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Molecular Mapping of 21 Features Associated with Partial Monosomy 21: Involvement of the APP-SOD1 Region

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Summary

We compared the phenotypes, karyotypes, and molecular data for six cases of partial monosomy 21. Regions of chromosome 21, the deletion of which corresponds to particular features of monosomy 21, were thereby defined. Five such regions were identified for 21 features. Ten of the features could be assigned to the region flanked by genes APP and SOD1: six facial features, transverse palmar crease, arthrogryposis-like symptoms, hypertonia, and contribution to mental retardation. This region, covering the interface of bands 21q21-21q22.1, is 4.7–6.4 Mb long and contains the gene encoding the glutamate receptor subunit GluR5 (GRIK1).

Introduction

Monosomy 21 is believed to be the only autosomal monosomy not resulting in death. However, this notion was questioned by Schinzel (1976), who suggested that cases with apparently full monosomy 21 might in fact be either partial deletions resulting from cryptic translocation or mosaics. High-resolution banding techniques (Cohen and Putnam 1972; Dutrillaux et al. 1973; Ikeuchi et al. 1976; Wisniewski et al. 1983) and/or in situ hybridization with chromosome 21 probes (Pellissier et al. 1987; Phelan et al. 1988; Viljoen et al. 1992; Hertz et al. 1993; Lopez-Pajares et al. 1993; Courtens et al. 1994; Gill et al. 1994; Yao and Jenkins 1994) in several probands initially considered to be cases of full monosomy 21 have shown in all cases except one (Pellissier et al. 1987) the presence of a segment of chromosome 21 translocated onto another chromosome. This leads to partial monosomy 21 with a phenotype depending in part on which segment of chromosome 21 has been deleted.

Despite the phenotypic variability between cases of apparently full or partial monosomy 21 reported in the literature since the development of chromosome banding, there are several features that are frequently described, including intrauterine and postnatal growth retardation, down-slanted palpebral fissures, low-set ears, arthrogryposis-like symptoms, hypertonia, heart defect, and mental retardation. The identification of the genes the deletion of which contributes to the pathogenesis of these features might be facilitated by attempting to define in molecular terms minimal regions of chromosome 21 the monosomy of which is associated with particular features. This is possible by studying genotype-phenotype correlations (Epstein 1990) in patients with partial monosomy 21.

We report the phenotypic, cytogenetic, and molecular analysis of six patients with partial monosomy 21. Genotype-phenotype correlations suggest that monosomy for the APP-SOD1 region covering the interface of bands 21q21-21q22.1 contributes significantly to the pathogenesis of 10 of the 25 "monosomy 21" features observed in these cases, particularly several facial anomalies, arthrogryposis-like symptoms, hypertonia, and mental retardation. These results are consistent with the phenotypic and molecular analysis of three nonring partial monosomy 21 cases reported elsewhere (Korenberg et al. 1991*b*; Hertz et al. 1993; Courtens et al. 1994).

Subjects and Methods

Clinical and Cytogenetic Data

All patients except subject GMU had a major dysmorphia and a psychomotor delay, which motivated chromosome analysis. Patient KB is the 6th child of 10 in a North Africa family (4 sisters and 5 brothers, all healthy), whose parents are nonconsanguineous with no history of miscarriage. The pregnancy was normal. The karyotype, showing a de novo interstitial deletion of chromosome 21 (fig. 1*a*), was 46,XY,−21,+del(21)

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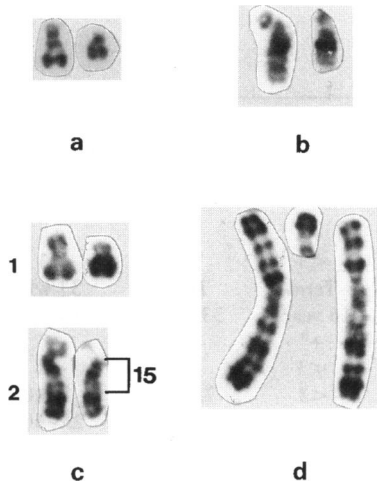

Figure 1 Karyotypic analysis. *a*, Patient KB: high-resolution R-banding (RTBG) of chromosomes 21. *b*, Patient LAE: high-resolution G-banding (GBTG) of chromosomes 21. *c*, Patient PES: 1, Standard-resolution R-banding (RHG) of chromosomes 21. 2, High-resolution R-banding (RTBG) showing normal chromosome 21 and the der(15)t(15;21) chromosome. Chromosome 15 centromere was identified by the DA-DAPI technique; furthermore, NOR staining for patient PES and her parents indicated that the der(15)t(15;21) chromosome was paternal in origin (data not shown). *d*, Patient GMU: high-resolution R-banding (RTBG) showing normal chromosomes 9 and 21 and the der(9),t(9;21) chromosome.

