, normal; A, accelerated; D, delayed growth.
- feature absent; + feature present; ++ severe; +++ very severe.

“ensembl genome browser” (www.ensembl.org) and in “UCSC genome browser” (www.genome.ucsc.edu), are shown in fig 1. They were, from centromere to telomere, RP4-753M9, RP5-996D20, RP11-191L9, RP11-536P6, RP11-255N20, RP5-1061O18, RP11-494O16, RP4-579N16, CTA-384D8, and cosmids LL22NCO3-n66c4, -n85a3, -n94h12, -n1g3. The BAC CTA-357F7, containing the “cat eye syndrome” locus,¹⁵ was differentially labelled and co-hybridised with each telomeric probe, in order to identify both chromosomes 22 unambiguously during metaphase.

To elucidate the mechanisms involved in the formation of the rearranged chromosomes 22, three specific probes were used: a synthetic peptide nucleic acid PNA-(CCCTAA)₃ oligonucleotide probe¹⁶ for detecting consensus telomeric TTAGGG repeats; a β satellite probe (Oncor P5096), to define the 22p breakpoint on the ring chromosomes; and a 5.8 kb probe,¹⁷ to detect ribosomal DNA sequences in the ring chromosomes. All the probes were labelled by random priming with either biotin-14dCTP (Bioprime DNA labelling system, Life Technologies) or digoxigenin-11dUTP (High

Figure 2 Determining the size of the deletion using dual colour FISH on metaphases of patients with 22q13 partial monosomy. Left: the entire metaphase of a patient with simple 22q13 deletion. Right: chromosomes 22 from patients with a simple deletion (top), a r(22) (middle), and a translocation (case 32) (bottom). The red signals correspond to BAC 357F7 which is juxta-centromeric on chromosome 22. The green signals correspond to the BAC 384D8, telomeric. Chromosomes are counterstained in blue with DAPI.

prime, Roche diagnostics, Meylan, France), hybridised to metaphase chromosomes and revealed using standard protocols. Commercial probes were used as recommended in the manufacturers' protocols.

The parental origin of 32 deletions was studied by microsatellite analysis (parents of patient 31 were unavailable). DNA from patients and their parents was extracted by standard methods. The DNAs were typed with 14 polymorphic microsatellite repeats mapped to the 22q13 region (fig 1). There were eight Genethon STR markers (D22S276, D22S1157, D22S282, D22S274, D22S1153, D22S1141, D22S1161, D22S1169) and six new markers (3GT, 4CA, 6CA, 1CA, 8GT, 7CT) which we designed using the following bio-informatic programs: "Tandem repeat finder" (www.c3.biomath.mssm.edu/trf.html), "Geneworks" (IntelliGenetics Inc, Oxford Molecular SA, Palaiseau, France), "Primer3" (www.genome.wi.mit.edu/cgi-bin/primer/primer3.cgi/), and NCBI BLAST (www.ncbi.nlm.nih.gov). All couples of primers used in this study were obtained from MWG-Biotech AG (mwg-biotech.fr), with one primer per couple carrying a 5' IRD 800 label. Polymerase chain reactions (PCR) were undertaken on genomic DNA with a commercial kit including Taq DNA polymerase, incubation buffer, and MgCl₂ (Q-BIOgene). Different annealing temperatures were tested for each couple of primers in order to obtain optimal amplification. Allelic inheritance was then visualised by electrophoretic migration of PCR products using polyacrylamide sequence gel and an automated sequencer (LiCor 4200).

RESULTS

Characterisation of the deletions by FISH analysis

In the r(22) patients, two breakpoints are expected to have produced the ring—one on the short arm, the other on the long arm. The most distal long arm breakpoint (case 1) was distal to BAC 384D8 (figs 2 and 3) and corresponds to the smallest deletion (about 160 kb according to "UCSC genome browser"). The most proximal long arm breakpoints were centromeric to PAC 753M9 and delineate deletions larger than 5.8 Mb (cases 16 and 17). These results showed the deleted segments to be of variable size within the 22q13.3 terminal band. In addition, we did not observe any telomeric

