

2q13 microdeletion syndrome: report on a newborn with additional features expanding the phenotype

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Abstract

In this paper we describe an additional newborn patient with craniofacial dysmorphisms, congenital heart disease, hypotonia and a 2q13 deletion of 1.7 Mb, whose clinical and genomic findings are consistent with the diagnosis of 2q13 microdeletion syndrome.

Introduction

In recent years, chromosomal microarray analysis (CMA) allowed the identification of a growing number of chromosomal imbalances within the human genome (Wolfe, 2018). These copy number variations (CNVs, defined as a greater than 1 kb segment of DNA that has variable copy number as compared to normal reference genome) include deletions and duplications (Yu, 2012), and involve single or multiple genes (Wolfe, 2018). CNVs may be either benign, or associated with diseases (Yu, 2012). Some regions of the genome are flanked by highly homologous sequences (segmental duplications, SDs, also known as low copy repeats) (Rudd, 2009). They are prone to mismatching and, then, to recurrent CNVs, some of which cause clinically recognizable phenotypes (i.e., Angelman, Prader-Willi, Smith-Magenis and Williams-Beuren syndromes) (Wolfe, 2018; Hladilkowa, 2015). The 2q13 region contains clusters of such SDs, which facilitate recurrent deletions and/or duplications. These imbalances are less described than those affecting other chromosomes (Hladilkowa, 2015). A recurrent pathogenic 1.71 Mb microdeletion is reported to date in around 50 patients (Wolfe, 2018). Their clinical phenotype is variable for the occurrence of mild (in the majority of cases) dysmorphic features, macro- or microcephaly, neurodevelopmental delay/behavior disorder (including hypotonia, impairment in fine and global motor skills, autism spectrum disorder, attention deficit and hyperactivity disorder), as well as congenital heart disease (CHD, the most frequent anomaly) and other congenital defects (i.e. scoliosis, renal/genital malformations) (Guivarch, 2018).

Hereby, we describe an additional newborn with craniofacial dysmorphisms, CHD, hypotonia and a 2q13 deletion of 1.7 Mb, whose diagnosis is consistent with 2q13 microdeletion syndrome. This new neonatal case report may provide additional genotypic and clinical data, as well as further insights into the possible biological and molecular bases of the 2q13 microdeletion syndrome.

Clinical report

This newborn female was the first born by vaginal delivery, from healthy non-consanguineous parents, at 40⁺² weeks of gestation after a naturally obtained and uneventful pregnancy. At birth her weight was 3200 g (39th percentile), length 50 cm (55th percentile), and occipitofrontal circumference (OFC) 34.5 cm (64th percentile). She was transferred on the second day of life from a first level birth center of the town, because of feeding difficulties, hypotonia and dysmorphic features. On admission to our Department she showed on physical examination: facial asymmetry for hypoplasia of the left side of the face, low hairline, broad nasal

bridge, pear shaped tip of the nose and short columella, small chin (Fig. 1a). Posteriorly-rotated left ear with thick helix, homolateral preauricular tag and pit (Fig. 1b), as well as inferotemporal epibulbar dermoid of the left eye and absent uvula were observed. A sacral dimple was also noted (Fig. 2). Generalized hypotonia and feeding difficulties completed her clinical profile. Brain ultrasound (US) showed a corpus callosum narrowing, between the anterior portion of the body and the genu. Abdomen and spinal cord US examinations showed no abnormalities. US heart evaluation revealed a subaortic ventricular septal defect. A whole spine X-ray was also performed, and found lumbar kyphosis without vertebral defects.

Array comparative genomic hybridization (a-CGH) analysis (100–150 Kb resolution, genomic assembly GRCh37.p13) identified a 2q13 deletion of 1.7 Mb, and indicated the positions 111,399,243 and 113,098,686 as the breakpoints of the rearrangement. The deleted region involved different genes, including partially *BUB1*, *ACOXL*, *BCL2L11*, *MIR4435-2HG*, *MIR4771-2*, *ANAPC1*, *MERTK*, *TMEM87B*, *FBLN7*, *ZC3H8* and *ZC3H6*. a-CGH was also performed in both parents, showing normal results and, thus, confirming the *de novo* origin of the genomic abnormality.

The patient recovered from her initial feeding difficulties around the seventh day of life. Hearing screening through transient-evoked otoacoustic emissions (TEOAEs) revealed abnormal results. Then, an audiological assessment to ascertain and characterize the hearing loss was started. It included to date auditory brainstem response (ABR), which showed a left unilateral moderately severe conductive hypoacusis. She was discharged at 1 month of age after an otherwise uneventful clinical course, and is included in a multidisciplinary (neurodevelopmental, surgical, audiology, ophthalmologic, cardiologic) follow-up. She actually (3 months old) shows a mild developmental delay.

