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Array report

Interstitial deletion 1p36.32 in two brothers with a distinct phenotype – Overgrowth, macrocephaly and nearly normal intellectual function

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ABSTRACT

We report on two adult patients, who both presented with overgrowth and one of them additionally with macrocephaly while carrying an 1p36 microdeletion of about 2.1 Mb. They are full brothers born to unaffected parents. Although both brothers attended special schools, they lived independently without a legal guardian and were able to succeed in regular jobs. One of the brothers received a professional education. Genetic analysis of the parents revealed neither the microdeletion nor a cryptical translocation or inversion. We suggest that the recurrent deletion is a result of germline mosaicism, a phenomenon reported only once in the context of the 1p36 microdeletion syndrome.

Our report confirms the recurrence of the apparently *de novo* 1p36 microdeletion due to a likely germline mosaicism of one of the parents. Furthermore, it illustrates the possibility of the distinct phenotype with a nearly normal intellectual outcome of the 1p36 microdeletion syndrome that might be due to the region involved in our patients.

1. Introduction

Microdeletion 1p36 is a well characterized microdeletion syndrome almost uniformly associated with intellectual disability (ID) of variable degree. Since about 90% of the patients were reported to have severe to profound ID, the developmental prognosis is rather unfavorable [Battaglia et al., 1993–2013]. Only 10% of the patients with microdeletion 1p36 had mild to moderate cognitive impairment. The recurrence risk depends on whether one parent is a carrier of the balanced chromosomal rearrangement and is estimated to be equal to the general population risk, if no translocation could be observed [Battaglia et al., 1993–2013].

Here we report on two adult patients carrying a small 1p36 microdeletion with nearly normal developmental outcome allowing for an independent daily living. Moreover, our observation provides a second report of the apparent germline mosaicism of 1p36 microdeletion.

2. Clinical description

Patient 1 and patient 2 are full brothers and the only children of healthy unrelated parents. The family history was unremarkable. Both parents attended mainstream schools and received a professional education. Mid-parental height is 186 cm.

Patient 1 (P1) is a 27-year-old man, who was referred for genetic counseling for the exclusion of Marfan syndrome because of overgrowth and low weight. He was born at the 38th GW with a weight of 2730 g (−1.33 SD) and a length of 53 cm (0.83 SD); occipitofrontal circumference (OFC) was not documented. The reduction deformity of the right arm and leg was noticed at birth and included oligosyndactyly of the right hand with mesomelic shortening of the right arm, length asymmetry of the lower extremities and the hypoplastic right foot with absent fifth metatarsal and fifth toe (Fig. 1A).

Except for the above mentioned malformations the medical history during childhood was unremarkable. Early developmental milestones were normal. Mild learning disability became apparent during medium school. P1 graduated from a special school for students with learning difficulties and worked as a painter. He did not require a legal guardian and lived independently without regular support from his parents.

Progressive maxillary retraction became apparent at the age of 26 years and required a surgical correction.

He was most recently assessed at the age of 27 years. His height was 196.6 cm (2.68 SD), OFC was 57.5 cm (1.1 SD) and weight was 70 kg (BMI 18.11). Minor facial anomalies included high forehead, deep set eyes and prominent ears.

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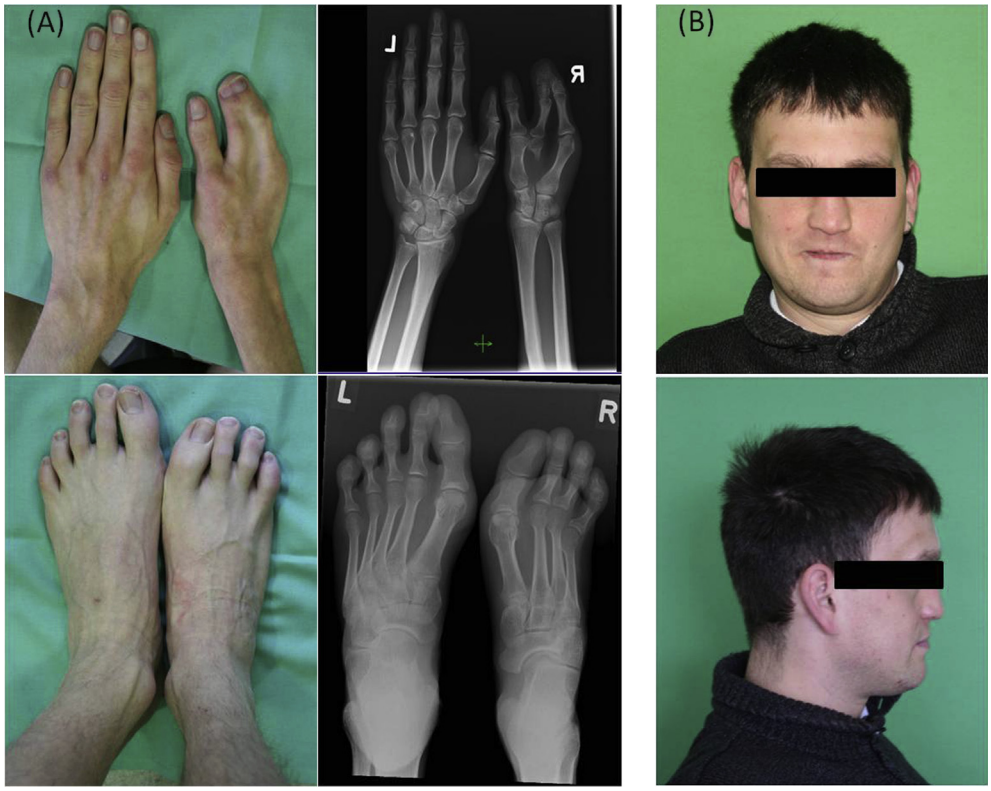

