Case Report

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Journal of Rare Disorders: Diagnosis & Therapy
ISSN 2380-7245

2015
Vol. 1 No. 2:13

DOI: 10.21767/2380-7245.100013

Craniosynostosis associated with Partial Monosomy 2q37.3 and Partial Trisomy 5q35 including *MSX2*

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Citation: König E, Engmann L, Kress W, et al. Craniosynostosis associated with Partial Monosomy 2q37.3 and Partial Trisomy 5q35 including MSX2. J Rare Dis Diagn Ther. 2015, 1:2.

Abstract

Context: Craniosynostosis, the premature fusion of one or more cranial sutures, is a common birth defect occurring either as an isolated malformation or in a syndromic context. Point mutations in known craniosynostosis genes detectable by Sanger sequencing account for only 20 % of craniosynostosis cases. In addition, chromosomal rearrangements i.e. deletions and duplications have been reported as a genetic cause for craniosynostosis. Among others partial trisomies 5q are associated with syndromic craniosynostosis.

Case Report: We report on a 7-year-old girl presenting with unilateral coronal and lambdoid craniosynostosis, microcephaly, craniofacial dysmorphisms and developmental delay. Initial sequencing analyses of the craniosynostosis associated genes *FGFR3* (exon 7), *TWIST1*, and *TCF12* did not detect any point mutations. Since chromosomal rearrangements may cause syndromic craniosynostosis we performed high resolution microarray-based comparative genomic hybridization (array CGH) to investigate genome-wide for gains and losses. This analysis detected a 2q37.3 deletion and a 5q35 duplication encompassing the gene *MSX2*. *MSX2* is involved in cranial development and gain-of-function mutations have been reported in craniosynostosis.

Conclusions: Our case confirms previous reports of association of distal trisomy 5q resulting in an extra copy of *MSX2* with syndromic craniosynostosis. Furthermore, it emphasizes the benefit of array CGH in genetic diagnostics of craniosynostosis patients, particularly in case of unclear syndrome classification due to clinical variability.

Keywords: Craniosynostosis; MSX2; Trisomy 5q; Monosomy 2q37; Array-Based Comparative Genomic Hybridization

Abbreviations: Array CGH = Microarray-Based Comparative Genome Hybridization; CNY = Copy Number Variant; DD = Developmental Delay; FISH = Fluorescence In Situ Hybridization; MR = Mental Retardation

Received: July 17, 2015; **Accepted:** August 03, 2015; **Published:** August 10, 2015

Introduction

Craniosynostosis is defined as the premature closure of the cranial sutures resulting in characteristic skull deformities. It is a rather frequent craniofacial malformation estimated to affect 1 in 2500 newborns [1]. There is a great variability in both phenotype and the underlying causes. Premature synostosis of the cranial sutures can occur either isolated (non-syndromic) or as part of a syndrome. Furthermore, clinical variability even within a family or between unrelated patients with the same genotype is well known for craniosynostosis. Causes for craniosynostosis can be environmental influences or genetic changes including point mutations or chromosomal aberrations [2,3]. So far genetic causes are mostly identified in syndromic craniosynostosis, e.g. mutations in *FGFR1-3, TWIST1, RAB23,* or *EFNB1* [4]. However, 15% of the craniosynostosis patients with additional clinical features i.e. syndromic craniosynostosis show chromosomal

rearrangements [4]. These rearrangements include partial deletions of 7p, 9p, and 11q as well as partial duplications of 5q, 13q, and 15q [5-9]. Due to the small number of patients with identical chromosomal aberrations, it is often difficult to determine the critical region or gene which contributes to the phenotype. Here we report a syndromic craniosynostosis patient with a 1.55 Mb deletion on 2q and a 7.85 Mb duplication on 5q leading to an extra copy of *MSX2* (OMIM 123101) identified by microarray-based comparative genome hybridization (array CGH).

