Frontonasal Dysplasia, Callosal Agenesis, Basal Encephalocele, and Eye Anomalies Syndrome With a Partial 21q22.3 Deletion

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We describe a girl with a phenotype characterized by frontonasal dysplasia, callosal agenesis, basal encephalocele, and eye anomalies who presents a 46,XX,r(21) karyotype. Array-comparative genomic hybridization using the Affymetrix 100K DNA oligoarray set showed an interstitial deletion 21q22.3 of approximately 219 kb. Conventional karyotype of both parents was normal, and it was not possible to perform the molecular studies. In this report we raise the hypothesis that the deleted genes located at 21q22.3 could account to the phenotype. © 2012 Wiley Periodicals, Inc.

Key words: frontonasal dysplasia; CNS midline anomalies; basal encephalocele; 21q22.3 deletion

INTRODUCTION

Frontonasal dysplasia (FND) is a genetically heterogeneous group of disorders with abnormal frontonasal process development. It has been reported, most of the times, as an isolated field defect [Sedano and Gorlin, 1988]. The involvement of other additional fields have been resulted in a growing number of different syndromes described within the spectrum of the FND and, some of these syndromes support a known genetic pattern of inheritance while others have been reported as unique or recurrent pattern syndromes [revised by Wu et al., 2007]. One of the syndromes within this spectrum comprises the syndrome of midline facial defects, basal encephalocoeles, callosal agenesis, and eye anomalies, recognized as a distinct entity [Leitch and Winter, 1996; Lees et al., 1998].

Here we describe and discuss the clinical and the molecular findings of a girl with this condition, who was previously evaluated within a sample of patients (case 6) with similar phenotype [Richieri-Costa and Guion-Almeida, 2004].

CLINICAL REPORT

A girl (Fig. 1A–C) was referred to our Hospital at the age of 6 months for assessment and management of median cleft lip. She was the first child and the mother had a previous pregnancy which resulted in a miscarriage of unknown cause and two other normal girls. The parents were non-consanguineous and phenotypically normal. The pregnancy was unremarkable with no exposure to known teratogens. Delivery was at term, by cesarean; birth weight and length were not recorded. At birth she was noted to have a median cleft lip. Examination at age 6 months showed weight of 6.6 kg (10th centile), length of 61 cm (3rd centile), OFC of 42 cm (50th centile), inner canthal distance of 3.2 cm (>97th centile), and outer canthal distance of 8.1 cm (97th centile). She had prominent frontal, hypertelorism, left palpebral ptosis, broad nasal root, and incomplete median cleft lip with median alveolar notch. Upper and lower limbs were normal. The follow up showed weight and height below the normal ranges and normal neuropsychological development but with mild learning disabilities. Ophthalmic examination with fundoscopy was normal. Audiological evaluation was normal. Endocrinological evaluation detected GH and TSH deficiency. Cranial CT and MRI scans demonstrated a large sphenoidal encephalocele extending in direction to the nasopharynx with part of the anterior frontal lobe projecting through it; mild enlargement of the lateral ventricles; calosal

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agenesis; anterior pituitary gland, stalk, optic chiasm, and anterior commissure were not visualized. Migrational defects or abnormal gyral pattern were not observed (Fig. 2A,B).

Karyotype was 46,XX,r(21). Screening of mutations of the ALX3 and TGIF genes were normal. Array-comparative genomic hybridization (aCGH) using the Affymetrix 100K SNP array detected an interstitial deletion of 219 kb, spanning from position 46.625.055 to 46.884.297 pb (build 37.2) and encompassing eight RefSeq annotated genes (three protein coding genes; three non-protein coding RNA, and two hypothetical genes) (http://www.ncbi.nlm.nih.gov/mapview) at 21q22.3. The karyotypes of the parents were normal and the deletion testing was not performed.

DISCUSSION

The girl here described presented with midline craniofacial defect, comprising a midline cleft lip, hypertelorism, sphenoidethmoidal encephalocele, corpus callosum agenesis, and palpebral ptosis with a de novo chromosome 21 ring. According to literature data different conditions have been named within this spectrum [Leitch and Winter, 1996; Ebara et al., 1998; Hodgkins et al., 1998; Lees et al., 1998]. Sakoda et al. [1979] first suggested that the association of basal encephaloceles, corpus callosum agenesis, and cleft lip and/or palate, later termed Sakoda complex by Tada and Nakamura [1985], is a distinct clinical entity. Clinical delineation of this condition was performed by Richieri-Costa and Guion-Almeida [2004] who evaluated ten cases and concluded that the condition is clinically homogeneous and phenotypically defined as FND, callosal agenesis, basal encephalocele (mainly sphenoidethmoidal type), and ocular anomalies (palpebral ptosis, orbital asymmetry, strabismus, and optic disc anomalies). According to these authors, facial and ocular anomalies are variable. In relation to the etiology, the authors have done some conjectures about TGIF gene as causative of this condition. Later, Ribeiro-Bicudo et al. [2012] screened for mutation the TGIF gene in six individuals with this combination of signs and no mutations were found. They also investigated the ALX3 and ALX4 genes in these individuals and

FIG. 1. Facial aspects of the patient at age 6 months (A) and at age 12 years (B,C).