Fig. 1. (A). Hands and feet of the patient 1. Note the oligosyndactyly of the right hand, with the hypoplasia of the distal ulna and radius and absence of the fourth and fifth metacarpals and fingers. The X-ray of the right hand revealed only four carpal bones that are partly fused, short metacarpals 1st, 2nd and 3rd, and bone syndactyly of the terminal phalanges of the 2nd and 3rd finger. The right foot was smaller and revealed the oligodactyly with the absence of the fifth toe and metatarsal bone. (B). Facial pictures of the patient 2. Note the high forehead, horizontal eyebrows, mild midface retrusion and a thin vermilion of the upper lip (upslanted palpebral fissures – covered).

Patient 2 (Fig. 1B) asked for counseling after the pathologic genetic diagnostic results of his brother. He considered himself as healthy person. Medical history is unremarkable.

He was born at 41st GW with a length of 48 cm (−2.2 SD) and a weight of 3270 g (−1.04 SD). OFC was not documented. His motor milestones were normal but speech development was mildly delayed (first words spoken at the age of 18 months). He attended a special school for students with learning difficulties and behavior abnormalities because of marked hyperactivity. He did not require a legal guardian, lived independently and worked as an unskilled construction worker.

He was evaluated at the age of 30 years: height 195.4 cm (2.51 SD), weight 118 kg (BMI 30.9 SD), OFC 60.5 cm (3.1 SD). He showed a flat face with a high forehead, horizontal eyebrows, upslanted palpebral fissures and thin vermilion of the upper lip.

None of the patients has undergone formal developmental and/or behavior evaluation. The conclusion of nearly normal intellectual level has been made approximately, based on the complete independence of both patients in daily life, their professional occupation and absence of necessity of the legal guardian.

3. Methods

Chromosomal analysis of peripheral blood lymphocytes was performed according to routine procedures using GTG-banding at approximately 400–550 band resolution per haploid set.

High resolution oligonucleotide array-CGH using a 244 K array (design 14693) was performed following standard and manufacturer's recommendations (Agilent, Santa Clara, CA, USA) in patient 1. Customized arrays were designed by using Agilent's Earray (https://earray.chem.agilent.com/earray/). An Agilent DNA microarray scanner (G2505C) was used and normalization was carried out with standard settings of the Feature Extraction software vers. 9.5. Data analysis was performed with Agilent's Genomic Workbench 5.0.14 The ADM-2 algorithm was applied to calculate aberrations. A minimum of three consecutive probes had to be affected for a call. The threshold was set to 5.9.

FISH analysis using bacterial artificial chromosome (BAC) clones RP11-70N12 (2,740,703-2,922,551) and RP11-237N15 (4,245,270–4,402,976) (NCBI37/hg19) localized in 1p36.32 were used for confirmation of the array result in patient 1 and for the analysis of patient 2 and their unaffected parents. As controls we used a probe for the subtelomeric region on 1q (TelVysion 1q, Abbott Molecular, Illinois, U.S.A) or BAC clone RP11-428D12 on 1p33 (hg19 49,144,722–49,330,421). To exclude an inversion of the affected region found in array-CGH we analyzed metaphase spreads as well as nuclei of the unaffected parents using BAC clones in the deleted region: RP11-70N12, RP11-168B8 (4,320,609–4,495,967) and one BAC clone proximal to the deleted region: RP11-990M19 (4,498,916–4,647,344).

4. Results

Conventional GTG cytogenetic analyses revealed normal male karyotype in patient 1.

Array CGH discovered a deletion in 1p36.32 of about 2.1 Mb: arr [hg19] (2,371,321x2,2,377,038-4,519,842x1,4,533,688x2) in patient 1 (Fig. 2).

Two adjacent and paternally inherited duplications of 185 kb and 302 kb respectively, were found on chromosome 14 (arr[hg19] 14q24.3(77,311,087x2,77,317,198-77,502,120x3,77,511,464x2), 14q24.3(78,096,225 x2,78,104,825-78,406,658x3,78,428,021x2)).