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Case Report

Application of Array-Comparative Genomic Hybridization to Clinical Diagnostics: Nicolaides-Baraitser Syndrome, A Case Report

Domenico Dell'Edera[1*], Annunziata Anna Epifania[1], Rosalba Ardea Dell'Edera[2], Maria Teresa Dell'Edera[2], Arianna Allegretti[1]

[1]Unit of Medical Genetics, "Madonna delle Grazie" Hospital, Matera, Italy

[2]Faculty of Medicine, West Vasile Goldis University, Arad, Romania

[*]**Corresponding author:** Domenico Dell'Edera, Unit of Medical Genetics, "Madonna delle Grazie" Hospital, Matera, Italy

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Abstract

Neurodevelopmental disorders are conditions characterized by a complex and heterogeneous etiology. Array-CGH is used as a first level investigation to study the genetic basis of these diseases. We report the case of a 3-year-old boy with neurodevelopmental disorders and dysmorphisms whose genome was studied by Array-CGH. Array-CGH detected a microdeletion of approximately 106 Kb involving the OMIM Morbid SMARCA2 gene. the SMARCA2 gene region involved is associated with Nicolaides-Baraitser syndrome (NCBR). Nicolaides-Braitser syndrome is an extremely rare condition, approximately 75 cases have been reported in the scientific literature. This paper highlights how the Array-CGH is useful for highlighting also extremely rare monogenic diseases.

Keywords: Array comparative genomic hybridization (array-CGH); Nicolaides–Baraitser syndrome (NCBRS); SMARCA2 gene; 9p24 microdeletion

Introduction

Neurodevelopmental disorders are conditions characterized by a complex and heterogeneous etiology [1]. Array-CGH is used as a first level investigation to study the genetic basis of these diseases. The array-CGH allows to detect the presence of pathological submicroscopic rearrangements (microdeletions and / or microduplications). Compared to the conventional karyotype, the technique based on Array-CGH is able to diagnose about 15%-20% more of the genomic pathologies responsible for neurodevelopmental disorders [2-8].

We report the case of a 3-year-old child with neurodevelopmental disorders and dysmorphisms whose genome was studied using the Array-CGH method. This case demonstrates the clinical utility and validity of the Array-CGH method in diagnosing an extremely rare syndrome, known as Nicolaides-Baraitser syndrome, an autosomal dominant disease [9]. This diagnosis was made thanks to the detection of a localized microdeletion on the short arm of chromosome 9 (9p24). The microdeletion of about 106 Kb involves the OMIM "Morbid" SMARCA2 [10] gene whose defect is associated with the Nicolaides – Baraitser syndrome (NCBRS, OMIM # 601358). Is characterized by severe intellectual disability (ID), seizures, short stature, sparse hair, typical face, brachydactyly, and prominent interphalangeal joints. It was first described in 1993 by pediatric neurologist Paola Nicolaides and clinical geneticist Michael Baraitser [11]. This study highlights how the Array-CGH is useful, as a first level test, to highlight even extremely rare monogenic pathologies.

Clinical Report

The subject of this study is a three-month-old child (M.F.). Her mother's prenatal history shows no evidence of teratogen exposure or any other relevant exposures or pathologies. Ultrasound reports during weeks 14 and 25 of gestation showed no morphological alterations. At the twelfth week of gestation the mother underwent Non-Invasive Prenatal Screening (NIPT) of fetal structural chromosomal aneuploidy by isolation and study of fetal DNA circulating in the maternal blood. The method is based on Massively Parallel Sequncing (MPS) using Next Generation Sequencing (NGS) technique. NIPT ruled out that the fetus had the most common chromosomal abnormalities (Down syndrome, Edwards syndrome, Patau syndrome).

The mother reports that the child was born at term with eutocic delivery. Stages of psychomotor development have been delayed. He started walking around 22 months. The lallation or babbling phase started late and ended at 18 months. At the age of 2 years was made diagnosis of "Global delay of development with compromise of communicative-relational skills". From the phenotypic point of view M.F. presents sparse scalp hair, long eyelashes, anteverted nares, short nasal bridge, thick nasal wings, long philtrum, wide mouth, the vermilion of the upper lip appears thin, while the vermilion of the lower lip appears often, thick eyebrows, microcephaly (Figure 1).

