Case Report

Array CGH - A Powerful Tool in Molecular Diagnostic of Pathogenic Microdeletions - Williams-Beuren Syndrome - A Case Report

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ABSTRACT: Williams-Beuren syndrome (WBS) (OMIM 194050) is caused by interstitial deletions or duplications of the *7q11.23* chromosomal region and characterised through a complex phenotype. We described a case diagnosed clinically and genetically confirmed through aCGH. Genetic assessment identified three microdeletions with a total size of 1.35 Mb located at *7q11.23*. The deleted regions encompasses more than 30 genes including several protein coding genes such as *ELN, LIMK1, FZDS, WBSCR22, WBSCR27, WBSCR28, STX1A, CLDN3, CLDN4, LAT2, ABHD11* or *EIF4H* .

KEYWORDS*: array CGH, 7q11.23 microdeletion, Williams-Beuren syndrome, global developmental delay*

Introduction

Submicroscopic deletions and duplications are involved in the pathogenesis of multiple clinical conditions characterised through global developmental delay (GDD), intellectual deficiency (ID), multiple congenital anomalies and dysmorphic features. Resolution of conventional cytogenetic methods does not allow detection of this type of chromosomal rearrangements, but development of array comparative genomic hybridization (aCGH) techniques has facilitated the identification and molecular characterization of submicroscopic and subtelomeric deletions and duplications. Furthermore, it allows identification of genomic breakpoints and genes content of the chromosomal regions affected by deletions or duplications [1,2].

Since 2010, genetic testing through aCGH for detection of microdeletetions or microduplications, also known as copy number variants (CNVs), is recommended by ISCA (International Standards for Cytogenomics Arrays) consortium to be used as first-line test in the assessment of individuals with GDD, ID, multiple congenital anomalies and dysmorphic features [3].

Williams-Beuren syndrome (WBS) (OMIM 194050) with an incidence of 1/7500 – 1/20000 live births and characterised through neurodevelopmental delay, DI, dysmorphic features, cardiovascular and connective tissue abnormalities, growth, endocrine and behavioral problems is caused by interstitial deletions or duplications of the *7q11.23* chromosomal region [4-6]. The first clinical cases were described in 1956 and 1961 by Schlesinger, respectively Williams and Beuren, while the genetic substrate of this condition represented by CNVs located on long arm of *chromosome 7 (7q11.23)* was unknown until 1993 [4,7-11].

Here we report a 5-year-old boy with 3 microdeletions in the region *7q11.23* involving multiple genes, including *ELN*. The main clinical features in this boy are neurodevelopmental delay, cardiac abnormalities and specific dysmorphic features. We performed aCGH to identify the breakpoints and genes content of the deleted regions. Based on this powerful method, we present the molecular characterisation of 3 de novo microdeletions (*7q11.23 (72,755,027-73,494,802) x1dn*; *arr 7q11.23 (73,508,114-73,952,117) x1 dn*; *arr 7q11.23 (73,980,005-74,142,690) x1dn)* of the WBS critical region identified in a patient with a severe and complex phenotype.

Methods

The extraction of genomic DNA was performed from blood lymphocytes of the patient using Wizard® Genomic DNA Purification Kit (Promega, Madison, WI, USA), following the manufacturers protocol. DNA quantity and quality was assessed using the Agilent 2010 Bioanalyzer (Agilent Technologies Inc., US). High-resolution microarray analysis was realized with the 135K oligonucleotide aCGH platform, on a 3×720K slide (Roche NimbleGen, Madison, WI, USA). DEVA

software (Roche NimbleGen, Madison, WI, USA) was used to data extraction. Copy number data was analyzed with Nexus 6.1 software (Nexus BioDiscovery, El Segundo, CA).