(q11.1q2107).The karyotypes of the parents were normal. Analysis of the chromosome 21 satellites suggested that the deleted chromosome 21 in patient KB was paternal in origin (data not shown).

Patient LAE is the first child of parents born in Mauritius. The mother suffered from three spontaneous miscarriages and had given birth to a stillborn child earlier and had a normal child after the patient LAE, who was delivered by cesarean section at 37 wk because of fetal suffering. The karyotype showed a de novo interstitial deletion of chromosome 21 (fig. 1*b*) and was 46,XX,−21,+del(21)(q11.2q22.2). The karyotypes of the parents were normal.

Patient PES is the second child of two of Caucasian parents and was born at term after a normal pregnancy. The karyotype was 46,XX,−21,+der(15)t(15;21)(q1209;q22.102), associating a monosomy 21(pter→q22.102) and a trisomy 15(pter→q1209) (fig. 1*c*). The karyotypes of the parents were normal, and nucleolus-organizing-region staining indicated that the der(15)t(15;21) chromosome was paternal in origin.

Patients JAF and JAM have been reported elsewhere (Rethoré et al. 1973). They are brother and sister, the only children of Caucasian parents. The karyotype analysis in both cases showed 46 chromosomes, with an abnormal G-like chromosome derived from a maternal (15;21) translocation, and was 46 XY or XX,−21,+der(15)t(15;21)(q13;q22.1)mat, leading to partial monosomy of chromosome 21(pter→q21) and to partial trisomy for the juxtacentromeric part of chromosome 15(pter→q13).

Subject GMU underwent cytogenetic analysis because she had a daughter with a typical trisomy 21 phenotype and 46 chromosomes with an abnormal 9p. The GMU karyotype was 45,XX,−21,−9,+der(9)t(9;21)(pter;q2103), leading to partial monosomy 21(pter→q2103) and deletion of the tip of the short arm of chromosome 9 (fig. 1*d*). Her children inherited two normal chromosomes 21 and the der(9) chromosome and therefore had a partial trisomy 21(q2103→qter) and a monosomy 9pter. The karyotypes of GMU's parents were normal.

The phenotype of each patient was recently determined by examination according to identical protocols (table 1). Their phenotypes include features that were reported with variable frequencies (table 1) in observations of apparently complete (Gripenberg et al. 1972; Halloran et al. 1974; Davis et al. 1976; Dziuba et al. 1976; Fryns et al. 1977; Houston and Chudley 1981; Herva et al. 1983; Wisniewski et al. 1983; Pellissier et al. 1987) or partial (excluding ring 21 and mosaicism) (Cohen and Putnam 1972; Dutrillaux et al. 1973; Laurent et al. 1973; Holbek et al. 1974; Wahrman et al. 1974; Ikeuchi et al. 1976; Fried et al. 1978; Otto et al. 1978; Yamamoto et al. 1979; Modi and Buckton 1982; Rethoré et al. 1982; Rivera et al. 1983; Wulfsberg et al. 1983; Yoshimitsu et al. 1983; Nielsen and Tranebjaerg 1984; Philip et al. 1984; Reynolds et al. 1985; Carpenter et al. 1987; Ackerman et al. 1988; Phelan et al. 1988; Estabrooks et al. 1990; Roland et al. 1990; Korenberg et al. 1991*b;* Viljoen et al. 1992; Hertz et al. 1993; Lopez-Pajares et al. 1993; Courtens et al. 1994) monosomy 21, by chromosome-banding analysis, in situ hybridization, or molecular analysis.