Case Report

We present a female patient with unilateral coronal and lambdoid craniosynostosis. She was born after an uneventful pregnancy to non-consanguineous parents of Caucasian origin. Her parents and her twin sister are healthy and do not show signs of craniosynostosis. Besides the craniosynostosis, she presents with microcephaly, plagiocephaly, strabismus, and craniofacial dysmorphisms (mild ptosis, down slanting palpebral fissures, a pointed nose, smooth philtrum, small mouth with a thin vermillion of the upper lip, and small, wide spaced teeth) (present case in (**Table 1**). She has broad thumbs, muscular hypotonia, and hyperflexible joints. At the age of 6 9/12 years her weight, length and head circumference were 20.2 kg (P25), 115.6 cm (P3-10), and 45.1 cm (2.6 cm <P3), respectively. She showed an overall developmental delay and speech delay. At the age of 6 months she underwent surgery of the fused coronal suture. MRI scan of head at the age of 7 years was inconspicuous.

Informed consent was obtained from the patient's parents. The patient's genomic DNA was extracted from peripheral blood. Initial sequencing analyses of the craniosynostosis associated genes *FGFR3* (exon 7), *TWIST1*, and *TCF12* did not detect any point mutations. Subsequently, the genomic DNA was investigated by array CGH using a high-resolution 1M oligonucleotide array according to manufacturer's protocol (SurePrint G3 Human CGH Microarray Kit, 1x1M, Agilent Technologies, Santa Clara, CA). Copy number variant (CNV) analysis was performed with CytoGenomics software (version 2.9.2.4, Agilent Technologies, Santa Clara, CA) with the following analysis settings: aberration algorithm ADM-2; threshold: 6.0; window size: 0.5 Mb; filter: 5 probes, log2ratio = 0.29. Array CGH analysis revealed two clinically relevant aberrations: a 1.55 Mb heterozygous deletion of 2q37.3-qter encompassing 32 genes (14 OMIM genes) and a 7.85 Mb duplication of 5q35.2-qter [ISCN 2013 karyotype: arr[hg19] 2q37.3(241,476,655-243,038,331)x1, 5q35 .2q35.3(172,856,313-180,712,263)x3] (**Figure 1**). The duplication 5q35.2-qter encompasses more than 100 genes (44 OMIM genes) including MSX2 (OMIM 123101). The array CGH aberration pattern of partial terminal monosomy and partial terminal trisomy suggests an unbalanced translocation. Up to now it was not possible to examine the detected aberrations by fluorescence in situ hybridization (FISH) and to confirm the presence of an unbalanced translocation in the index patient. Material of the parents for karyotyping and FISH was not available.

Discussion

We present a patient with craniosynostosis, additional dysmorphic features, and developmental delay. Array CGH revealed a partial monosomy 2q and a partial trisomy 5q indicative of an unbalanced translocation. Each of these aberrations may occur separately and is associated with typical phenotypes. Characteristic facial features of the 2q37 deletion syndrome include a prominent forehead, depressed nasal bridge, thin, arched eyebrows, deep-set eyes with upslanting palpebral fissures, full cheeks and a thin upper lip [10]. So far no association with craniosynostosis was reported. Furthermore, 30% of the patients have additional clinical features like cardiac, gastrointestinal, renal and genitourinary malformations [10].

Cryptic translocations resulting in duplications of 5q35-qter have been reported as cause of Hunter-McAlpine syndrome (OMIM 601379). In general, partial trisomy of distal 5q leads to a variable phenotype with the most common features comprising short stature, mental retardation (MR), microcephaly, and craniofacial features including strabismus, hypertelorism, down slanting palpebral fissures, low-set dysplastic ears, prominent nasal tip, long philtrum, small mouth, and thin upper lip [9, 11-14]. In addition, digital dysmorphism, hernias, cardiac malformations, and craniosynostosis were reported as less common clinical features. To our knowledge, 13 craniosynostosis cases including our patient with partial 5q trisomy have been described to date [8, 9, 12, 15-21]. A comparison of clinical features is presented in **table 1**. The largest duplications associated with craniosynostosis phenotype start at chromosomal band 5q31 [15, 18]. So far, more proximal duplications have not been associated with premature closure of cranial sutures.

