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A new familial case of microdeletion syndrome 10p15.3

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ABSTRACT

In 2012 a small terminal deletion in the short arm of chromosome 10 in the region 10p15.3 was reported as a novel microdeletion syndrome. By now 21 patients, including a single familial case, have been reported. Characteristic findings comprise variable cognitive impairment or developmental delay, disorder of speech development, as well as various dysmorphic signs. We here report on a new patient, an eight year old girl, with a microdeletion syndrome 10p15.3. She is a foster child showing intellectual deficits, disorder of speech development, behavioral problems, congenital heart defect, and several dysmorphic signs. The same microdeletion was subsequently found in the six year old maternal half-sister, showing very similar developmental and cognitive issues, including major speech impairment. The mother has not obtained a school degree. She was described as being a dissocial person with severe alcohol abuse and showing minor cognitive disability. Thus inheritance of the microdeletion from a probably symptomatic mother can be assumed. The patients presented here add up to the as yet small number of reported cases of microdeletion 10p15.3 and thereby might help to establish a more comprehensive clinical spectrum of this rather newly discovered syndrome.

1. Introduction

Besides monogenic defects and classical chromosomal aberrations submicroscopic chromosomal imbalances comprising microdeletions and microduplications account for a major group of clinically important genetic alterations. A number of previously well-defined genetic syndromes were identified as microdeletion or microduplication syndromes. The diagnostic use of array-CGH to address clinically unclear or nonspecific conditions, in particular syndromic intellectual disability, allows the identification of novel recurrent micro-imbalances representing new microdeletion/microduplication syndromes (Carvill and Mefford, 2013; Vissers et al., 2010). Quite recently a small subgroup of patients with similar microdeletions in the short arm of chromosome 10 was defined as a new microdeletion syndrome 10p15.3. To date only 23 patients, and among them only one familial case, showing variable chromosomal breakpoints and deletion sizes, have been reported. Clinical data was available from only 15 of the 21 published patients (DeScipio et al., 2012; Vargiami et al., 2014). Characteristic clinical findings in affected individuals described so far comprised variable cognitive impairment or developmental delay, speech delay and disorder of speech development, as well as uncharacterized dysmorphic signs (DeScipio et al., 2012; Vargiami et al., 2014). However, this rather nonspecific phenotype still needs to be refined by adding detailed information from further patients. We here report on a new familial case of microdeletion syndrome 10p15.3. The two eight and six year old maternal half-sisters were raised as foster children.

2. Clinical reports

Written informed consent was obtained from the patients' surrogates.

2.1. Clinical description of the family

The two affected girls are two of three maternal half-sisters – each with a different father - born within three years. The mother was referred to as having a reduced intelligence in the borderline range and having not obtained any school degree. Moreover, she was reported as an alcoholic and drug addict during all three pregnancies. All three children were withdrawn from the mother shortly after birth due to her dissocial and neglecting behavior and

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have been raised as foster children. The third, allegedly normal 7 year old half-sister and the mother of the three children were not presented in our department and no genetic analysis was performed.

2.2. Patient 1

The eight year old index patient described in detail here is the oldest of the three daughters. She was referred to our human genetics department due to intelligence deficit with rather low estimated IQ, disorder of speech development, behavioral problems and minor dysmorphic facial signs. An early global developmental delay including motor and speech delays were documented. The language and speech development was not only delayed but was also abnormal regarding typical developmental stages. Further, an inborn complex cardiac defect with a CAVSD (combined atrioventricular septal defect) and double orifice mitral valve was surgically corrected at the age of 3 months. In addition, the girl suffered from episodes of severe constipation. The result of a colon biopsy could not confirm a possible diagnosis of Hirschsprung's disease. Dysmorphic signs in the index patient were a broad nasal bridge, hypertelorism, short palpebral fissures, epicanthal folds, slightly deep set ears, widely spaced teeth, broad based tapered fingers, bilateral clinodactyly of big toes and fifth toes and bilateral position anomalies of toes with overriding second and fifth toes. Furthermore, pelvic obliquity, genua valga and flat feet were observed (Fig. 1).