All subjects are mentally retarded, except for GMU, who is an assistant pediatric nurse. The IQ of patient KB could not be assessed with accuracy, because of his consistent refusal, ever since he had been very young, to perform an evaluation test. Psychologists estimated his IQ to be 40–60. Patient LAE has a very severe psychomotor delay: at the age of 3 years 8 mo, he could neither walk nor speak a word and was therefore untestable. Patient PES had a Therman Merill test, at the age of 16 years, which gave a global IQ of 30. Patients JAF and JAM have severe mental delay: their IQ were estimated to be 17 (JAF, when 15 years old, by the Borel Maisonny test) and 20 (JAM, when 7 years 10 mo, by the Brunet-Lezine test) (Rethoré et al. 1973).

Patients KB, LAE, PES, and subject GMU are shown in figure 2. Pictures of patients JAF and JAM have been published previously (Rethoré et al. 1973).

Molecular Analysis

The copy numbers of chromosome 21 single-copy sequences were evaluated by a slot blot hybridization

Table 1

Phenotypic Analysis of Subjects

FEATURE (Frequency in Full/Partial Monosomy 21[a])	SUBJECT (Sex)					
	KB (M)	LAE (F)	PES (F)	JAF (F)	JAM (M)	GMU (F)
Intrauterine growth retardation (75%/65%)	−	+	+[b]	+[b]	+[b]	−
Birth weight (percentile)	10–25	<3	<3	<3	<3	50–75
Delivery time	Term	37 wk	Term	Term	33 wk	Term
Age	16 years	3 years 8 mo	16 years	33 years	23 years	31 years
Postnatal growth retardation (100%/62%)	−	+	+[b]	+[b]	+[b]	−
Height (percentile)	3–10	<3	<3	<3	<3	90–97
Weight (percentile)	<3	<3	<3	75–90	3–10	>97
Head circumference (percentile)	25–50	<3	<3	25–50	25–50	50–75
Microcephaly[c] (38%/39%)	−	+[d]	−	−	−	−
Prominent occiput (25%/7%)	−		−	+	+	−
Short neck (50%/23%)	+	+	+	+	+	−
Low hairline (13%/10%)	+	+	+	+	+	−
Prominent nasal bridge (38%/32%)	+	+	+	+	+	+
Large nose (25%/13%)	+	+	+[b]	+[b]	+[b]	−
Down-slanting palpebral fissures (88%/32%)	−	+	−	−	−	+
Epicanthus (25%/23%)	−	−	+	−	−	+[e]
Hypertelorism (50%/19%)	+	+	−	−	−	−
Low-set ears (88%/26%)	−	+	+[b]	+[b]	+[b]	−
Large ears (50%/26%)	+	+	+	+	+	−
Broad and/or "fish-shaped" mouth (38%/19%)	+		+	+	+	−
Cleft palate (63%/3%)	−	+	−	−	−	−
Highly arched palate (13%/36%)	+	+		+	+	+[e]
Retrognathia (75%/32%)	−	+	−	+	+	+[e]
Kyphosis (25%/10%)	+	−	+	+	+	+
Arthrogryposis-like symptoms[f] (75%/32%)	+	+	+	+	+	−
Transverse palmar crease, L/R (25%/26%)	+/+	+/+	+/+	−	−	−
Clinodactyly of fifth finger, L/R (38%/16%)	−		−/+	−	−	−
Syndactyly of toes, L/R (25%/13%)	−		+/+[g]	+/+[g]	+/+[g]	−
Genital anomaly: cryptorchidism (100%/42%)	+				+	
Congenital heart disease (50%/42%)	−	−	−	−	−	−
Hypertonia (63%/32%)	+	+	+	+	+	−
Mental retardation (IQ) (88%/93%)	+ (~50)	+ (<10)	+[b] (30)	+[b] (17[h])	+[b] (20[i])	−

[a] For full monosomy 21, $n = 8$; for partial monosomy 21, $n = 31$.
[b] Also described in trisomy 15q1.
[c] Based on height.
[d] Below 3d percentile.
[e] Also described in monosomy 9p.
[f] Including restriction of joint mobility plus flexion deformity and/or malposition of fingers and toes.
[g] Second and third toes.
[h] At age 15 years.
[i] At age 7 years 10 mo.