repeat on the ring chromosomes using the specific probe PNA-(CCCTAA)₃ (data not shown). We have located the short arm breakpoints either to 22p11 (15/17 cases)—a region known to be enriched in satellite DNA—or to 22p12 containing the rDNA (2/17 cases). Dual colour FISH with the BAC 357F7 probe showed the degree of mosaicism to be very low, and nearly all r(22) patients had one copy of the ring in the large majority of the metaphases analysed (98% to 100%). Complete monosomy 22 and dicentric or pulverised rings were extremely rare (0% to 2%), suggesting that rings of chromosome 22 are remarkably stable. However, one patient (case 1) was different from the others, having 8% of cells with dicentric and pulverised r(22) and 2% of cells with loss of the ring. Despite the remarkable stability seen in metaphase for all patients, micronuclei were observed. These most often contained the ring chromosome 22, as demonstrated by dual colour FISH (data not shown).

In our series of 12 simple 22q13 deletions (figs 2 and 3), the large majority of deletion breakpoints (8/12) appeared to be located in the region proximal to PAC 753M9 and correspond to deletions larger than 5.8 Mb. The smallest deletion (case 18) resulted in the loss of only 160 kb from 22q. The apparent non-homogeneous distribution of breakpoints in simple 22q13 deletions could result from a failure to detect small size deletions using standard or high resolution cytogenetics. It should be noted that large deletions from this sample had all been primarily identified by standard cytogenetics, which may have introduced a bias favouring the more visible deletions. In contrast, the smallest deletions (cases 18, 19, and 20) had been primarily identified by FISH.

Among the four patients with an unbalanced translocation, three (cases 30, 31, and 33) had 46 chromosomes, with the deleted chromosome 22 showing two β satellite fluorescent signals (data not shown)—one located normally on the short arm and the other at the end of the long arm. The fourth patient (case 32) had only 45 chromosomes, with an entire chromosome 15 translocated in tandem onto the distal 22q13 band of one chromosome 22 (fig 2). The β satellite probe showed a positive signal close to the junction of the translocation, suggesting that the short arm of the translocated chromosome 15 was retained. Though involving a smaller number of cases, the breakpoints appear to be distributed similarly to those observed in the cases of ring chromosome 22 (fig 3).

Finally, taking into account the possible bias in the simple 22q13 deletion sample, our results indicated that whatever the rearrangement involved, the deletions were extremely variable in size. We estimate their extents to range from 160 kb to 9 Mb, according to marker positions determined from an integrated map of the genome. Interestingly, several patients (cases 2, 3, 19, 20, 30, and 31) had a deletion breakpoint located between BAC 494O16 and PAC 579N16. In order to define this breakpoint, three PACs located in this interval—RP3-355C18, RP5-898 I4, and RP3-402G11 (Sanger Institute)—were hybridised to patients' metaphases. Five patients (cases 2, 3, 19, 30, and 31) were shown to share the same breakpoint located between PACs 402G11 and 579N16, a distance of 100 kb. This small interval has not yet been sequenced and corresponds to a gap.¹⁸

Parental origin of the deletions determined by microsatellite analysis

The parental origin of 32 deletions was evaluated by microsatellite analysis in order to determine a possible parent-of-origin effect on the phenotype. Not all patients could be tested for parental origin using Genethon microsatellite markers because the most distal one, D22S1169, was excluded from the smaller deletions. The six microsatellite

Figure 3 Determining the extent of the deletion in 33 patients with 22q13 partial monosomy. The different cases from this study have been grouped with respect to the type of deletion: r(22): cases 1 to 17; simple del 22q13 deletions: cases 18 to 29; and translocations t(22): cases 30 to 33. For each type of anomaly, cases are ordered based on the size of the deletion, smallest to largest. In the left column are listed the FISH clones (bold) and the microsatellite markers (italic), ordered from centromere (CEN) to telomere. The sign // placed before a marker means it is included in the above FISH clone. "NI" means non-informative marker. The deleted loci are represented by white squares, the non-deleted ones by dark squares. The parental origin of each rearrangement in the last line: M, maternal origin; P, paternal origin; (-), inconclusive analysis.

