enzymes in the proband were significantly reduced. We concluded that the proband was a heterozygote for both IDH_1 and RPE.

Discussion

Biochemical studies showed that the proband had half normal activities of IDH_1 and RPE, suggesting that she was a heterozygote for both enzymes. The gene for IDH_1 has been assigned to sub-band 2q33.3 by Narahara *et al*.[4] High resolution GTG and RBA banding analysis showed that the segment 2q32.1→q34 was deleted in the proband in agreement with their observations. On the other hand, the gene for RPE has been assigned to the segment 2q32→qter by Gross *et al*,[5] using interspecific hybridisation. From the gene dosage effect, our observations suggest that the gene for RPE is located on the more proximal portion of this segment, 2q32.1→q34. Further studies of patients with similar deletions of the long arm of chromosome 2 are required to elucidate the critical band for the expression of RPE.

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Apparent monosomy 21 owing to a ring 21 chromosome: parental origin revealed by DNA analysis

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SUMMARY   A three and a half year old mildly retarded boy is presented. Karyotyping showed monosomy 21 (45,XY,−21) in all 50 metaphase spreads examined from two lymphocyte cultures, and in 20% of cells examined from cultured fibroblasts; the remaining 80% of cells showed a ring 21 chromosome (46,XY,r(21)(p1q22)). Molecular studies using chromosome 21 specific DNA probes confirmed the monosomy in blood and showed that the ring 21 chromosome was paternal in origin. Parental karyotypes were normal.

In a recent review it was concluded that karyotypes with a ring 21 chromosome (46,r(21)) can be associated with three distinct phenotypes.[1] In the classic form there is severe retardation with marked dysmorphism and a poor prognosis for long term survival. At the other end of the spectrum, some subjects with this karyotype are entirely normal, being ascertained either by chance or, in the case of males, through investigation of azoospermia. The third phenotype, documented in a total of four patients, is characterised by mild mental retardation and minor facial dysmorphism.[1-4] We now present the clinical, cytogenetic, and molecular findings in a further patient with this 'mild' ring 21 chromosome syndrome, who was particularly unusual in that all metaphase spreads examined from lymphocyte culture showed monosomy 21 (45,XY,−21), thus providing a unique opportunity to determine parental origin using chromosome 21 specific DNA probes.

Case report

The three and a half year old male patient was the

second child of a healthy and unrelated 31 year old father and 32 year old mother, who already had a healthy son. Pregnancy was uneventful and drug free. Delivery occurred at 37 weeks after spontaneous onset of labour; birth weight was 2800 g (25th centile). Apart from mild jaundice which was treated with phototherapy, there were no problems in the neonatal period.

During infancy he had frequent upper respiratory tract infections and was investigated at the age of one year when he presented with pyrexia and purpura. A blood film showed thrombocytopenia (platelets=19×10^9/l, normal range=150 to 400 $\times$ 10^9/l), with reduced megakaryocytes in bone marrow. The thrombocytopenia resolved spontaneously but recurred during infection. Hypogammaglobulinaemia was also noted with very low IgA (5 mg/dl, NR=25 to 75 mg/dl) and IgG (75 mg/dl, NR=500 to 1000 mg/dl) but normal IgM (70 mg/dl, NR=30 to 150 mg/dl). This persisted until treatment with human gammaglobulin was started at the age of 18 months, after which the incidence of infection dropped dramatically.

Developmentally he began walking at 15 months and was able to use five or six words with meaning at two years. Formal assessment at three and a half years indicated that global development was within the normal range with the exception of marked delay in verbal skills attributable to severe speech dyspraxia.

On examination at three years, height and head circumference were on the 50th centile and weight on the 10th centile. Facial examination showed dolichocephaly with a prominent forehead, high anterior hairline, curly hair, notched central upper incisors, and epiblepharon (fig 1). A fluctuant left hydrocele was also noted. No other dysmorphic features were apparent. Neurological examination was normal.