method described elsewhere (Rahmani et al. 1989; Blouin et al. 1990). This method, originally designed for assessing the copy number of any single chromosome 21 sequence in cases of partial trisomy 21, is also applicable to the study of partial monosomy 21 (Blouin et al. 1990; Pangalos et al. 1992). DNA was purified from blood by standard techniques. Various amounts of denatured DNA from a normal control (C), a trisomy 21 patient (D), and the subject to be analyzed (P) were loaded onto a nylon membrane. Since DNA from full monosomy 21 was not available, trisomy 21 DNA was used as a control for the validation of each copy-number-determination experiment (revealing three copies for the chromosome 21 probe tested). The membrane was successively hybridized with a reference probe and chromosome 21 probes (^{32}P dCTP–labeled inserts). Intensities of the signals on autoradiograms were quantified by densitometric scanning (Shimadzu TLC CS 930 scanner). Linear regressions between reference and chromosome 21 probe signals for C, D, and P were computed, and the number of copies (one or two) of a given chromosome 21 sequence in the DNA from the studied sub-

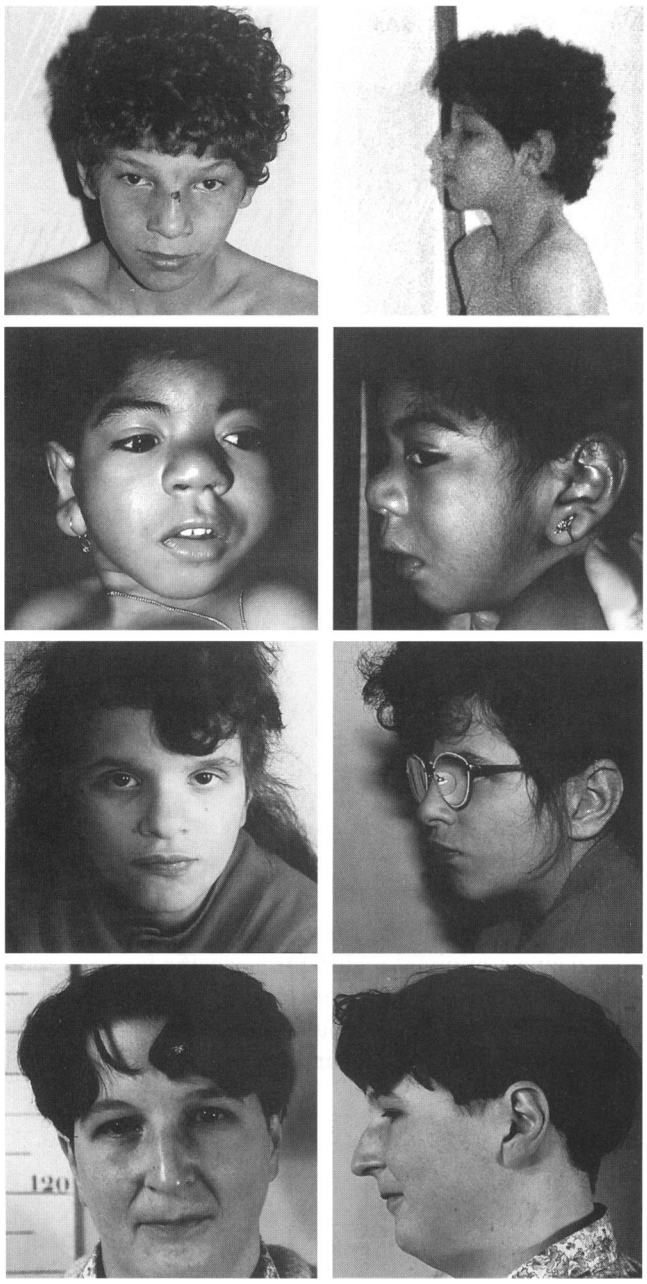

Figure 2 *Top row,* Patient KB at age 14 years. *Second row,* Patient LAE at age 3 years 6 mo. *Third row,* Patient PES at age 16 years. *Bottom row,* Patient GMU at age 31 years.

ject P was determined by statistical comparison of its regression slope with those of C and D. The copy numbers of the following sequences were estimated: APP (Goldgaber et al. 1987), CD18 (Kishimoto et al. 1987), ETS2 (Boulukos et al. 1988), IFNAR (Uzé et al. 1990), PFKL (Levanon et al. 1987), and SOD1 (Lieman-Hurwitz et al. 1982) cDNAs and the anonymous DNA probes D21S13, D21S15, D21S16, D21S17, and D21S19 (Stewart et al. 1985), D21S1 and D21S11 (Watkins et al. 1985*a*), D21S52, D21S54, D21S55, D21S58, D21S59, and D21S65 (Watkins et al. 1985*b*), D21S42 (Korenberg et al. 1987), and D21S144 (Van Camp et al. 1989). The order and localization of these sequences on chromosome 21, as shown in figure 3, are consistent with recent genetic linkage mapping data and physical mapping data (Cox et al. 1990; Gardiner et al. 1990; Burmeister et al. 1991; Petersen et al. 1991; Delabar et al. 1992, 1993*a;* Tanzi et al. 1992; McInnis et al. 1993). COL1A1 (chromosome 17) (Chu et al. 1982) and COL1A2 (chromosome 7) (Myers et al. 1981) were used as reference probes.

