FIG 1 (b) Full frontal view of index case.

slight dysmorphism, and variable mental retardation.

Our patient differs from those already reported in that she is less severely affected. This is possibly because the deleted segment of 12p is smaller (fig 2). Of the reported cases, there is most similarity between our own and that of Magenis *et al.*³ There is less similarity with the patient of Tenconi *et al.*⁴ who, like our infant, showed prominent mottling of the skin, a broad nose, and only slight micrognathia.

De novo 2q+ masquerading as Smith-Lemli-Opitz syndrome

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SUMMARY We report a female infant diagnosed shortly after birth as having Smith-Lemli-Opitz syndrome. Despite previously re-

FIG 1 (c) Oral view of index case.

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ported normal G banded karyotypes, a high resolution banded chromosome analysis identified 46,XX,2q+. The importance of attention to established features of clinical syndromes, as well as persistence in investigation when diagnostic uncertainties exist, are discussed.

Identification of cytogenetic abnormalities by high resolution banding techniques has provided valuable diagnostic information in evaluating dysmorphic subjects, but subtle deletions, duplications, and inversions may be extremely difficult or impossible to identify. A newborn infant, clinically diagnosed as having Smith-Lemli-Opitz (SLO) syndrome with normal chromosomes, was later discovered to have a *de novo* partial chromosome duplication. Identification of a chromosomal cause, as opposed to an autosomal recessive aetiology, for the patient's clinical findings significantly affected genetic counselling for the parents. Attention to established criteria for diagnosis of SLO syndrome as well as thorough cytogenetic scrutiny in karyotypic evaluations is emphasised.

Case report

The proband was referred for re-evaluation of her diagnosis of SLO syndrome at three years of age because she exhibited more advanced development than expected. She was a 1660 g female delivered by caesarean section for fetal distress at 35 weeks' gestation. Pregnancy was complicated by premature rupture of the membranes at 34 weeks, requiring antepartum admission to hospital. Apgar scores were 4 and 8 at one and five minutes, respectively. The infant was depressed, hypotonic, and small for gestational age. A single umbilical artery was noted. Her immediate postnatal course was complicated by respiratory distress syndrome, hyperbilirubinaemia requiring phototherapy, poor feeding ability treated by oral-gastric gavage, and chlamydia conjunctivitis. There was no evidence of neonatal sepsis. The

TABLE Features of present patient compared to those found in Smith-Lemli-Opitz syndrome.

Features present	Features absent
Low birth weight	Microcephaly
Failure to thrive	Ear malformations
Feeding difficulties in infancy	Syndactyly of toes 2 and 3
Mental deficiency	Inner epicanthic folds
Anteverted nostrils	Strabismus
Ptosis	Broad maxillary alveolar ridges
Simian crease	Micrognathia
Dilated cerebral ventricles	Digital whorl predominance
Seizures	
Unusually blonde hair	

patient's evaluation consisted of negative amino acid screen, metabolic screen, and TORCH titres, normal thyroid function, and a 46,XX G banded karyotype. Initial genetic evaluation concluded that this infant's clinical history and physical examination were consistent with SLO syndrome (table). The infant was discharged at four weeks of age. Due to lethargy, poor feeding, and seizure activity she was readmitted one week later at which time *E coli* meningitis was diagnosed. Following antibiotic treatment, the infant recovered fully. The patient had significant developmental delay, first walking at 22 months and talking at 24 months. At three years intellectual testing and language skills were compatible with that of a 14 month old. Ophthalmological and audiometric evaluations were normal. Evaluation of this child included a CT scan of the brain which demonstrated moderate ventriculomegaly, a normal EEG, a normal EKG, and a normal echocardiogram. A repeat G banded chromosome analysis was performed by a second cytogenetics laboratory. Results were again

FIG 1 The proband at three years of age. Note broad nasal bridge, long philtrum, anteverted nostrils, open, bow shaped mouth, and ptosis.

reported as normal, 46,XX. Physical and speech therapy were begun at two and a half years of age. The speech therapist, surprised by the patient's progress, questioned the diagnosis of SLO syndrome and referred her for re-evaluation. Family history was remarkable for a paternal first cousin who died at birth owing to a hypoplastic left heart. No chromosome studies had been done on this infant. There was no consanguinity in the family and the proband's six year old male sib was normal.

Physical examination revealed an active, alert child. Height was 96 cm (75th centile), weight 13 kg (25th centile), and head circumference was 48 cm (35th centile). Head and facial features included bright blonde hair, wide palpebral fissures, anteverted nostrils, broad nasal bridge, long philtrum, a bow shaped mouth usually kept open, and a high arched palate (fig 1). The ears were normally formed and placed. Other notable physical features included bilateral fifth finger clinodactyly, a right sided simian crease, bilateral second toe clinodactyly, and a sacral dimple. Dermatoglyphics revealed loop patterns on all digits and bilateral proximal triradii.

