Figure 7 Scanning electron microscope picture of hair from II.1 showing pili torti et canaliculi.

Figure 8 Scanning electron microscope picture of hair from III.6 showing pili torti et canaliculi.

syndrome, ectrodactyly-ectodermal dysplasia with normal lip and palate, uncombable hair-retinal pigmentary dystrophy-juvenile cataract-brachymetacarpia, and familial clefting syndrome with ectropion and dental anomaly. The dental abnormalities in (2) consist of persistence of deciduous teeth, delayed eruption, and the hypertrichosis is localised or generalised. In (4) trichodental dysplasia, missing teeth, peg shaped incisors, and shell teeth are the most common dental abnormalities.[4–6] The hair is fine, sparse, dull, and slow growing.

Congenital absence of teeth is most probably autosomal dominantly inherited.[7] It has been speculated that a common genetic defect may give rise to different phenotypic manifestations, including missing, malformed, and even ectopic and malpositioned teeth. The maxillary teeth that develop in the critical marginal areas of the dental lamina, namely the lateral incisors, canines, and second premolars, seem most susceptible.[8]

The findings in our patients, with different phenotypic manifestations of agenesis of the premolars or lateral incisors, point towards an autosomal dominant mode of inheritance. The sister IV.4 of patient IV.3 only showed agenesis of certain teeth and no pili torti et canaliculi on scanning electron microscopy. This is probably the result of variable expression of the ectodermal dysplasia.

Congenital pili torti et canaliculi is a hair shaft abnormality that has previously been described in Marie Unna hypotrichosis, and together with cleft lip/palate in the EEC-syndrome. The alopecia in Marie Unna hypotrichosis resembles androgenetic alopecia, but, in addition, hair loss occurs at the perimeter of the scalp as well, giving the patients monk-like features.[9] In the EEC syndrome, several other pathological findings are present,[10] not seen in any of our patients.

In conclusion, the combination of pili torti et canaliculi and dental abnormalities has not been described before and could represent a new pure hair-tooth ectodermal dysplasia.

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Skin pigmentary anomalies in a mosaic form of partial tetrasomy 3q

EDITOR—In the March 1999 issue of the journal, Portnoi *et al*[1] reported a patient with hyperpigmentation distributed along the lines of Blaschko[2 3] with mosaicism for partial tetrasomy for the chromosomal region 3q27-q29. Here we describe a patient who displays a very similar pattern of skin hyperpigmentation (fig 1A, B) associated with mosaicism for a small partial terminal triplication of 3q (fig 2) leading to functional tetrasomy with the following karyotype obtained from lymphocytes: mos 46,XY, trp(3)(q27.1-qter)[47]/46,XY[4]. Both parents were found to have a normal karyotype. The proband is a 5 year old boy, the first child of healthy, unrelated parents. During early pregnancy intrauterine growth retardation was suspected, but no anomalies were recorded during the following months except reduced fetal movements. He was born by caesarean section 3 weeks before the calculated date of birth because of HELLP syndrome. His birth weight and length were 2810 g and 49 cm, respectively. Owing to his pigmentary skin anomalies, soon after birth the diagnosis of a hypomelanosis of Ito was made. He was retarded in all developmental milestones, as he was not able to sit before the age of 8 months or walk before 21 months and started to speak at about 2 years. Coarse facial features (fig 1A) with pronounced supraorbital ridges, broad nasal bridge, long philtrum, large prominent ears, and hypoplastic enamel structures were noted. He has a