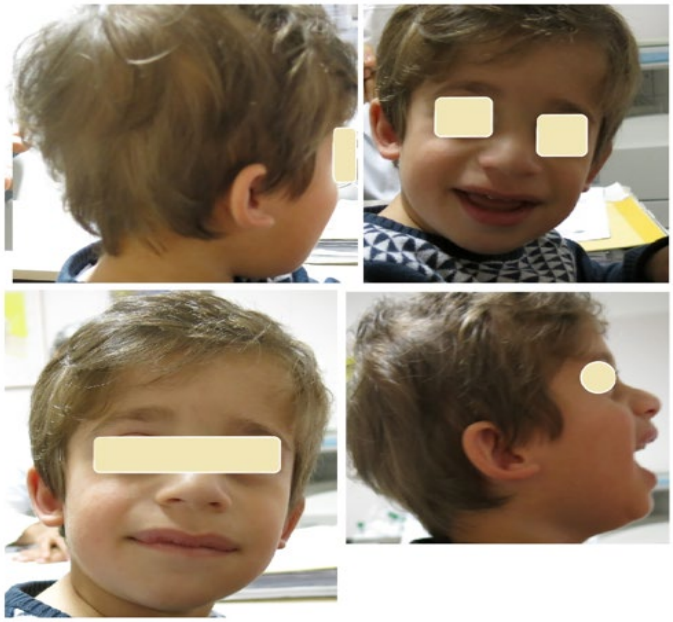

Figure 1: M.F. presents sparse scalp hair, long eyelashes, anteverted nares, short nasal bridge, thick nasal wings, long philtrum, wide mouth, the vermilion of the upper lip appears thin, while the vermilion of the lower lip appears often, thick eyebrows, microcephaly.

In order to assess the possible presence of genetic alterations, a genomic analysis was carried out using Array Comparative Genomic Hybridization (Array-CGH).

Materials and Methods

Cytogenetic and Array-CGH

Cytogenetic and array-CGH analyses were performed on peripheral blood of the patient, her parents. High resolution chromosomes were GTG banded using the standard procedure. Genomic DNA was extracted from peripheral blood leukocytes using "QIAamp® DSP DNA Blood Mini" from Qiagen (DNA IQTM System) (Qiagen S.r.l., Italy) commercial kit, in accordance with the manufacturer's specifications. Array-CGH analysis was performed using ISCA V2, 4x180K oligo platforms (Oxford Gene Technology), with 25Kb probe spacing (higher resolution in ISCA region). Experiments were conducted according manufacturer's protocol. Commercial reference DNAs (male and female) provided by Promega G1521 were used for the analysis. The slides were scanned with Innoscan 710 Microarray Scanner, captured images were analyzed with CytoSure Interpret Software version 4.10. Genomic region analysis was performed according to the human reference sequence hg19GRCh37. The copy number variations (CNVs) founded in the proband were compared with genomic variants present on different databases (DECIPHER: https://decipher.sanger.ac.uk - UCSC Genome Browser: https://genome.ucsc.edu – Clinical Genome Resource (Clingen) (http://clinicalgenome.org) -Troina Database of Human CNVs: (http://gvarianti.ho- melinux.net/gvariantib37/index.php).

Results

Array-CGH performed on M.F. detected a microdeletion on the short arm of chromosome 9 (9p24.3: 2070955_2176423) of 106 Kilo bases (Kb) (Figure 2). The chromosomal region contains the OMIM "Morbid" gene SMARCA2. SMARCA2 gene contains 34 exons spanning 178.2 kb and coding for the protein called Probable global transcription activator (SNF2L2) (Figure 3). SNF2L2 becomes part of a protein complex known as SWI/SNF (Switch/Sucrose Non-Fermenting o anche BAF complex). SNFL2 is involved in chromatin remodeling and regulation of gene expression during nervous system development[12]. SMARCA2 gene controls DNA spiralization and despiralization processes. In this way SMARC2 controls gene expression. SMARCA2 gene has been implicated in the regulation of the cell cycle and in oncogenesis: it acts as a cancer repressor, preventing cells from growing and dividing too quickly or uncontrolled [12].

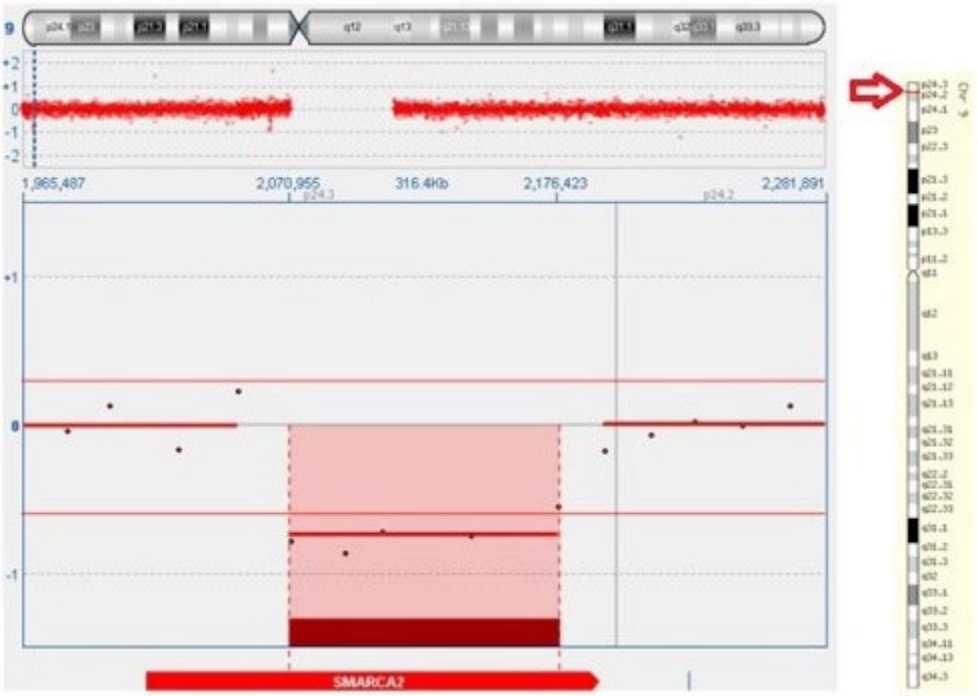

Figure 2: Microdeletion on the short arm of chromosome 9 (9p24.3: 2070955_2176423) of 106 Kilo bases (Kb). The chromosomal region contains the OMIM "Morbid" gene SMARCA2.