Despite two previously normal karyotypes, chromosome analysis, using high resolution G banding, was repeated because of the discrepancy between the patient's findings and those seen in SLO syndrome. The results showed evidence of additional genetic material on the distal long arm of chromosome 2 (46,XX,2q+). Parental chromosome analyses were normal without evidence of translocation or duplication.

Discussion

SLO syndrome is an autosomal recessive disorder characterised primarily by growth and mental deficiency, microcephaly, abnormalities of external male genitalia, syndactyly of the second and third toes, digital whorl patterns, and considerable facial dysmorphism.¹ The clinical diagnosis of SLO syndrome in our patient was based on numerous features which she had in common with those of this disorder (table) as well as her initial normal chromosome analysis. The absence of microcephaly, overlapping but not true syndactyly of the second and third toes, digital loop patterns, and relatively mild intellectual and developmental impairment prompted us to question the diagnosis of SLO syndrome in this child and led eventually to our discovery of a chromosomal abnormality.

Remarkable clinical variability in SLO syndrome has been identified.² Borderline normal intelligence has also been reported as being compatible with this diagnosis.³ Additionally, the diagnosis in females is often more difficult because of the absence of

genital abnormalities which are found in males with this syndrome. This undoubtedly accounts for the reported increased male to female ratio.

Many patients with multiple malformations with reportedly normal chromosomes may actually possess cytogenetically undetectable abnormalities. A substantial portion of genetic material would have to be deleted, duplicated, or inverted for cytogenetic identification to be possible. The single extra band discovered on the distal long arm of chromosome 2, which was not noted in the patient on two previous cytogenetic analyses, is readily visible (fig 2). The detection of unbalanced translocations in mentally retarded subjects with previously reported normal karyotypes has been substantially improved by cytogenetic advances.⁴ Due to the small size of the extra chromosome segment, and because both parents' chromosomes were normal, it was not possible to determine the origin of the additional chromosomal material.

Elucidation of an unbalanced chromosome complement in our patient significantly altered genetic counselling information for the family. Instead of the 25% recurrence risk of SLO syndrome as was given previously, the recurrence risk for a subsequent offspring with a de novo chromosomal disorder is vastly reduced to much less than 1%. Additionally, prenatal diagnosis can be offered to determine the chromosomal status of subsequent pregnancies.

Persistence in searching for the aetiology of this child's disorder resulted in a completely different diagnosis from that determined initially. The patient's diagnosis, although atypical of SLO syndrome, would have undoubtedly remained unchanged if not for detailed cytogenetic analysis. Chromosome analysis is appropriate for persons with features

FIG 2 Chromosomes 2 of the proband. Note dark band on the distal long arm of chromosome on the left (2q+).

resembling those of SLO syndrome, especially when atypical clinical or developmental signs are present. Although limitations in our diagnostic abilities exist, when patient's presentations do not conform to established descriptions of clinical syndromes, an exhaustive search for other aetiologies must be made.

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Incontinentia pigmenti in a boy with Klinefelter's syndrome

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SUMMARY A boy with the cutaneous lesions of incontinentia pigmenti is described. Chromosomal analysis revealed the 47,XXY karyotype of Klinefelter's syndrome. Since incontinentia pigmenti trait is usually lethal in males, the possibility of the second X chromosome protecting against fetal death is discussed.

It has been suggested that the pattern of inheritance of incontinentia pigmenti (IP) best fits that of an X linked dominant trait which is lethal in males.^{1 2} Nonetheless, male cases have been recorded and constitute 2 to 3% of all reported cases.^{1 2} All but two of these male cases occurred as sporadic new mutations. We describe a patient with incontinentia pigmenti and Klinefelter's syndrome, a combination which has only been previously reported once.³

Case report

A boy aged one year presented to the Dermatology Clinic with a history of linear, whorled, macular, streaky pigmentation predominantly over the right side of the trunk but also extending on to one leg (figure). This was noticed in the first month of life

but was not present at birth. No preceding inflammatory, vesicular, or warty skin eruption was observed by the parents or any of the baby's medical attendants.

At birth he was light for dates (2050 g at 41 weeks' gestation). Neonatal blood films showed no evidence of eosinophilia. At his 18 month assessment his weight and head circumference were below the 3rd centile. He was noted to have small epicanthic folds, low set ears, elfin facies, and his skull was wider posteriorly than anteriorly, but psychomotor development was normal. As his testes were small and soft, Klinefelter's syndrome was suspected and chromosome analysis revealed a karyotype of 47,XXY. He was assessed again at the age of two when he had developed conical, hypoplastic canine teeth. However, his hair was normal and his eyes were normal apart from a transient strabismus.

His father was aged 29 at the birth of the child and his mother 26. They were both Caucasian and were not related. His mother had had one previous pregnancy which spontaneously aborted after 12 weeks' gestation. Both parents were examined fully and neither had any sign of pigmentary disturbance, its residual changes, or other features of incontinentia pigmenti. The mother's teeth were normal and both parents had normal karyotypes. Xg(a) blood groups were carried out by Dr Tippet on the proband and his parents. All were Xg(a-).

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