Meta Gene 2 (2014) 72–82

Contents lists available at ScienceDirect

Meta Gene

Interstitial 12p deletion involving more than 40 genes in a patient with postnatal microcephaly, psychomotor delay, optic nerve atrophy, and facial dysmorphism ☆

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ARTICLE INFO

Article history:
Received 31 October 2013
Accepted 31 October 2013
Available online 11 January 2014

Keywords:
Microcephaly
Mental retardation
Array CGH

ABSTRACT

Interstitial deletions of chromosome 12p are rare, and the phenotype spectrum is therefore still unknown. The thirteen patients reported so far suffer from developmental delay, optic nerve hypoplasia, micropenis, hypoplastic hair and skin, oligodontia, brachydactyly, and arterial hypertension. We report a *de novo* 12p12.2–p11.22 deletion of 9.2 Mb detected by array CGH analysis in a boy with global developmental delay, muscular hypotonia, postnatal microcephaly, facial dysmorphism including small ears, epicanthus, broad nasal bridge and hypoplastic nostrils. In addition, the patient had optic nerve atrophy, inverted nipples, micropenis, and a hemangioma. The deleted region encompasses more than 40 reference genes. We compare phenotype and deletion extent of our index patient to that of previous reports and thereby contribute to the understanding of interstitial 12p deletion phenotypes.

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2214-5400/$ – see front matter
http://dx.doi.org/10.1016/j.mgene.2013.10.014

Knowledge of the pattern of this deletion phenotype will help clinicians to diagnose this abnormality in their patients and to counsel the parents accordingly. Further descriptions may be able to contribute to the clarification.

Introduction

Deletions of the short arm of chromosome 12 are rare with only thirteen patients reported since the first description of an infant carrying the deletion 12p11p13 in 1975 (Bahring et al., 1997; Boilly-Dartigalongue et al., 1985; Fryns et al., 1990; Glaser et al., 2003; Lu et al., 2009; Macdonald et al., 2010; Magenis et al., 1981; Magnelli and Therman, 1975; Malpuech G et al., 1975; Nagai et al., 1995; Orye and Craen, 1975; Soysal et al., 2011; Stumm et al., 2007; Tenconi et al., 1975). A number of common features of patients with interstitial 12p deletions have emerged including global delay, cardiac anomalies (AVSD, VSD, ASD II), microcephaly, and optic nerve atrophy (Table 1). Still, the spectrum of the clinical phenotype remains unknown. Here, we describe a boy with a *de novo* interstitial deletion of chromosome 12. We characterized the extent of the deletion by array CGH and compared the phenotypic characteristics of the patient with those of previously published case studies.

Material and methods

Karyotype

For chromosome analysis peripheral blood lymphocytes from the index patient, his brother, and his parents were karyotyped using standard protocols for cultivation and GTG banding at a level of 550 bands in accordance with the International System for Human Cytogenetic Nomenclature (ISCN) (Mitelman, 1995).

Array CGH analysis

We obtained blood samples from the index patient and his parents after written informed consent. Genomic DNA was isolated from peripheral blood lymphocytes according to standard procedures. Patient and female reference DNA (Promega, Mannheim, Germany) were labeled with Cy3 and Cy5 using the Genomic DNA Enzymatic Labeling Kit (Agilent, Santa Clara, CA) according to the manufacturer's protocol. The mixture was hybridized on a 180 K oligonucleotide array (Agilent, Santa Clara, CA) for 16 h in a hybridization oven. Image data were analyzed using Feature Extraction 9.5.3.1 and CGH Analytics 3.4.40 software (Agilent Technologies, Santa Clara, CA) with the following analysis settings: aberration algorithm ADM-2; threshold: 6.0; window size: 0.2 Mb; filter: 5 probes, log2ratio = 0.29. Genome coordinates are shown according to human genome build GRCh37(hg18).

Results

Phenotype

The boy is the second child of non-consanguineous and healthy parents of German descent (Fig. 1A). His mother reported two previous miscarriages and unilateral ear fistulas of two maternal half siblings. The index patient was born at term following an uneventful pregnancy without complications: birth weight 3390 g (40th centile; −0.22 SD), length 50 cm (35th centile; 0 SD), occipitofrontal head circumference (OFC) 34 cm (15th centile; −0.79 SD). He was first presented at 4 weeks-of-age for cyanotic spells, an eye movement disorder of intermittent exotropia and discrete anisocoria. At that time, a small persistent ductus arteriosus was diagnosed. At an age of eight months, he presented at our hospital because of a respiratory syncytial virus (RSV) bronchiolitis and an anal herpex simplex virus (HSV) 1 infection. On clinical investigation, he had significant psychomotor delay. Griffith testing revealed a developmental age of 10.5 months at the chronological age of 23.5 months (developmental quotient < 45%). Facial dysmorphism was noted *i.e.* small ears, epicanthus, broad nasal bridge, and hypoplastic nostrils (Fig. 1B, Supplemental Fig. 1). In addition, the patient showed a dystrophic