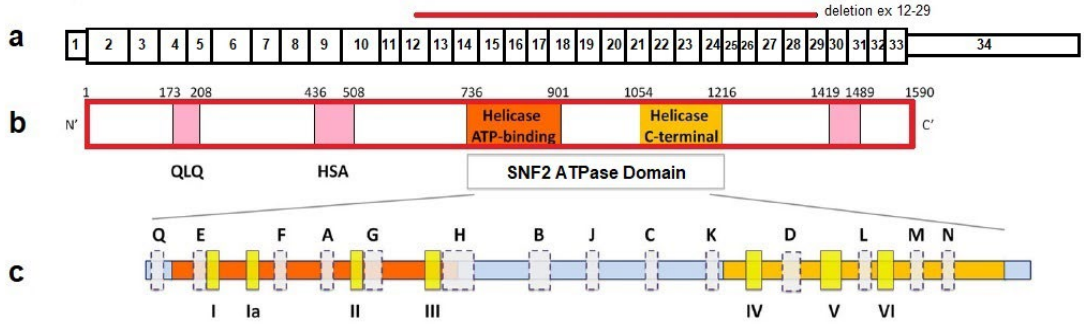

Figure 3: Diagram of SMARCA2. a) SMARCA2 gene contains 34 exons spanning 178.2 kb. b) Schematic of SMARCA2 protein showing the main domains Nelicase ATP- binding and Helicase C-terminal. c) SMARCA2 ATPase domain highlighting the seven canonical helicase - related sequence motifs (I, Ia–VI; yellow boxes) characteristic of SNF2 group of proteins, and 14 additional conserved blocks (A - N, light gray boxes with dashed line) as reviewed by Flaus et al. [2006].

Clinical elements of patients with mutations in genes coding for proteins that are part of the SWI/SNF complex (ARID1B, ARID1A, SMAR CA4, SMARCB1, SMARCE1, SOX11, ARID2, DPF2, SMARCA2, PHF6) are variable, constitute a clinical continuum of which the most severe form is the Nicolaides-Baraitser syndrome (NCBRS) [13,14]. Mutations that cause Nicolaides-Baraitser syndrome lead to the production of an altered protein; altering the function of the SWI/SNF complex on chromatin remodeling. At least 50 mutations in the SMARCA2 gene have been found to cause Nicolaides-Baraitser syndrome [15]. These changes can impair normal cell development in different tissues, including neural tissue. Most of the causal mutations of SMARCA2 affect the ATPase domain (Helicase ATP-binding and Helicase C-terminal) which extends from exon 15 to exon 25 [15-17]. The deletion found in M.F. it involves about 17 exons (from exon 12 to exon 29) and includes ATPase domain of the SMARCA2 gene (Figure 2). Nicolaides-Braitser syndrome is an extremely rare condition and seems to be more frequent in Asian countries. To complete the

diagnosis, the Array-CGH investigation was extended to M.F.'s parents. Both parents do not have deletion in the short arm of chromosome 9. Such results have allowed to confirm that the microdeletion found in the little M.F. turns out to be "de novo".

Conclusion

Use of Array-CGH as a first level test in cases of intellectual disability and neurodevelopment disorders is a valid method for diagnosing genomic diseases. Moreover, the Array-CGH allows to define with precision the altered genomic region and the "OMIM Morbid genes" contained in it. This study confirms that for some neurodevelopmental pathologies and/or multiple congenital abnormalities until a few years ago considered idiopathic, the CGH Array demonstrates that these are caused by submicroscopic chromosome imbalances. Over the years, we have also witnessed an evolution of cytogenetic techniques: the initial primary investigation, consisting of karyotype, has been gradually replaced by Array-CGH analysis. Probably, in the years to come, further benefits will be brought by the introduction of Next Generation Sequencing (NGS) technologies into clinical practice.

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Statement of Ethics

Published research is comply with the guidelines for human studies and it's was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Authors declare under their own responsibility that the subjects studied have given their written consent to publish their case. The signed consent is kept in the Cytogenetic and Molecular Genetics unit.

Authors' Contributions

Arianna Allegretti, Annunziata Anna Epifania and Domenico Dell'Edera made substantial contributions to conception and design. Rosalba Ardea Dell'Edera and Maria Teresa Dell'Edera, contributed to the acquisition, analysis and interpretation of data. Arianna Allegretti were involved in drafting the manuscript. Domenico Dell'Edera gave final approval of the version to be published. All authors read and approved the final manuscript.

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