Discussion

The cytogenetic band 2q13 is enriched in clusters of highly homologous sequences, which facilitate the occurrence of deletions and/or duplications, quite recurrent in size and breakpoints (Hladilkowa, 2015). Among these rearrangements, a recurrent 1.71 Mb deletion is associated with a congenital syndrome (around 50 patients reported to date) manifesting with variable phenotype, which includes psychomotor development disabilities, mild craniofacial dysmorphisms and CHD, and currently defined as 2q13 deletion or microdeletion syndrome (Wolfe, 2018; Guivarch, 2018).

The phenotype of the present patient (showing craniofacial dysmorphisms, CHD and neurodevelopmental delay), although being overlapping with that of most 2q13 deletion subjects described to date, seems to be more severe (specifically for the eye and ear involvement), sharing clinical signs with the oculo-auricular-vertebral spectrum (OAVS). This latter disorder affects craniofacial morphogenesis, and involves structures derived from the first and second pharyngeal arches (Passos-Bueno, 2009). Its manifestations include asymmetric ear anomalies with or without hearing loss, hemifacial microsomia resulting in facial asymmetry, orofacial clefts, ocular (including epibulbar dermoids) and vertebral defects. Cardiac, genitourinary and cerebral malformations may be associated. Several chromosomal/genomic anomalies are observed in patients showing an OAVS phenotype. However, 2q13 deletions are not reported (Beleza-Meireles, 2014).

The deleted region of our patient encompasses eleven genes, nine protein coding ones (*BUB 1* partially deleted, *ACOXL1*, *BCL211*, *MERTK*, *FBLN7*, *TMEM87B*, *ANAPC1*, *ZC3H8* and *ZC3H6*), and two coding for microRNA (miRNAs, *MIR4435-2HG* and *MIR4771-2*).

The dysmorphism and head circumference anomaly generally observed in cases with this deletion may depend on *FBLN7* (fibulin 7) haploinsufficiency. This gene encodes fibulin-7, a glycoprotein which plays a role in the formation of facial bones (Guivarch, 2018). Its involvement may explain the hemifacial hypoplasia of our newborn, showing also absent uvula and small chin, as well as homolateral eye and ear involvement. Fibulin-7 cooperates with other proteins involved in heart development. Such function may clarify the association with CHDs reported in 2q13 deletion patients (Russell, 2014), and observed also in our newborn. *TMEM87B* (transmembrane protein 87B) is likely related with developmental delays, autism spectrum disorders (ASDs), and other psychiatric phenotypes as well as CHD (Guivarch, 2018; Yu, 2016; Russell, 2014), and its defect may be consistent with the neurological (generalized hypotonia and feeding difficulties) and cardiac findings

of our patient. Disruption of *ACOXL* (acyl-CoA oxidase like, affecting fatty acid metabolism) (Wolfe, 2018; Yu, 2012) and *BCL2L11* (BCL2 like 11, which encodes an antiapoptotic protein expressed in the frontal cortex and in the cerebellum, thus increasing apoptosis and the correlated risk of ASDs) (Sheikh, 2010) may contribute to neurodevelopmental and ASD phenotypes of these subjects (Wolfe, 2018; Yu, 2012). *ANAPC1* (anaphase promoting complex subunit 1), a neurodevelopmental facilitator mainly expressed in the brain and the lymphoid organs, and *MERTK* (MER proto-oncogene, tyrosine kinase) are candidate genes for the psychosis phenotype of 2q13 CNV carriers (Wolfe, 2018). The latter is also associated with retinal defects and autosomal recessive retinitis pigmentosa. It may have, thus, a role in the ocular development, which is disrupted (epibulbar dermoid) in our patient.

In the rearranged DNA of our newborn there are also two genes coding for miRNAs, that may influence the expression of the phenotype. They are short (20-24 nt) non-coding RNAs, that are involved in post-transcriptional regulation gene expression. Between them, the *MIR4435-2HG* gene is ubiquitously expressed in different tissues, mainly brain, heart and lymphoid organs. In the latter ones are also highly expressed *ZC3H8* and *ZC3H6* (zinc finger CCCH-type containing 8/6). Defects in one of these genes may cause a greater predisposition to infections (including otitis), and contribute to the phenotype of our proband, as well as to that of 2q13 deletion patients, in which such risk is described (Wolfe, 2018).