The phenotype of our patient overlaps with the clinical findings of both partial 2q monosomy and partial 5q trisomy, respectively. However, some clinical features like craniosynostosis, microcephaly, and short stature are more likely due to the distal 5q duplication and associated MSX2 triplication. Kariminejad et al. presented a patient with similar chromosomal aberrations compared to our case i.e. 5q34-qter trisomy and 2q37.3-qter monosomy [9]. Their patient showed metopic and unilateral coronal synostosis, microcephaly, hypertelorism, down slanting palpebral fissures, epicanthal folds, small nose and small mouth with thin lips, long philtrum, high arched palate, and inguinal hernia (**Table 1**). In addition, development was delayed [9]. Clearly their patient and our case show a similar chromosomal rearrangement and a great phenotypic similarity. Regarding candidate genes in the aberrant regions there is convincing evidence that MSX2 gain-of-function is the genetic cause for the premature closure of the cranial sutures.

MSX2 plays an important role in cranial development. The Pro148His gain-of-function mutation of *MSX2* was identified as the genetic cause of Boston-type craniosynostosis (OMIM 604757) in a large family [22]. In transgenic mice this missense mutation was shown to cause premature closure of the cranial sutures [23]. Furthermore, the gain-of-function effect leads to an increased DNA binding affinity of the mutated protein without changing the site specificity [24]. Recently, two families were reported with a novel point mutation at the same position as the Boston-type mutation leading to an amino acid change p.P148L [25,26]. So far no functional studies on this