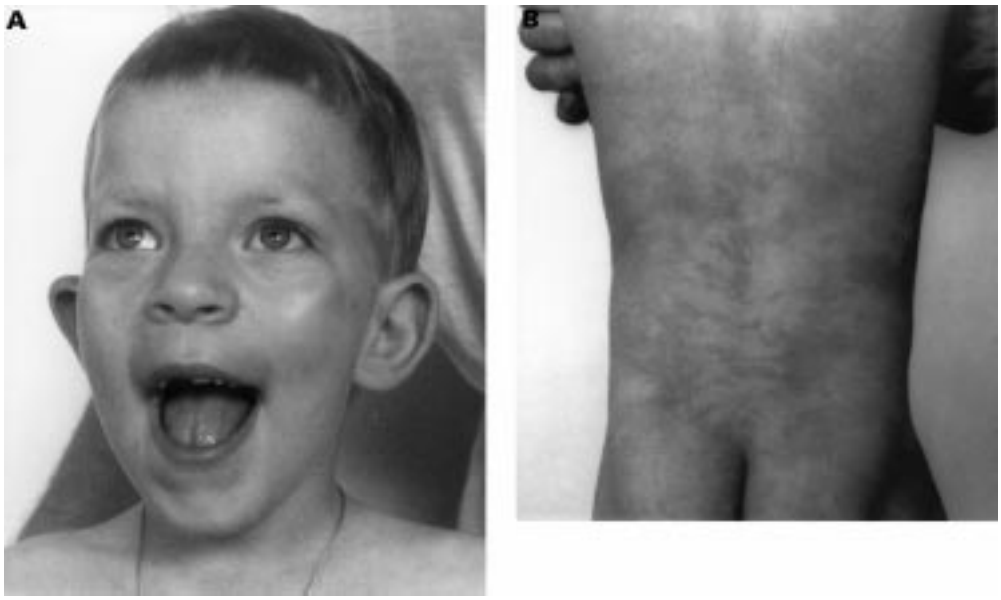

Figure 1 Clinical features of the patient aged 5 years. (A) Front view. Note hypertelorism and prominent ears. (B) Hyperpigmentation following the lines of Blaschko.

bilateral single palmar crease, but his father shows this feature on his right hand as well. At the age of 2 years his weight of 12 kg (25th centile), length of 84 cm (10th-25th centile), and head circumference of 50.5 cm (75th centile) indicated disproportionate growth curves. Psychomotor examination showed a general retardation of about 6-8 months. Magnetic nuclear resonance imaging of the brain showed periventricular lesions of the white matter with no further anomalies. Despite our request to perform a skin biopsy from the light and dark pigmented areas of his skin to allow cytogenetic analysis of these tissue samples as well, his parents have so far refused this. Since, currently, there is no medical necessity to perform this type of analysis, we had to respect their wishes.

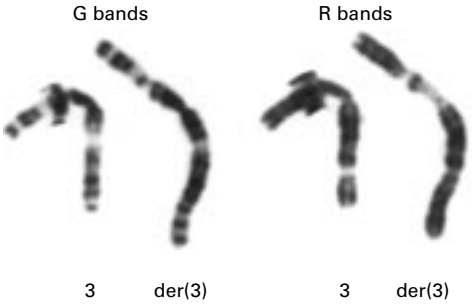

Figure 2 Partial GTG and RTG karyotype of the normal and the derivative chromosomes 3.

At the age of 5 years the proband was investigated again. He is currently 113 cm (50th-75th centile) tall, weighs 19.5 kg (50th-75th centile), and his head circumference is 53.5 cm (90th centile). He is cooperative and understands questions and commands quite well but his articulation is still rather poor despite regular speech therapy. Motor development in particular with regard to fine movements is about two to three years behind normal. At the cytogenetic level, the size of the partially tetrasomic segment seems to be identical to the previously reported case.[1] We performed FISH analysis using the same YAC clones (806_d_8, 760_f_3, 781_f_8, 883_d_12) as described to determine

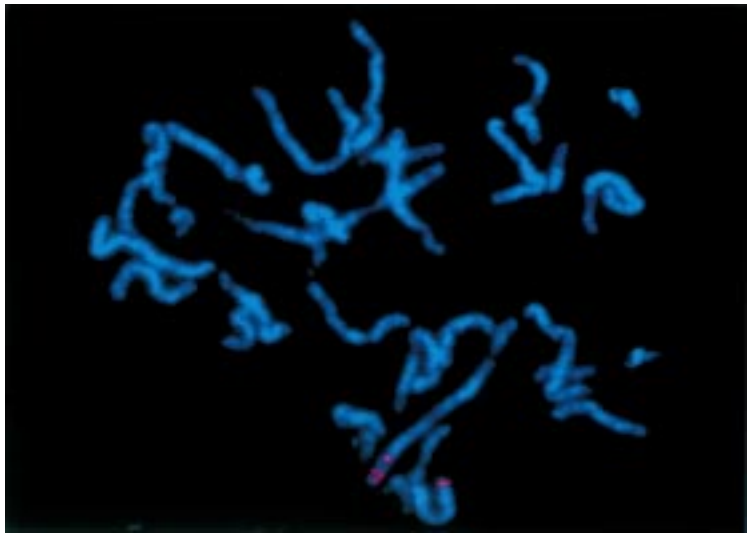

Figure 3 Partial metaphase cell showing the localisation of the YAC clone 883_d_12 on the normal and the derivative chromosome 3. Note that the inverted orientation of the inserted fragment was confirmed by the relative position of the hybridisation signals.

how similar at the molecular level the chromosomal breakpoints are. A triplication was confirmed for two YACs (781_f_8 and 883_d_12) whereas the more proximal YAC, 806_d_8, showed only one signal on the rearranged chromosome. Furthermore, the YAC 760_f_3, which is just a few megabases proximal to 781_f_8, does not map to the triplicated region. This indicates that the breakpoint in 3q27.1 is not identical at the molecular level in both patients, but is more distal in our proband. From the hybridisation pattern of the triplicated YAC clones it can be concluded that the terminal triplication on the derivative chromosome 3 occurred because of an insertional inverted duplication (fig 3). FISH analysis using a probe specific for the subtelomeric region of the long arm of chromosome 3 (Vysis) showed additional interstitial signals on the derivative chromosome 3 (results not shown).

