potential autism susceptibility loci on chromosome 16p,[12 13] the location of *TSC2*.

In summary, we have identified a novel missense change at a highly conserved residue within the region of GTPase activating domain homology of the *TSC2* gene in two four generation TSC pedigrees with a total of more than 40 affected members. This is, to our knowledge, by far the largest known group of TSC patients carrying the same mutation. Therefore, we anticipate that these families will be important in the future identification of modifier gene effects in TSC. In one family, an association of TSC with significant neuropsychiatric disease has already been documented. Further studies will be required to understand biochemically the functional consequences of this exon 34 missense mutation and to characterise more completely the clinical and neuropsychiatric manifestations of TSC in these families. Understanding the relationship between naturally occurring germline *TSC2* mutations and neuropsychiatric disease could elucidate the underlying biology of TSC and potentially facilitate studies aimed at prevention and/or early diagnosis.

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Interstitial deletion of 3p22.2-p24.2: the first reported case

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H X Liu, P T S P Oei, E A Mitchell, J M McGaughran

Department of Cytogenetics, Starship Children's Hospital, Auckland, New Zealand
H X Liu
P T S P Oei

Department of Paediatrics, University of Auckland, Auckland, New Zealand
E A Mitchell

Northern Regional Genetic Service, Building 18, Auckland Hospital, Grafton, Auckland, New Zealand
J M McGaughran

Correspondence to: Dr McGaughran, juliemc@ahsl.co.nz

Autosomal deletions or chromosomal haploinsufficiency syndromes are observed in 1 in 7000 live born infants[1] and may cause multiple malformations, growth failure, and mental retardation. Deletions on the short arm of chromosome 3 have been reported in 35 cases and have been divided into two groups: deletion 3p syndrome[2] with breakpoints between 3p24 and 3p25 and proximal deletion 3p syndrome[3] with different breakpoints between 3p11 and 3p21.2. The first reported case of an interstitial deletion of chromosome 3p22.2-p24.2 in a 6 year old male with developmental delay is presented here.

Case report

The proband was the fourth child born, in England, to healthy, unrelated, white parents. There was no family history of note. He was born vaginally following spontaneous onset of labour at 41 weeks of gestation after an uneventful pregnancy and weighed 3140 g (10th centile). A murmur was noted shortly after delivery and echocardiography confirmed the presence of a small, perimembranous ventricular septal defect. His early milestones were reported as normal, but he was referred for assessment of developmental delay when aged 16 months. He made good progress following input from a child development unit. He walked at 23 months and had speech delay. He was reassessed three months after arrival in New Zealand at the age of 3.5 years. He had global developmental delay and it was felt he had some hearing impairment. His language skills were poor, only speaking occasional two to three word sentences by the age of 4 years, although his comprehension was felt to be good. He was a sociable child with no behavioural difficulties. He needed nappies at

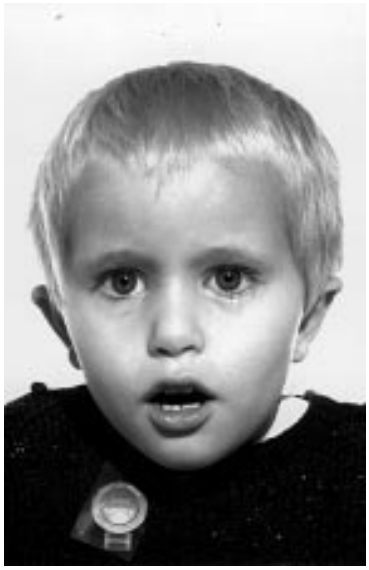

Figure 1 Facial appearance of the patient.

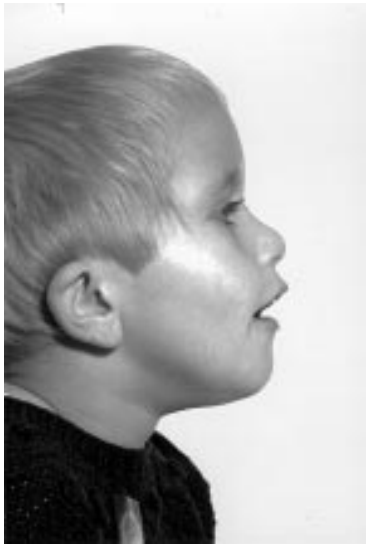

Figure 2 Profile showing midface hypoplasia and posterior angulation of the ear.

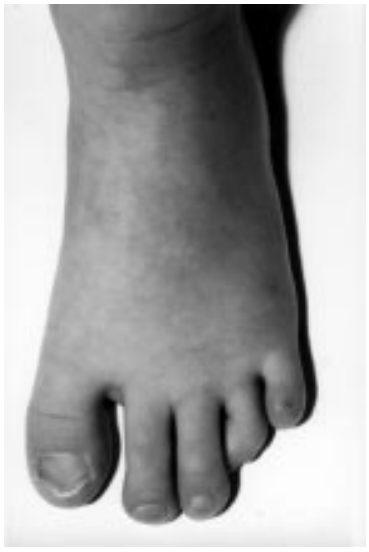

Figure 3 Appearance of the proband's feet with incurving of the fourth toe and wide gap between the first and second toes.

