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Short clinical report

A case of microdeletion of 19p13 with intellectual disability, hypertrichosis, synophrys, and protruding front teeth

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ABSTRACT

We present a *de novo* 1.4 Mb deletion of chromosome 19p13.11-p13.12 in a 16 year old boy with intellectual disability, autistic features, microcephaly, hearing impairment, hypertrichosis, synophrys, protruding front teeth, and other dysmorphic features. By comparing our patient to reported cases with overlapping deletions, we have refined the minimal critical region of hypertrichosis, synophrys, and protruding front teeth to 305 kb, a region containing seven genes. *CASP14*, which is considered a good candidate gene for hypertrichosis, is not included in this region, questioning the causal relationship.

1. Introduction

Deletions of 19p13.11-p13.12 are rare [1–8]. The reported phenotypes vary according to the size of the deletion, but associated features include mild to moderate intellectual disability, cardiac malformations, brain malformations, sensorineural deafness, ear tags, stenosis of external ear canals, split hand foot malformation, hypertrichosis, and synophrys. For example, mild congenital cardiac malformations and sensorineural and/or conductive hearing loss have been said to be confined to a 359 kb interval at 19p13.12 [1] and *DDX39* (MIM610049) has been suggested as a candidate gene for brain malformations [2]. Features of branchial arch defects are confined to the 0.8 Mb region deleted in the patient reported by Kosaki et al. [3], *EPS15L1* has been suggested as a good candidate gene for split hand foot malformation, SHFM [4,5], while *CASP14* (MIM605848) is considered a candidate gene for hypertrichosis [6]. We present a patient with deletion of 19p13.11-p13.12, and discuss genotype–phenotype correlations and comparisons with other reported cases.

2. Clinical report

2.1. Clinical description

This 16 year old male is the first child of healthy, non-consanguineous, Caucasian parents, and has a healthy younger sibling. The pregnancy was followed closely due to reduced foetal movements, and he was delivered at 41 weeks gestation by an emergency caesarean section due to weak heart sounds. Birth weight was 2450 g (3rd percentile), and birth length 51 cm (25th percentile).

Motor milestones were mildly delayed: he sat at age 7 months, and walked unsupported at age 20 months. Language development was also delayed. Intellectual disability and autistic behaviours were evident from an early age. Skull X-ray at age 16 months showed early closure of the metopic suture and late closure of the anterior fontanelle. He suffered from recurrent middle ear infections and ventilation tubes were placed several times before age 11 years. He had bilateral sensorineural hearing impairment with a mild conductive element, narrow external ear canals, and hypermobile joints with dislocations of both the right (several) and left (single) patellae. He entered puberty at age 10–11 years. He had dark hairs on the legs from age 5–6 years, and needed daily shaving from age 13 years.

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On examination at 2 years and 9 months of age, he had microcephaly (head circumference −3 SD), broad eyebrows, synophrys, hypotelorism, downslanting palpebral fissures, small epicanthal folds, strabismus, hypermetropia, protuberant external ears and mild syndactyly of 2nd and 3rd toes bilaterally. At age 14 years, in addition, the following dysmorphic features were noted: high palate, protruding front teeth, and low set ears. Several teeth had been extracted due to dental crowding. Hypertrichosis was evident on the arms, hands, and thorax. For dysmorphic features, see Fig. 1.

The patient is institutionalised and attends a special school for children with intellectual disability and autistic features. During the last year he has had several moderate infections with fever, thrombocytopaenia with platelet count 80 × 10-9/L (ref 150–400 × 10-9/L), and mild neutropenia. Histological investigation of bone marrow was normal.

Analyses performed to date, with normal results: Urine metabolic screening, chromosome analysis with G-banding, MRI of the central nervous system, chest X-ray, ultrasound of the upper abdomen, and the retroperitoneal space, complete skeletal survey, and echocardiography.