Several explanations for the variable expressivity (Girirajan, 2012) and reduced penetrance observed in 2q13 deletion patients are supposed, such as differences in gene content due to variable deletion breakpoints (Hladilkova, 2015). Specifically, a more severe clinical expressivity (like that showed by our newborn, including craniofacial dysmorphisms, ocular involvement with epibulbar dermoid and vertebral lumbar kyphosis) occurs because of the combined loss of more candidate genes present in the critical rearrangement (Russell, 2014). However, localization and width of such recurrent deletion is quite overlapping among the patients described in the literature. Therefore, besides the possible role played by genes contiguous to the deleted region (as occur in contiguous gene syndromes), there could be other plausible causes: in the “two hit” hypothesis, the 2q13 deletion could represent a “first hit” (i.e. a risk factor) for a second one, represented by an additional genomic imbalance (deletions and/or duplications), observed in some of the patients described to date (Hladilkova, 2015), but which is absent in our proband; otherwise, other genomic mutations may unmask recessive alleles.

In the present patient, as whole genome sequencing was not performed, it cannot be ruled out that another genetic variant was contributing (or modify) to her phenotype. Moreover, epigenetic factors may also exacerbate the expressivity of the clinical picture (Guivarch, 2018). Our report is the first description of an OAVS phenotype in a 2q13 microdeletion patient. We cannot establish to date if such association is casual, or if a genetic bond exists between them. In regard to this, it could be supposed that loss of *FBLN7*, which is expressed in the branchial arches (Russell, 2014), may be associated with development anomalies of the structures derived from the first and second pharyngeal arches (which are affected, indeed, in the OAVS).

Moreover, a further research on *FBLN7* gene networks (<https://genemania.org/search/homo-sapiens/FBLN7/>, access 05/07/2020) identified a physical interaction network involving 3 genes (*EDEM2*, *ASPH*, *CLNS1A*), a co-expression network involving 17 genes (*GLYATL2*, *IZUMO2*, *SMYD2*, *BMPER*, *AHDC1*, *PRELID2*, *NEIL1*, *MDGA1*, *TLL1*, *TTC6*, *CDH7*, *EMID1*, *G6PC2*, *SH3GL3*, *AMBN*, *DOC2A*, *BCL7A*), and a shared protein domain network involving *TLL1*. Among the aforementioned genes, three are associated with clinical phenotypes overlapping with the 2q13 deletion syndrome: *TLL1* (cardiac malformations), *ADHC1* (hypotonia, corpus callosum hypoplasia) and *ASPH* (facial dysmorphism). No *FBLN7* gene pathway has been described yet.

This report may provide useful data about the clinical and genomic features of 2q13 deletions, and expand the phenotypes associated with this rearrangement, which does not have to date a recognizable set of specific manifestations (Riley, 2015). It strengthens the importance of microarray analysis in cases of congenital malformations and/or dysmorphic features without a clinical picture suggestive for known disease (Pavone, 2019; Pavone, 2019; Viaggi, 2012).

Obtaining an early genetic diagnosis in the neonatal age, like occurred in the present case, is relevant for proper management of the patient, which includes individualized follow-up (enabling prevention of future comorbidities, such as infections, hearing loss, orthopedic and neuropsychiatric disorders) and genetic counseling for the family (recurrence risk for later pregnancies) (Lefebvre, 2016).

Further functional studies of the 2q13 genes, identification of single gene mutations (Iyer, 2015), as well as extended comparative analysis of a larger number of age-matched patients with overlapping features, may allow a more precise clinical and genomic characterization (Corsello, 2018). This is also useful to define genotype-phenotype correlations (Serra, 2019).

Declarations

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No funding was granted for this research.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship

EP performed neurological and developmental assessment, revised the manuscript, and gave final approval of the version to be submitted. GS collected and analyzed the clinical data, and drafted the manuscript. MG contributed to clinical management of the patient and interpretation of the genetic data. MS contributed to clinical management of the patient, and in drafting the manuscript. GC conceptualized the study, performed genetic assessment, revised the manuscript and gave final approval of the version to be submitted.

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Conflict of interest

The authors declare that they have no competing interests.

Ethical considerations

Written informed consent was obtained from both parents at the time of admission of our patient. The study was approved by the Mother and Child Department of the University of Palermo (Palermo, Italy). All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figure 1a : note facial asymmetry for hypoplasia of the left side of the face, low hairline, broad nasal bridge, pear shaped tip of the nose, short columella and small chin; **1b** : the left ear is posteriorly-rotated, with thick helix and preauricular tag and pit.

Figure 2 : sacral dimple.