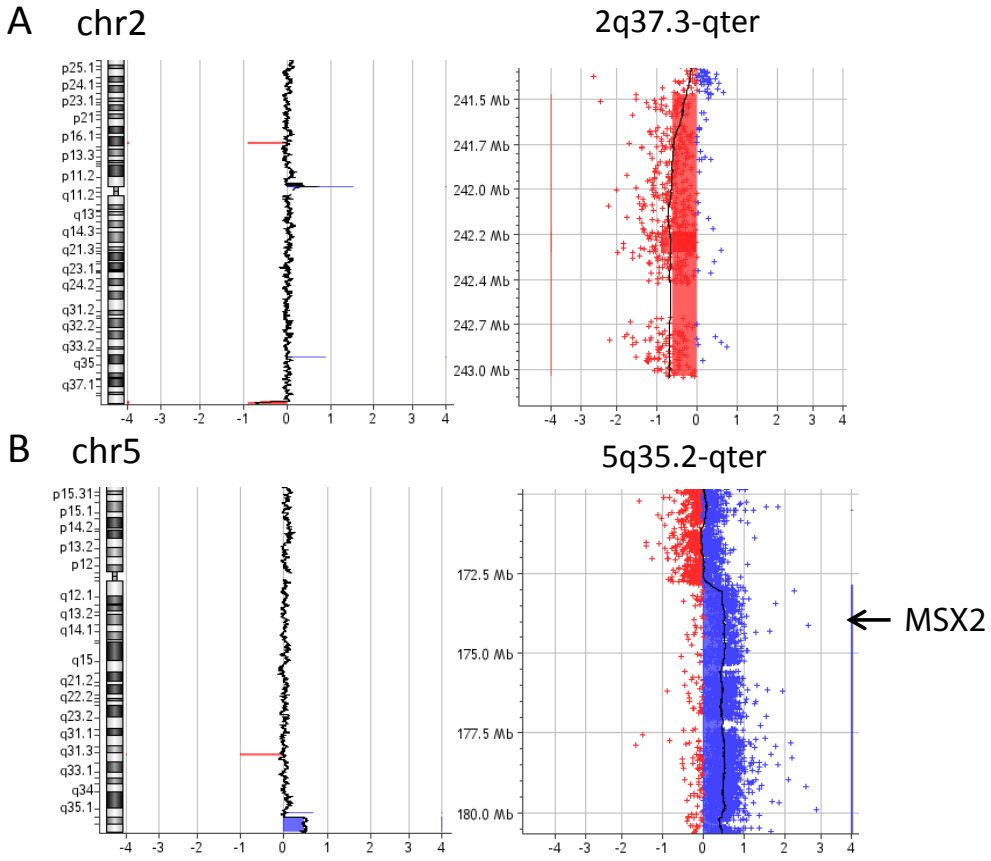

Figure 1 Array CGH profiles of chromosome 2 and chromosome 5. A) Detection of a 1.55 Mb deletion encompassing 2q37.3-qter. On the left magnification of the deleted region shaded in red. B) Identification of duplication of 7.85 Mb from 5q35.2-qter. On the left magnifiation of the duplicated area shaded in blue. Localization of *MSX2* marked by an arrow

Table 1: Comparison clinical features of patients with partial 5q trisomy and craniosynostosis.

characteristics	Summary of 9 patients*	Bernardini et al. [20]	Pelegrino et al. [32]	Kariminejad et al. [9]	Present case
Partial 5q trisomy	+	5q35 - qter	160kb interstitial duplication incl. *MSX2*	5q34 - qter	5q35.2 - qter
Coexisting hromosomal imbalance	+	-	-	Del 2q37.3	Del 2q37.3
Sex	6F / 3M	F	F	M	F
Age at examination	4 days – 12 years	4 months	19 months	12 months	7 years
MR/DD	7/9	+	+	+	+
Craniosynostosis	Metopic (4/9) Sagittal (6/9) Coronal (2/9) Lambdoid (3/9)	Metopic, Sagittal, Lambdoid	Coronal	Metopic, Coronal	Coronal, Lambdoid
Microcephaly	8/9	+	+	+	+
Epicanthal fold	4/9	-	N/A	+	-
Downslanting palpebral fissures	6/9	+	-	+	+
Small nose	6/9	+	N/A	+	+
Long philtrum	7/9	+	N/A	+	Smooth philtrum
Thin lip	8/9	+	N/A	+	+
High arch palate	6/9	+	+	+	N/A
Low set ears	8/9	+	+	+	-
Cardiac abnormality	5/9	+	-	-	N/A
Limb abnormality	7/9	Rhizomelia	-	-	Broad thumbs

F, female; M, male; MR/DD, mental retardation/developmental delay; N/A, not available

*[8, 12, 15-19, 21]

mutation have been done. In contrast to these gain-of-function mutations, haploinsufficiency due to loss-of-function mutations or deletions of *MSX2* results in foramina parietale with and without cleidocranial dysplasia (OMIM 168550 / 168500) which is characterized by deficient parietal bone ossification [27-30]. *MSX2* knock-out mice resembled the human phenotype leading to the assumption that *MSX2* gene dosage is critical for proper skull ossification [31]. We therefore propose that the copy gain of *MSX2* leads to craniosynostosis in our patient. The additional clinical features, especially the developmental and speech delay, are most likely explained by the large rearrangements and the genes located therein.

In summary, this case report clearly demonstrates the importance of chromosomal rearrangements and CNVs as a genetic cause of craniosynostosis. It is well known that in approximately 80% of craniosynostosis cases standard molecular genetic testing i.e. Sanger sequencing, of known craniosynostosis genes does not detect any causal mutation [4]. Therefore, CNV screening methods like array CGH should be included in the genetic testing algorithm for craniosynostosis patients who tested negative for typical point mutations. This will enable diagnosis in yet unsolved syndromic as well as non-syndromic cases.

Financial support:

This work has been funded by the German Federal Ministry of Education and Research (BMBF grant 01GM1109F) as part of the consortium on rare complex craniofacial disorders (FACE).

Conflicts of interest: None

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