Results

Molecular Definition of Partial Monosomies 21

Figure 4 shows the results of typical graphical processing of data obtained from gene-dosage experiments using chromosome 21 probes SOD1 and D21S17 and COL1A2 as a reference probe for patient PES. Slope D21S17/COL1A2 is significantly lower than slope D but is equal to slope C, whereas slope SOD1/COL1A2 is significantly lower than slopes D and C, suggesting a deletion of SOD1. The conclusion that SOD1 is deleted is further confirmed by testing the correlation SOD1/D21S17: slopes C and D are the same, whereas slope P is significantly lower, indicating that the copy-number ratio between SOD1 and D21S17 is identical in C and D, whereas this ratio is decreased in P. Therefore, D21S17 and SOD1 are present in two and one copies, respectively, in patient PES.

Gene-dosage experiments were performed in the five patients and subject GMU, leading to the molecular definition of the deletion of chromosome 21 in each case (fig. 3). Results for patients KB, PES, and LAE have been reported elsewhere (Delabar et al. 1992). In patient KB, the molecular analysis revealed two independent deletions, a pattern that was not observable on the karyotype. For the other patients, the size and extent of the deletions deduced from this molecular approach were consistent with cytogenetic observations.

Genotype-Phenotype Correlations

The genotype-phenotype correlations were analyzed by comparing the features present (positive sign) in the patients with the genotype. We excluded from this analysis the features (denoted by footnotes b and e in table 1) that might have resulted from the other aneusomy associated with the partial monosomy 21, i.e., trisomy for the juxtacentromeric part of chromosome 15 in patients PES, JAF, and JAM and monosomy for the distal part of the short arm of chromosome 9 in subject GMU (de Grouchy and Turleau 1984; Buyse 1990). When two (or more) patients with different deletions both (all) presented an identical feature, the region of chromosome 21 present in one copy in both (all) was defined as the