markers that we designed were located in a more distal region of chromosome 22 long arm (fig 1). Markers 3GT, 4CA, and 6CA were located between PAC 1061O18 and BAC 494O16; marker 1CA was included in the PAC 579N16; and markers 7CT and 8GT were included in the BAC 384D8. Finally, the parental origin of the rearranged chromosome was determined in 27 of 32 patients (fig 3), microsatellite analysis remaining inconclusive in cryptic deletions (cases 1, 2, 3, 18, and 19). Among all 27 informative cases, the origin of the deletion was found to be paternal in 74% of patients and maternal in only 26% of patients (table 2). There was an evident excess of deletions of paternal origin and, interestingly, this paternal/maternal discrepancy seems to be more frequent in rearrangements with small size deletion (fig 3). In addition, patients with deletions of equivalent size were compared and showed no evident phenotypic differences,

regardless of whether the deletion was of paternal or maternal origin. This indicates there is no parent-of-origin effect as regards the severity of the phenotype associated with 22q13 deletions—in agreement with the non-imprinted status of human chromosome 22.^{19, 20}

Phenotype-genotype correlations

In table 1 we summarise the clinical features observed most often in our series. These include hypotonia, global developmental delay, expressive speech delay, prominent or dysplastic ears, and behavioural disorders. Although these clinical signs are rather non-specific, the presence of other clinical findings has been observed by us and others to be extremely variable.⁴ Patients are classified in increasing order of deletion size for each type of rearrangement. In the last column of table 1 we report the approximate size (in megabases) of the deletions, in order to facilitate phenotype-genotype comparisons.

Hypotonia, most often acquired rather than neonatal, was present in 27 of 33 patients (82%). This appears to be a common clinical sign, not only in individuals with simple 22q13 deletion but also in r(22) patients. Six subjects did not present any sign of hypotonia, and four of these had a deletion smaller than 310 kb. In contrast, two patients with a large deletion encompassing 8 Mb had very severe hypotonia. Thus hypotonia does not appear to be a constant clinical sign associated with the 22q13 deletions, particularly when these are of small size. Nevertheless, all patients with a deletion exceeding 4 Mb had hypotonia, and its severity increased with the size of the deletion.

Table 2 Parental origin of the deletion in 22q13 partial monosomies

Chr 22 anomaly	Informative cases nb	Paternal origin nb (%)	Maternal origin nb (%)
r (22)	14	11 (78.6%)	3 (21.4%)
del (22)	10	6 (60%)	4 (40%)
t (22)	3	3 (100%)	0 (0%)
Total	27	20 (74%)	7 (26%)

nb, number of cases.

Global developmental delay, particularly of motor milestones, was observed in all the patients of our series, although it can be mild in patients with small size deletions. This clinical feature clearly increased in severity in proportion to the size of the deletion, irrespective of the rearrangement involved.

Expressive speech delay was constant (100%) in patients where this feature could be ascertained. It was always severe, and constituted the most characteristic clinical feature observed in our patients, regardless of the type of rearrangement. However, in our series, the correlation between the degree of severity and the size of the deletion was not evident, as severe language impairment was observed in patients with very small deletions.

Facial features were generally not severely dysmorphic, but large or dysplastic ears were frequently but not always present (82%).

Like expressive speech delay, behavioural disorders were a constant clinical feature (100%) in patients aged more than one year. These included hyperactivity, sleep troubles, aggressive outbursts, or confusional states. Nevertheless, owing to their reduced autonomy, patients with a large deletion appeared less severely affected by behavioural disorders than the others. It was noted that the severity of behavioural disorders increased with age, so that the personality of the patients appeared to change progressively. This observation was particularly evident in patients with cryptic 22q13 deletion, and there was no discrepancy related to the type of chromosomal anomaly.

Seizures were observed in only eight of the 33 patients (24.2%). These were not correlated with the type of rearrangement or the size of the deletions, as they were present in patients with 0.9 Mb and 7.2 Mb deletions.

Finally, though the majority of our patients showed normal growth, there was a tendency to accelerated growth in those with simple deletions or translocations (37.5%), and in contrast, a tendency to delayed growth in r(22) patients (23.5%).

Overall our results showed a positive correlation between the severity of the phenotype and the size of the deletion for all types of deletion, regardless of their parental origin. In addition, we noted a clear evolution of the phenotype with age.

DISCUSSION

Our molecular characterisation of 33 22q13 deletions, including both simple terminal deletions and r(22) chromosomes, allows us to establish and compare phenotype-genotype correlations for these two syndromes and to answer some questions about the mechanism of their formation.