FIG. 2. A,B: Brain MRI of the patient showing a large sphenoidethmoidal encephalocele and corpus callosum agenesis.
similarly no changes were found. So far, the etiology of the FND, callosal agenesis, basal encephalocoele, and ocular anomalies syndrome remains unclear. In the present study, due to the presence of the chromosome 21 ring in patient, we performed an aCGH that detected a 21q22.3 interstitial microdeletion of about 219 kb. The phenotype of the patients with ring chromosome 21 can be highly variable ranging from normal to dysmorphic features, multisystem involvement, and intellectual disability [Bertini et al., 2008; Specchio et al., 2011; Arslan et al., 2011]. This variability of the phenotype has been explained by the instability of the ring chromosome that generates different degrees of mosaicism, as well as the size and structure of the ring [Ahzad et al., 2010; Specchio et al., 2011]. In our case, the aCGH detected a 219 kb interstitial deletion at 21q22.3 and, no low grade mosaicism was found. Deletion of the most terminal region of the chromosome 21 (21q22.2–q22.3) has been reported and related to phenotype ranging from mild, with minor dysmorphic features and mild intellectual disability, to severe, with dysmorphic features and major malformations [Ehling et al., 2004; Bertini et al., 2008; Roberson et al., 2011]. In general, the most specific clinical signs relating to 21q22 deletions include intra-uterine growth retardation, microcephaly, seizures, corpus callosum abnormalities, eyes anomalies, micrognathia, dysplastic ears, intellectual disability, and speech problems [Oegema et al., 2010; Roberson et al., 2011]. Corpus callosum abnormalities are present in our case who also presented with mild facial phenotype. According to DECIPHER database (the DECIPHER consortium, http://decipher.sanger.ac.uk/), three deletions and three duplications have been found encompassing the deleted region of our patient. Apparently normal phenotype was referred in cases presenting two of these three deletions.

In relation to genes encompassing the region deleted in our patient, three of them are coding proteins genes: ADARB1, POFUT2, and COL18A1 gene. The COL18A1 gene encodes the alpha chain of type XVIII collagen, a multiplexin extracellular matrix protein that contains multiple triple-helix domain (collagenous domains) interrupted by non-collagenous domains. Homozygous or compound heterozygous null mutations in COL18A1 cause a rare condition namely Knobloch syndrome, which is characterized by high myopia, vitreoretinal degeneration with retinal detachment, macular abnormalities, occipital encephalocoele, epilepsy, ataxia, septum pellucidum agenesis, neuronal migration defect, and cerebellar malformation [Sartie et al., 2000; Suzuki et al., 2002; Paisán-Ruiz et al., 2009]. The phenotype of our patient is not consistent with Knobloch syndrome. According to DECIPHER database there is no evidence of haploinsufficiency of COL18A1 gene causing disease and, deletions of this gene were reported in apparently normal individuals in the Database of Genomic Variants (http://projects.tcag.ca/). Thus, it is likely that COL18A1 gene deletion is not associated to the phenotype in our case.

ADARB1 gene (OMIM 601218) encodes the enzyme responsible for pre-mRNA editing of the glutamate receptor subunit B by site-specific deamination of adenosines. This gene has two transcripts of 8.8 and 4.2 kb that were strongly expressed in brain and in many human adult and fetal tissues. ADARB1 gene has not been associated with human disease but the homozygous mice to Adar2 are prone to seizure and died young [Higuchi et al., 2000]. POFUT2 gene (OMIM 610249) is an O-fucosyltransferase that use thrombospondin (THSB; MIM 188060) type 1 repeats as substrates. This gene also has not been associated with human disease however, in Caenorhabditis elegans, the changed expression of the ortholog of POFUT2 gene (Pad2) display severe body malformation and abnormal neuronal development [Menzel et al., 2004]. Research in Database of Genomic Variants (http://projects.tcag.ca) showed that deletions of the ADARB1 and POFUT2 genes were not observed in normal controls. Thus, it is not clear if theses genes could be influencing the phenotype in our patient.

In conclusion, it is possible that the 21q22.3 deletion can be related to the phenotype of our case and, investigation of the genes within this region could be helpful to clarify the etiology of the FND, callosal agenesis, basal encephalocoele, and ocular anomalies syndrome. However, it is not possible to exclude that the phenotype could be related to other genes, not located in the interval deleted in our patient, since the parents’ DNA samples were not available for study.

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REFERENCES