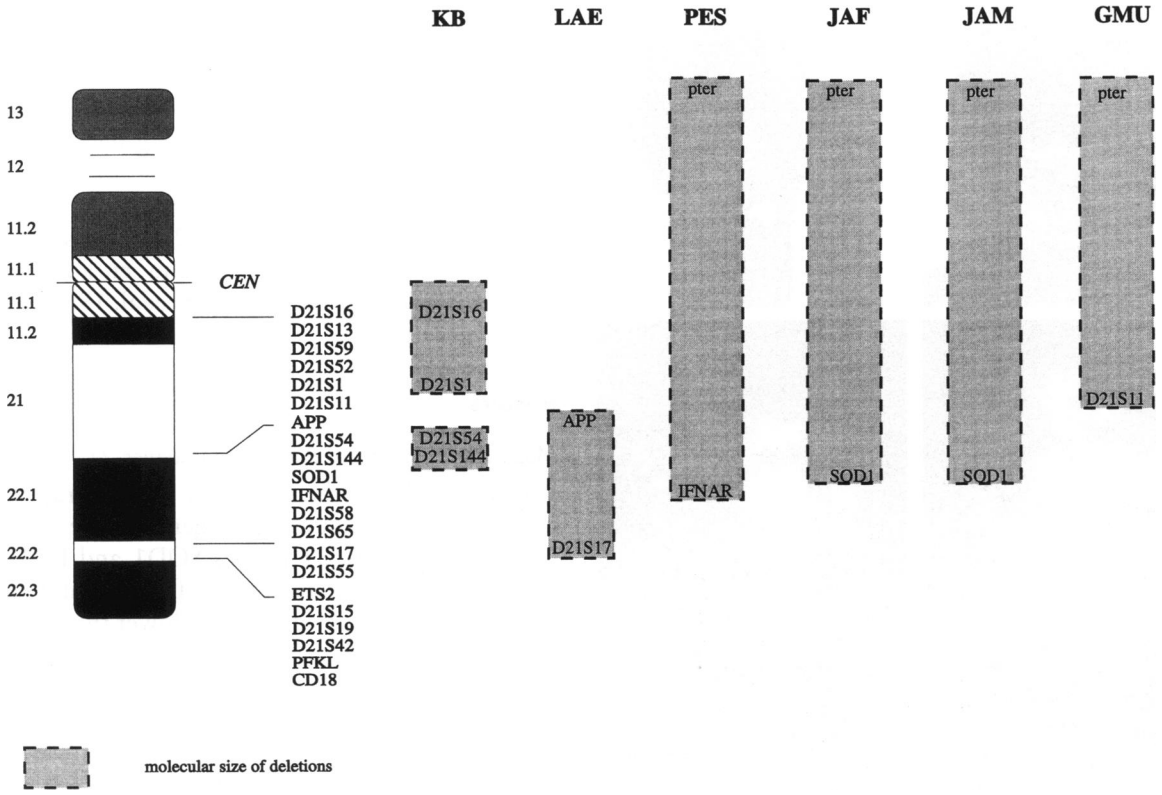

Figure 3 Molecular definition of the partial monosomies 21

minimal region (Epstein 1990). Moreover, some features that were observed only in patient LAE, who carries a deletion of chromosome 21 without apparent other chromosome imbalance, could be ascribed to the monosomy of the region flanked by probes D21S11 and D21S55. By definition, the chromosome 21 sequences that define a minimal region for a specific feature represent the external boundaries of the region. Thus, six minimal regions (fig. 5) could be defined for 21 of the 25 features observed in our patients. For two features

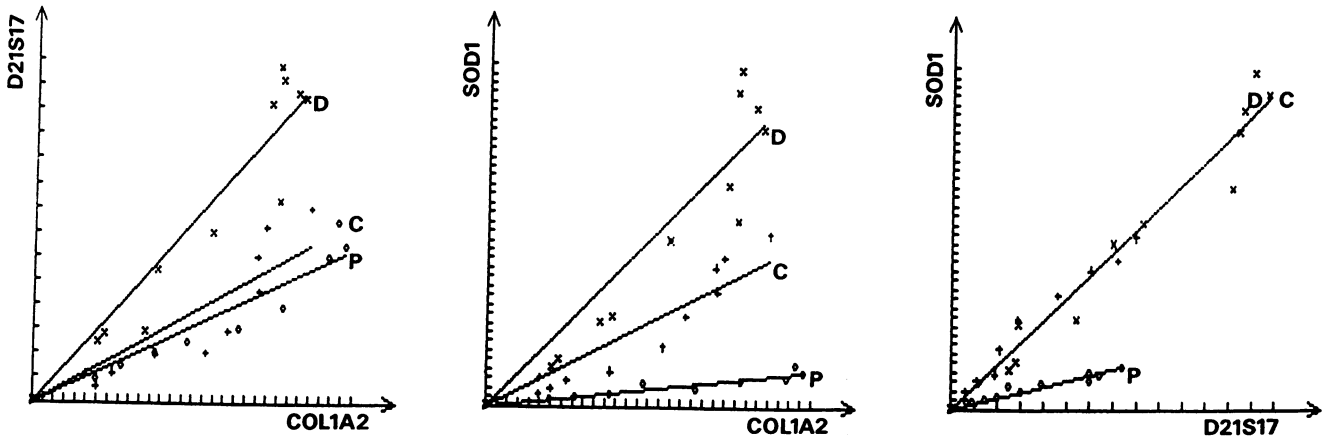

Figure 4 Example of chromosome 21 sequence copy-number determination, graphically showing processing of the autoradiogram densitometric data obtained after successive hybridizations of the same membrane with chromosome 21 probes D21S17 and SOD1 and the reference probe COL1A2 (for detailed description of the method, see Blouin et al. 1990). The membrane was loaded with DNAs from a control (C), a trisomy 21 subject (D), and patient PES (P). Slopes (±SD) of the linear regressions between probe signals (n = 12) are as follows: *left,* C = 0.25 ± 0.02; D = 0.50 ± 0.03; and P = 0.21 ± 0.01; *middle,* C = 0.61 ± 0.04; D = 1.20 ± 0.07; and P = 0.13 ± 0.01; and *right,* C = 2.44 ± 0.09; D = 2.43 ± 0.08; and P = 0.62 ± 0.03. Differences between slopes were assessed by t-test.