Is there any difference between the r(22) and the del(22)(q13) syndromes?

We have shown that in patients with simple 22q13 deletion or r(22), the severity of the phenotype, and in particular the behavioural disorders, may increase with age. Consequently, any phenotype comparison should take into account the age of the patients, which previous studies did not. In contrast to earlier reports, our results show that clinical features are very similar in patients with simple 22q13 deletion and r(22) patients when they are within the same age bracket and have similarly sized deletions. This phenotypic similarity between the two syndromes is in agreement with the remarkable stability of the ring observed in metaphase in nearly all the r(22) patients. Nevertheless, despite the stability observed in metaphase, micronuclei were present in cultures of all r(22) patients. Micronuclei are caused by the ring structure itself, which induces difficulties in sister chromatid separation at cell division, resulting in an increased rate of cell death.²¹ In support of this, we have demonstrated by FISH that the

micronuclei contain the r(22). We may suppose that cell death associated with the ring structure itself is responsible for the growth failure present in several r(22) patients, in contrast with the accelerated growth often observed in patients with simple 22q13 deletion. In support of this hypothesis, patient 1—who showed more severe growth failure than other r(22) patients—also had the most unstable ring, with 10% of abnormal cells. However, we cannot exclude the possibility that the variable phenotypes reported in r(22) patients in other studies are a consequence of destabilising structures in the ring, such as telomere repeats or strongly amplified rDNA sequences. None of these particularities was observed in our patients with r(22), as telomere repeats were absent and rDNA sequences discrete.

In cases where rig 22 is highly unstable, various additional clinical signs could be expected in the r(22) patients, which differentiate them from patients with simple 22q13 deletion. An increased number of cells with dicentric r(22) could result in some phenotypic features of “cat eye syndrome”,²² combining pre-auricular skin tags or pits with iris colobomata. In contrast, the presence of a large number of cells with loss of the r(22), resulting in loss of the NF2 gene and other tumour suppressor genes on chromosome 22, could increase the risk of developing neurofibromatosis^{23–26} and also tumours of the nervous system.^{27–30}

The 22q13 deletions are most often paternal in origin

The expression of the phenotype was not affected by parental origin of the deleted chromosome in either the 22q13 deletion syndrome or the r(22) syndrome. Nevertheless, we showed a strong excess of paternal origin of the 22q13 deletions for all classes of rearrangement. Such an excess was particularly evident for r(22) and for translocations involving an acrocentric short arm, but was also present for simple 22q13 deletions. In addition, this excess was observed to be stronger for small size deletions. This observation is consistent with the moderate increase in paternal origin observed in the simple 22q13 deletions of our series, as these are of large size. A preferential paternal origin of 22q13 deletions has not previously been reported,¹⁰ probably because of the small number of cases with molecular characterisation. Nevertheless, among the few de novo 22q13 deletions analysed in this way, seven were of paternal origin^{1 3 7 31 32} and three were maternal in origin,^{1 4 5} which is consistent with our results. A high recombination frequency is known to be associated to subtelomeric regions both in male and female meioses.^{33–35} Interestingly, subtelomeric regions, particularly in 22q, are enriched in dinucleotide (GT)_n repeats, which can enhance the recombination frequency.^{36 37} This property of (GT)_n repeats could result from their ability to bind the hRad51 recombinase protein preferentially,^{38 39} or to form Z-DNA.⁴⁰ The enhanced recombination associated with (GT)_n repeats has been shown to be greater in males.^{36 37} The reason for this increased recombination in males remains unknown, but could be related to differences between male and female meiosis.⁴¹ Finally, it is possible that the high recombination rate observed in the male subtelomeric 22q region could be the cause of an increased paternal origin of the 22q13 deletions observed in our series.

Possible sequences favouring the occurrence of 22q13 deletions

In our series, we have shown that several breakpoints were located in the same interval (PAC 402G11–PAC 579N16), suggesting that there might be sequences in this interval that confer susceptibility to chromosome rearrangements. This interval of about 100 kb, located between sequences AL022328 and AL096767, has not yet been sequenced¹⁸

(and data from the "UCSC genome browser"), and constitutes the most distal gap of the seven described in the 22q telomeric region. It has been suggested that such gaps in the sequence databases contain sequences that are unclonable with the available host-vector systems.¹⁸ Interestingly, unclonable sequences have been shown to correlate with genomic instability,⁴² which may lead to the deletions observed within this region. Six other gaps are located in the subtelomeric 22q region,¹⁸ and these may also favour the occurrence of 22q13 deletions.