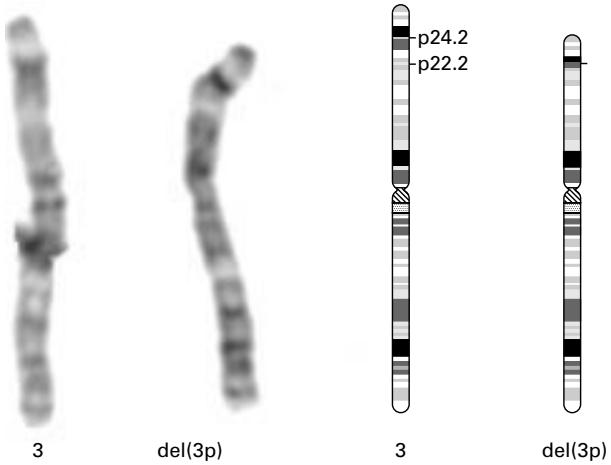

Figure 4 A partial karyotype showing the del(3) (p22.2p24.2) chromosome and ideogram.

night and help with toiletting in the daytime. He had no other health problems.

On examination at the age of 5.5 years, his height was 100.5 cm (4 cm <3rd centile), weight 16.2 kg (3rd-10th centile), and head circumference 52.7 cm (75th centile). He had mild bilateral fifth finger clinodactyly. He had midface hypoplasia and a prominent forehead, shown in figs 1 and 2. He had posterior angulation of his ears and a thin upper lip. His nipples were widely spaced. His big toes were short and relatively broad and his fourth toe curled under the third toe (fig 3). The fifth toenail was hypoplastic and there was a wide gap and deep groove between the first and second toes. There were no other dysmorphic features and the remainder of the examination was unremarkable.

Audiological assessment showed a right unilateral sensorineural hearing loss (40-45 dB loss). *X* ray of his foot was carried out because of the unusual appearance of the toes. No significant bony abnormality was seen.

CYTOGENETIC AND FISH STUDIES

Cytogenetic G banded studies on the peripheral blood lymphocytes showed a de novo interstitial deletion of bands p24.2 to p22.2 in the proximal short arm of chromosome 3 (banding level of 550). The resulting karyotype was a de novo 46,XY,del(3)(p22.2p24.2) (fig 4). This finding was confirmed on examination of 60 cells.

Fluorescence in situ hybridisation (FISH) studies were used to confirm the cytogenetic deletion. A whole chromosome 3 painting probe (Oncor, Inc) showed continuous hybridisation along both the short and long arms of both homologues of chromosome 3. Locus specific YAC clones (966g05 locus D3S3714/D3S3680, 938g11 locus D3S1266, 937h04 locus D3S3564, 792d07 locus D3S3678, 802g01 locus D3S658, Max Planck Institute for Molecular Genetics) overlapping the cytogenetic breakpoints showed loss of signal for the locus D3S1266 and D3S3564. The final karyotype has been interpreted as: de novo 46,XY,del(3)(p2.2p24)[60]. ish(wcp3, D3S3714/D3S3680x2, D3S1266−, D3S3564−, D3S3678x2, D3S658x2).

Discussion

Terminal 3p deletions have been described in 24 cases and interstitial proximal 3p deletions[3 5–14] in 11 cases and are felt to show distinct phenotypes. In the terminal 3p deletion syndrome, the patients have pre- and postnatal growth retardation, mental retardation, and developmental delay. A number of craniofacial anomalies are also described, including flat occiput, triangular face, hypertelorism, epicanthic folds, synophrys, ptosis, broad and flat nose, and downturned corners of the mouth. The patients also have small hands and supernumerary digits. In the proximal 3p deletion syndrome, the patients have a characteristic facial appearance with narrow forehead, epicanthic folds, short palpebral fissures, broad nasal bridge, and low set, poorly formed ears. Developmental delay is also described. Joint abnormalities may be present

including decreased joint mobility, ulnar deviation of the hands, camptodactyly, and calcaneovalgus deformity of the feet.

There have been no deletions published spanning the region 3p22.2-p24.2. In the case reported here, the proband had a number of mild dysmorphic features, global developmental delay, and short stature. These features are frequently described in patients with chromosome deletions and they are likely to be related to the monosomy of the region p22.2-p24.2. This is apparently the first case report with this deletion, which is surprising as, although the features are relatively mild, the combination of growth failure and developmental delay usually leads to a paediatrician checking the karyotype, as these are features associated with chromosomal abnormalities. In this case, it may be that the early response of the patient to effective intervention by the child development team delayed any further testing. The deletion may usually be associated with a milder phenotype and so chromosome analysis is not undertaken. There are other possible explanations for the mild phenotype. A cryptic rearrangement and low level mosaicism were excluded using locus specific probes and an extended examination of 60 metaphases. However, it is not possible to rule out epigenetic modification of the phenotype because of duplication elsewhere in the genome or that the phenotype is mild because the deletion is in a "protected" genomic region.

A meaningful correlation between this deletion and the clinical phenotype is not possible until further cases are described. It may then be possible to contribute further to the knowledge of the morbid anatomy of the human genome.

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