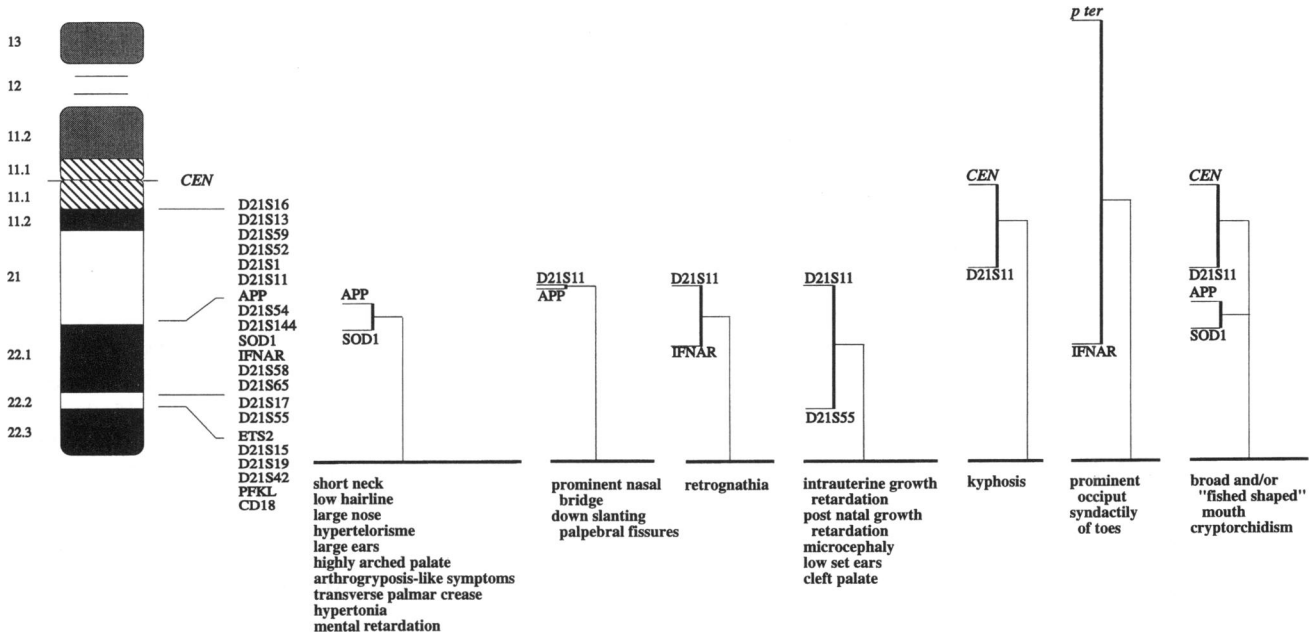

Figure 5 Molecular mapping of 23 features associated with partial monosomy 21

(broad and/or "fish-shaped" mouth and cryptorchidism), two noncontiguous regions—namely, centromere-D21S11 and APP-SOD1—were deleted in common in the patients presenting these features. The APP-SOD1 region is the minimal region for 10 of these features.

Discussion

Phenotypic and molecular analysis of patients with partial monosomy of chromosome 21 was used to define minimal regions of chromosome 21 involved in the clinical features that are usually associated with apparently full or partial monosomy 21. This type of approach (Epstein 1990) has been used elsewhere in other human aneuploidies, including Down syndrome (trisomy 21) (McCormick et al. 1989; Rahmani et al. 1989; Korenberg et al. 1990*b*, 1994; Delabar et al. 1993*b*), "cri du chat" syndrome (5p−) (Overhauser et al. 1994), and 18q− syndrome (Kline et al. 1993) and has led to the construction of a phenotypic map for each of these syndromes.