2.2. Methods

Genomic DNA was extracted from peripheral blood using standard methods, genotyped by the commercially available SurePrint G3 Human CGH Microarray Kit, 2 × 400 K and analysed using Agilent

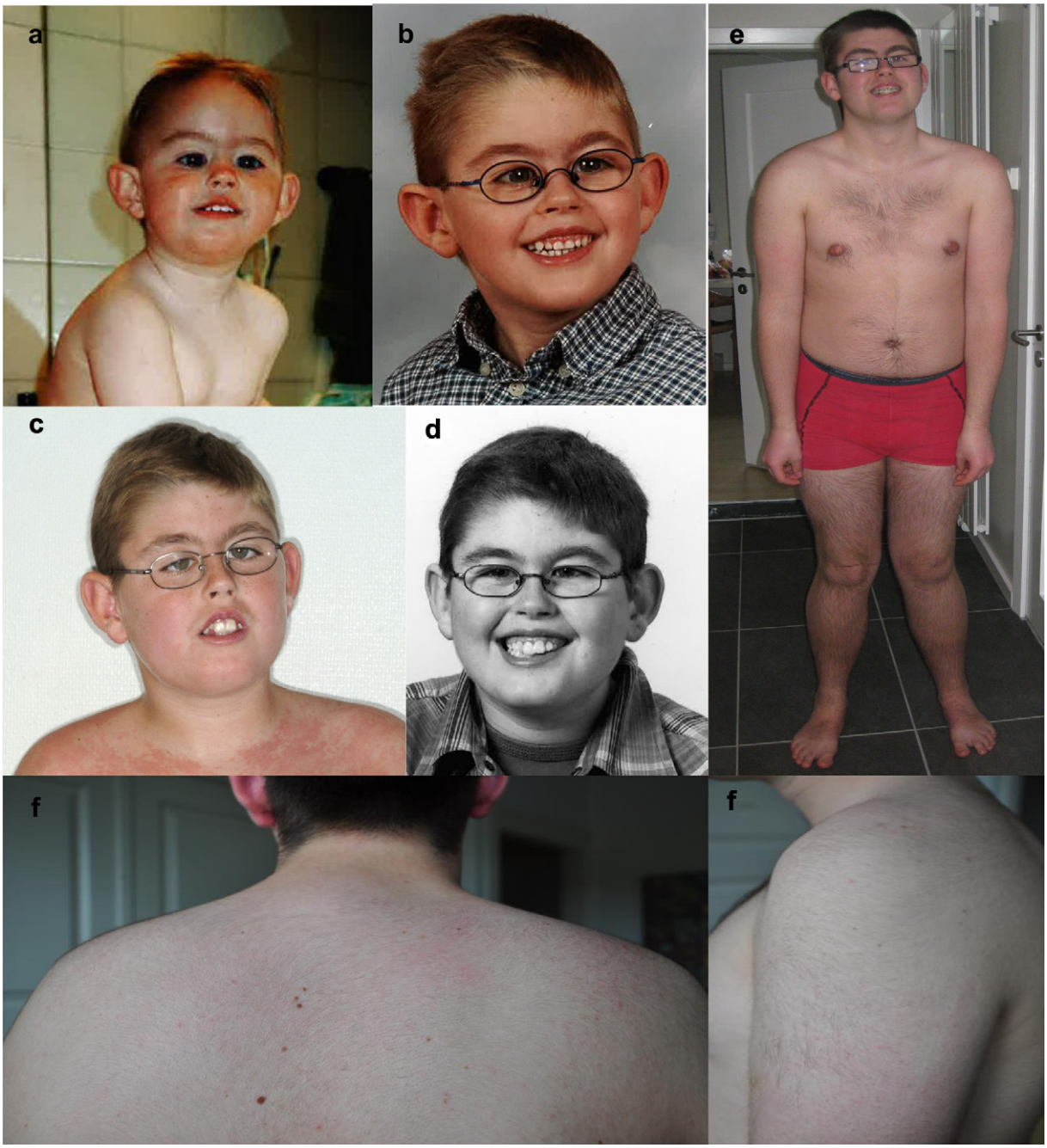

Fig. 1. Photos of the patient at ages: a: 18 months, b: 6 years, c: 9 years, d: 12 years, e: 15 years, f: 16 years. Note low hairline with frontal upsweep, broad eyebrows, synophrys, hypotelorism, protruding front teeth (he is wearing braces in photo e), protuberant ears, and hypertrichosis.