Cytogenetics

Karyotyping was performed on unbanded and GTG banded preparations after standard culture techniques. The patient showed monosomy 21 (45,XY,−21) in all 30 and 20 metaphase spreads respectively examined from two lymphocyte cultures initiated from separate blood samples, and in two (20%) of 10 cells observed from cultured fibroblasts. The remaining 80% of fibroblast cells had a ring chromosome with a diameter approximately two-thirds the size of the long arm of a chromosome 21. The karyotype of this latter cell line was interpreted as 46,XY,r(21)(p1q22), a more precise cytogenetic assignment of the long arm breakpoint of the ring chromosome not being
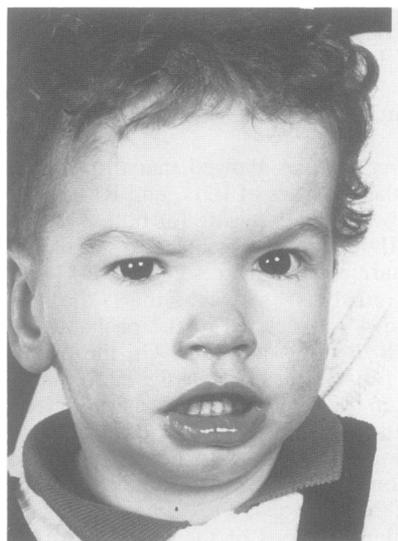

FIG 1 *The patient aged two years.*

possible. Lymphocyte cultures of the parents showed normal karyotypes.

Molecular genetics

MATERIALS AND METHODS
DNA was prepared from peripheral blood leucocytes and samples of 4 µg were digested with *Hinf*I for 'fingerprint' analysis or with *Hind*III for analysis with the chromosome 21 specific probe. Electrophoresis in 0·8% agarose, probe preparation, and hybridisation were as previously described.[5] The probes used were 6·3 and 15·1·11·4[6] for the 'fingerprint' analyses and the chromosome 21 specific probe was pPW245D.[7]

RESULTS
Since lymphocyte karyotyping had indicated that the patient was monosomic for chromosome 21, the opportunity arose to determine the origin of the retained chromosome 21. Identical amounts of DNA (4 µg) prepared from peripheral blood from the mother, father, and child were digested with *Hind*III, fractionated by agarose gel electrophoresis, and then Southern blotted. Hybridisation of the blot with probe pPW245D, which detects the anonymous chromosome 21 locus *D21S8*, showed the pattern seen in fig 2. Each subject carried a constant band at 4·5 kb and it can be seen that the intensity of this band was reduced in the patient (lane C) consistent with the monosomy. The mother
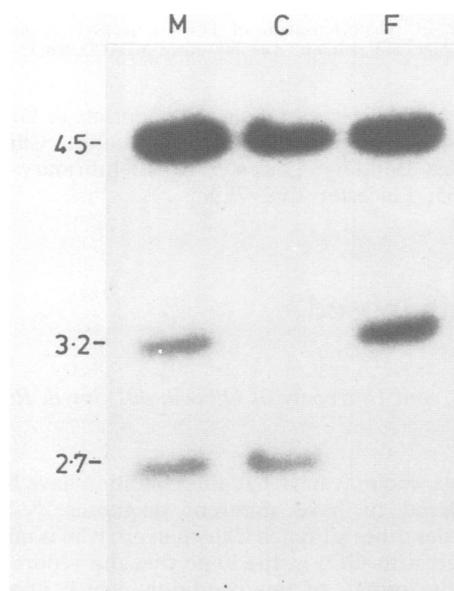
FIG 2 *Demonstration of parental origin of the ring 21 chromosome. Equal amounts of DNA (4 µg) from the mother (M), child (C), and father (F) were analysed by Southern blotting with probe pPW245D. The mother is heterozygous for alleles of 2·7 kb and 3·2 kb, the father is homozygous for the 3·2 kb allele, and the child is hemizygous and carries the 2·7 kb allele from his mother.*

(lane M) was heterozygous for the two alleles of an RFLP system shown by the probe with bands at 3·2 kb and 2·7 kb. The father (lane F) was homozygous for the 3·2 allele. The patient had a band at 2·7 kb but had not inherited a band at 3·2 kb from his father, which indicates that the single chromosome 21 retained in the patient was maternal in origin. This thus implies that the ring chromosome in fibroblasts was paternally derived.