2.3. Patient 2

The index patient's 6 year old half-sister showed similar facial features as well as global developmental delay with especially pronounced disturbance of speech development and behavioral problems like low frustration tolerance and temper tantrums. However, organ malformations were not observed. At the time of human genetic examination a still not normally developed language was obvious. The intellectual ability had not yet been determined, but by estimation was in the borderline or lower normal range. Dysmorphic signs comprised a flat nasal bridge with wide intercanthal distance, epicanthic folds, relatively short palpebral fissures, large and slightly deep set ears, prognathism, dental diastema, short tongue ligament with fixation of the tip of the tongue, broad based tapered fingers with hyperextensibility of the interphalangeal joints, minimal partial syndactyly of toes 2–4 and 2–3, respectively, and position anomalies of toes with overriding 3rd toes and subduction and clinodactyly of fifth toes on both feet.

3. Genetic testing

Conventional chromosome analysis in the index patient revealed a normal 46, XX karyotype; fragile X-Syndrome was excluded by *FMR1* gene diagnostics.

Array-CGH in the index patient revealed a microdeletion 10p15.3 (minimal deletion size of 334,51 kb). An additional intragenic microdeletion within *CLK4* gene in 5q35.3 was classified as a variant of unknown significance (arr[hg19] 5q35.3(178,045,689–178,092,106)x1, 10p15.3(116,476–450,983) x1) (annotation to LOVD database patient ID #00057174).

Array-CGH in the 6 year old half-sister revealed the same 10p15.3 microdeletion found in the index patient (arr[hg19] 10p15.3(116,476–450,983)x1) (Fig. 2).

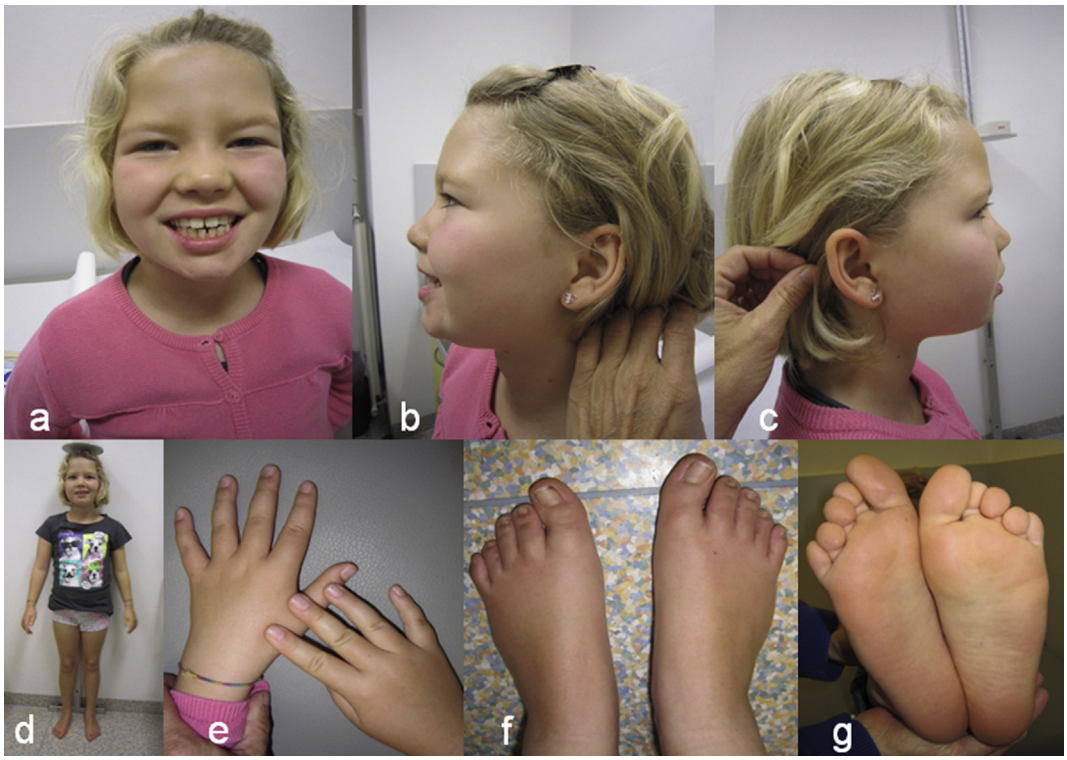

Fig. 1. a, b and c: The eight year old index patient exhibits mild facial dysmorphy with broad flat nasal bridge, hypertelorism, epicanthal folds, short palpebral fissures, slightly deep set ears, and dental diastema. d: Bilateral flat feet, mild genua valga and minor body asymmetry with pelvic obliquity. e: broad based tapered fingers. f and g: clinodactyly of both big toes and position anomalies of toes with overriding fifth and second toes and slightly subducted toes 2 and 3.