In our series, and in the literature, there is a relative high frequency of rings (22) and translocations which involve both the subtelomeric 22q region and the short arm of an acrocentric (22p or others). Moreover, in the present study, we have shown that the 22p11 band is the most commonly involved at the breakpoints of the r(22). The p11 band of acrocentric chromosomes contains several types of high copy number, tandemly repeated DNA, including satellites I, II, III, and β satellite.^{43–46} We therefore searched for specific sequence homology between the 22q subtelomeric region and the various satellite DNAs from the 22p11 band. We found the G+C rich portion of the satellite I DNA sequence to be interesting, as it contains one Alu family member per repeat.⁴⁷ Numerous Alu sequences are also present in the subtelomeric regions of chromosomes,⁴⁸ and in particular in 22q.⁴⁹ Interestingly, Alu elements are known to be the site of unequal recombination,⁵⁰ leading to various cytogenetic alterations, including deletions, rings, or translocations.

Thus our study suggests that the particular sequence of the subtelomeric 22q region, enriched in numerous unclonable gaps, as well as Alu elements, could be the cause of the relative frequency of 22q13 deletions.

The minimum critical region

Two patients of our series have a similar 160 kb cryptic deletion, delineated by a breakpoint distal to the BAC 384D8, known to contain the ARSA gene. These patients, who presented mild global developmental delay and severe language impairment, are monosomic for a chromosome segment including only the ProSAP2/SHANK3, ACR, and RABL2B genes. This confirms that the minimum critical region for the 22q13 monosomy syndrome does not include the ARSA gene, and emphasises that a probe distal to ARSA must be used if all the 22q13 deletions are to be diagnosed. Among the three deleted genes, it has been suggested that ProSAP2/SHANK3 is involved in the severe language impairment that characterises the 22q13 deletion syndrome.^{11–51} Indeed, ProSAP2/SHANK3 is preferentially expressed in the cortex and cerebellum⁵² and encodes a protein involved in the postsynaptic density of excitatory synapses. Moreover, the fact that behavioural disorders are present in both patients also suggests that the ProSAP2/SHANK3 gene could be involved in the appearance of this feature, which we have shown to be part of the phenotype that increases in severity with age.

Conclusions

Although the incidence of the deletion is not yet established, the increasing number of 22q13 deletions that have been reported recently indicates that these types of deletion may be occurring more often than previously thought. Therefore, any patient with mild global developmental delay, severe speech delay, and behavioural disorders—which may be moderate in young subjects—should be studied by FISH in order to search for a cryptic 22q13 deletion. Moreover, in order to prevent or slow down any aggravation of their behavioural disorders, health care provision should be adapted to the particular needs of these patients.

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Authors' affiliations

J J Luciani, D Depetris, C Mignon-Ravix, M-G Mattei, Inserm U 491, Faculté de Médecine, Marseille, France
P de Mas, G Bourrouillou, Service de Génétique, CHU Purpan, Toulouse, France
A Bottani, Division de Génétique Médicale, Faculté de Médecine, Geneva, Switzerland
M Prieur, Service de Cytogénétique, Hôpital Necker-Enfants Malades, Paris, France
A Philippe, Unité de Génétique Clinique, Hôpital Necker-Enfants Malades
P Jonveaux, Laboratoire de Génétique, CHU Brabois, Vandoeuvre-les-Nancy, France
B de Martinville, Laboratoire de Génétique Médicale, Hôpital Jeanne de Flandre, Lille, France
B Delobel, Laboratoire de Cytogénétique, Hôpital Saint-Antoine, Lille
L Vallee, Service de Neurologie Infantile, Chru de Lille, Lille
M-F Croquette, Alliance 22, Frelinghien, France

Correspondence to: Dr Marie-Geneviève Mattei, Inserm U 491, Faculté de Médecine, 27 Boulevard Jean Moulin, F-13385 Marseille, France; genevieve.mattei@medecine.univ-mrs.fr

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