Of the six patients whom we studied, two had an interstitial deletion of chromosome 21 and four had a partial monosomy 21 resulting from either a de novo (patient PES and subject GMU) or an inherited (sibs JAF and JAM) translocation. In the translocated cases, the associated chromosome imbalance was the source of a potential difficulty for phenotypic analysis. Several features that were observed in these patients have been described not only in monosomy 21, but also in trisomy 15q1 or monosomy 9p distal (de Grouchy and Turleau 1984; Buyse 1990). These features could be due to monosomy 21 but were excluded from the genotype-phenotype correlations. The other features have not been described as associated with trisomy 15q1 or monosomy 9p distal. Therefore, they were assumed to result from the partial monosomy 21. This analysis mapped the molecular boundaries of single minimal regions for 21 of the 25 features observed in our patients (fig. 5). The APP-SOD1 region was the richest, with 10 features, 3 of them—arthrogryposis-like symptoms, hypertonia, and mental retardation—being among the most frequently reported in descriptions of monosomy 21. On the basis of the *Not*I contiguous maps reported at human chromosome 21 workshops (Delabar et al. 1993*a;* Orti et al. 1994), this region is expected to be 4.7–6.4 Mb long.

The phenotypic and molecular analysis of three cases with partial monosomy 21 has been reported elsewhere: a case with an interstitial deletion from D21S16 to D21S54 with normal intelligence and quasinormal appearance (Korenberg et al. 1991*b*); a patient with a deletion, from 21pter to APP, associated with a monosomy 11qter (Hertz et al. 1993); and a patient with a deletion, from 21pter to D21S210 (a probe between D21S11 and APP) (Warren et al. 1993), associated with a monosomy of distal 1q (1q44→1qter) (Courtens et al. 1994). In these two last cases, many of the observed features might result either from the monosomy 21 or from the associated aneusomy (de Grouchy and Turleau 1984; Buyse 1990; Courtens et al. 1994). These three observations show no discrepancy with our phenotypic mapping data and can be used to define more precisely the minimal

regions for two features: intrauterine growth retardation (between D21S11 and SOD1) and highly arched palate (between D21S54 and D21S213, a probe located between D21S54 and SOD1) (Chumakov et al. 1992; Delabar et al. 1993*a*).

Subject GMU, who was karyotypically analyzed not because she was dysmorphic but because she gave birth to a daughter with Down syndrome, had an almost normal phenotype with no mental retardation and some features that might result from the associated loss of terminal 9p. Therefore, the deletion of the proximal part of chromosome 21, including band 21q11 and part of band 21q21 down to probe D21S11, seems not to have a major effect on the phenotype. A similar conclusion was reached by Korenberg et al. (1991*a*, 1991*b*) in their analysis of a case of monosomy from D21S16 to D21S54. This suggests that it is the deletion of genes distal to D21S54 that is deleterious for mental development. It is therefore likely that the mental retardation in patient KB results from the deletion of the region flanked by probes D21S54 and SOD1. So far, only one gene has been identified in this region, the glutamate receptor subunit GluR5 gene (glutamate receptor ionotropic kainate 1 [GRIK1]) (Bettler et al. 1990), which maps genetically between APP and SOD1 (Gregor et al. 1993) and is located distal to D21S213 on a YAC contig (Delabar et al. 1993*a*; Orti et al. 1994). GluR5 subunit is one of the constituents of the high-affinity kainate-receptor channels, of which the function in the nervous system is not yet understood (Seeburg 1993). In rodents, GRIK1 is expressed in subsets of neurons throughout the developing and adult central and peripheral nervous system, and during embryogenesis this expression is detected in areas of neuronal differentiation and synapse formation (Bettler et al. 1990). This strongly suggests that GRIK1 is involved in the formation and functioning of a large number of neuronal circuits. Therefore, this gene may be considered as a candidate gene for contributing, when deleted, to the pathogenesis of mental retardation and possibly hypertonia.

Variation in phenotypic expression is a constant characteristic of any human aneuploidy. Thus, the very profound mental retardation observed in patient LAE as compared with patient KB might be ascribed to variation in the phenotypic expression of the deletion of the APP-SOD1 region. Alternatively, it may suggest that the deletion of genes distal to SOD1 also contributes to impair mental development, as suggested by Korenberg et al. (1991*a*). The study of other patients with monosomy for the distal part of chromosome 21 should allow the definition of other regions of chromosome 21, in addition to the APP-SOD1 region, that contribute to the pathogenesis of mental retardation and other features. The juxtatelomeric part (~1 Mb) can be excluded from significant involvement because the phenotypic and molecular analysis of subjects with ring 21 indicates that monosomy of the region distal to D21S44 (Korenberg et al. 1990*a*) and D21S112 (McGinniss et al. 1992), both probes located distal to CD18, has very little or no consequence for phenotype or mental development.

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