Correct family relationships were confirmed by DNA minisatellite 'fingerprint' analysis.[6]

Discussion

The clinical features in this child are similar to those observed in several other published cases of ring 21 chromosome. In particular, his facial appearance bears a strong resemblance to that of the cases reported by Gardner *et al*[1] and Crandall *et al*,[8] both of whom had a high prominent forehead with a high anterior hairline and curly hair. Thus, patients with both the mild and severe ring 21 chromosome phenotypes may have a similar facial appearance,

although microcephaly will serve as a characteristic distinguishing feature of the severe form. Thrombocytopenia and hypogammaglobulinaemia have also been noted in other cases of ring 21 chromosome.[9]

It is probable that the different phenotypes in cases of ring 21 chromosome reflect varying long arm breakpoints, mosaicisms because of somatic instability of the ring resulting in its loss, or double or unequal sized rings with differing duplications and deletions, or possibly even the presence of an undetected normal cell line. The size of the ring 21 chromosome and the relatively mild phenotypic features in the present case suggest that only the very distal segment of the long arm band 22 was deleted. This patient, however, is particularly unusual in that karyotyping from cultured lymphocytes showed only pure monosomy 21, a finding confirmed using several chromosome 21 specific probes. This unusual situation afforded a ready opportunity for identifying the parental origin of the de novo ring 21 chromosome, which in this patient was paternally derived.

To our knowledge, the parental origin of a de novo ring 21 chromosome has been identified using molecular techniques in only one other patient.[10] In that child, a boy with a large percentage of cells showing a secondary double ring 21 chromosome, the ring was identified as having originated from the boy's mother on the basis of increased intensity of a maternally derived RFLP.

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Is geroderma osteodysplastica underdiagnosed?

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SUMMARY A girl with mild geroderma osteodysplastica is reported in order to raise the profile of this autosomal recessive condition which may be underdiagnosed. The important signs of this syndrome include a droopy, jowly face with a degree of malar hypoplasia and mandibular prognathism, lax, but non-hyperelastic skin, most marked over the extremities, and osteoporosis which may be associated with fractures and vertebral collapse.

Patients with geroderma osteodysplastica (GO) look older than their chronological age because of congenital lax skin with decreased elastic recoil, which gives them a droopy, jowly appearance. Joint hyperextensibility, most marked in the metacarpophalangeal joints, and a generalised osteoporosis are important associated findings. The latter is often accompanied by susceptibility to bone fractures, including vertebral compression, with a decreased upper/lower body segment ratio. The term GO was first used to describe an extended Swiss family that was the subject of a number of reports.[1] [2] The inheritance was originally reported as X linked recessive because three affected branches of the family were connected through unaffected women. However, autosomal recessive inheritance is now accepted because males and females in the original family were involved with equal severity, and there was a high level of consanguinity in the region.[3] Furthermore, the two families reported by Hunter *et al*[3] are best explained on that basis. Only one additional family has been reported,[4] but other

patients who may have had this condition have been considered to have different diagnoses.[5] [6] This paper describes a French Canadian girl who is mildly affected with GO, in the hope that the report will raise the profile of this condition, which may be under-recognised.

Case report

The proband was the only child of a healthy, unrelated French Canadian couple. Her maternal half-sib required surgery for congenital heart disease but was otherwise well, and three maternal first cousins once removed had died of a mucopolysaccharidosis. The pregnancy had been complicated by threatened labour at 32 weeks, which led to bed rest until delivery at 38 weeks. At birth she weighed 1760 g and was noted to have lax skin with the veins showing through. Her early childhood was uncomplicated, although she bruised easily and had delayed motor milestones. She was having difficulty in grade one and suffering headaches and abdominal pain on school days. During investigation of her school problems a diagnosis of Ehlers-Danlos syndrome had been made, and she was referred to the genetics clinic by her private physician.

On examination at the age of six years six months, she was a shy, cooperative child who was 116 cm tall (50th centile), weighed 21 kg (50 centile), and had an OFC of 49·1 cm (25th centile). Her upper:lower segment ratio was 0·81 (checked on separate days), suggesting a short trunk (fig 1). Her hair pattern, distribution, and structure was normal. Her ears were in the normal position, had a normal shape, and were not hyperelastic. She had a long, square face with significant malar hypoplasia and mandibular prognathism (fig 2). The eyes were grey-blue with occasional Brushfield spots; the inner canthal