The patient described by Portnoi *et al*[1] was claimed to be the first with a pure partial tetrasomy of 3q but he is of normal intelligence and does not show dysmorphic features. As can be judged from the distribution of normal versus abnormal cells in lymphocytes and skin fibroblasts, in particular from the dark pigmented areas, the percentage of partially tetrasomic cells in their patient is much lower than in our case. This could be the explanation why the proband described here exhibits psychomotor retardation and dysmorphic features. However, the observation of Portnoi *et al*[1] that in the partial tetrasomic cells for 3q27.1-qter a more intensive skin pigmentation is obvious can clearly be confirmed in the unique karyotype-phenotype constellation present here. It was proposed that because of a gene dosage effect caused by the partial tetrasomy, one or more genes involved in skin pigmentation are responsible for the hyperpigmented brown streaks following the lines of Blaschko (fig 1B). No obvious candidate gene responsible for this effect has been mapped so far to this chromosomal segment; however, the melanoma associated antigen *p97* gene[4] might be involved. Although the partial tetrasomy 3q27.1-qter in both patients is caused by different chromosomal rearrangements, a break in band 3q27.1 must have occurred in both of them during the first postzygotic cell divisions. Molecular studies with mapping of chromosomal breakpoints allowed us to exclude the involvement of a single gene in both affected subjects. In conclusion, partial tetrasomies for an autosomal segment are rare and deserve more attention when they are associated with an unusual phenotype.

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Reduction of the genetic interval for lymphoedema-distichiasis to below 2 Mb

EDITOR—Primary lymphoedema (MIM 153200) is a chronic tissue swelling, most frequently of the lower limbs, which occurs as a consequence of a failure of lymph drainage.[1] It arises from an intrinsic abnormality of the lymphatic system and generally shows an autosomal dominant pattern of inheritance with reduced penetrance, variable expression, and variable age of onset.[2] There is a strong genetic input into primary lymphoedema, with 35% of all patients showing a positive family history.[3 4] The swelling can be present at birth, as in Milroy disease, but more commonly it becomes clinically apparent during puberty, which is known as Meige disease.[5–7]

A variant of pubertal onset lymphoedema is lymphoedema-distichiasis (LD) (MIM 153400). This syndrome is a rare form of primary lymphoedema which is associated with distichiasis, a congenital anomaly in which aberrant eyelashes arise inappropriately from the site of the meibomian gland openings.[4 8] The disease shows an autosomal dominant pattern of inheritance with incomplete penetrance.[9] A recent study of three families by our group reported linkage of LD to chromosome 16q24.3.[10] The locus was placed between the markers D16S422 and D16S3074, a distance of ~16 cM according to the Généthon sex averaged map.

Subsequently, more members of family 3 have been ascertained (fig 1) along with an additional family with an affected father and three affected children (not shown). All subjects were carefully phenotyped based on the presence of distichiasis, which provides a clear criterion with which to define affected status. This was established following slit lamp examination by an ophthalmologist unaware of any other clinical signs. DNA of the newly ascertained subjects was extracted from peripheral venous blood by a standard procedure using a Nucleon genomic DNA extraction kit (Nucleon Biosciences, Strathclyde, UK). Polymorphic microsatellite markers were PCR amplified and electrophoresed through an 8% denaturing polyacrylamide gel on a conventional gel rig. Gels were run at a constant 50 mA and the DNA bands were visualised with silver staining.[11]

The microsatellite markers D16S511, D16S422, D16S402, D16S3037, D16S520, and D16S3074 were PCR amplified in the newly ascertained subjects from family 3 and for the new family. The latter was consistent with linkage to the LD locus. All newly ascertained subjects from family 3 were consistent with linkage, using distichiasis as the sign of affected status. Fig 1 shows the expanded pedigree, with the same numbering for the previously typed subjects as in our original publication.[10] It is of interest that IV.5 (fig 1), who was assumed to be unaffected and non-penetrant in the previous study, was found by slit lamp examination to have limited distichiasis. There are therefore no members of any of the four families we have studied who carry the "affected" haplotype but have no signs.

Analysis of an additional six markers within the LD locus, D16S486, D16S498, D16S543, D16S2625, D16S539, and D16S3061, produced a reduction in the distal interval by ~2 cM as a result of a recombination event in an affected family member (fig 1, IV.4). Another subject (III.5) was included as of unknown status in the initial report. He had a slightly abnormal lymphoscintigraphy result at 30 minutes, which was well within normal limits at 60 minutes, but no lymphoedema. Recent examination has