Clinical Report

The proband is the first child of healthy unrelated Caucasian parents. He was born at 39 weeks of gestation by caesarean delivery due to breech presentation, after a normal full-term pregnancy. Apgar score was 7, 9 at 1, 5 min, respectively and birth parameters where at mean: (birth weight: 2800 g; birth lenght: 48 cm; and head circumference: 35 cm). From the first month of life, the child was diagnosed with a severe congenital cardiac malformation: coarctation of the aortic arch associated with pulmonary artery stenosis and patent ductus arteriosus. So that, he required surgical interventions performed at age of 3 and 8 months, respectively.

The boy had a delayed psychomotor development: he started walking and emitted his first syllables at 16 months. At the age of 3 years was referred to the Pediatric Psychiatry Service because of speech delay and behavioral disorder. Physical and clinical evaluation revelead a reduced growth (L = 100 cm (25th percentile), W = 15 kg (25th percentile) and HC = 47 cm (less than 3rd percentile)) associated with mild ID (IQ = 49) and speech delay (his vocabulary consisted of only 10 simple words). The boy presented additional problems such as hyperkinetic episodes with self-aggression, autistic spectrum features, namely stereotypes and repetitive play, transient hypercalcemia, strabismus and distinctive facial dysmorphism characterised through broad forehead, flat nasal bridge, short upturned nose, long philtrum, and wide mouth with full lips and small jaw.

Based on the severe and complex phenotype of unknown etiology, the child was admitted for evaluation to Medical Genetics ambulatory, Clinical Hospital of Craiova, Romania. Genetic assessment through aCGH identified three microdeletions with a total size of 1.35 Mb located at *7q11.23 (chr7: 72,755,027-73,494,802; 73,508,114-73,952,117 and 73,980,005-74,142,690, National Center for Biotechnology Information coordinates) (Fig.1).*

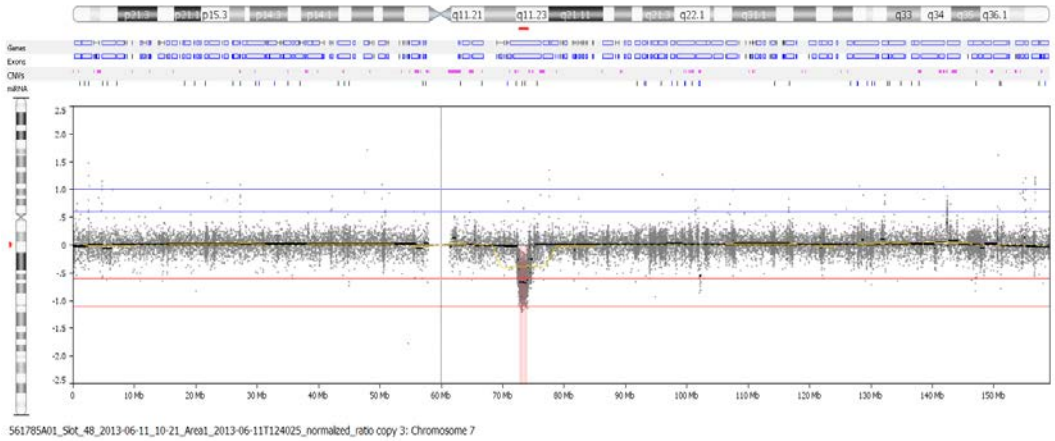

Fig.1. Array CGH result on chromosome 7. Image generated with Nexus 6.1 software (Nexus BioDiscovery, El Segundo, CA). Data extraction (signal intensities) was performed with DEVA software (Roche Nimblegen)

Fig.2. Molecular kayotype of the patient generated with Nexus 6.1 software (Nexus BioDiscovery, El Segundo, CA).

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According to the aCGH analyses result, the molecular karyotype of the patient was arr 7q11.23 (72,755,027-73,494,802) x1 dn; arr 7q11.23 (73,508,114-73,952,117) x1 dn; arr 7q11.23 (73,980,005-74,142,690) x1 dn (Fig.2).

The deleted regions encompasses more than 30 genes including several protein coding genes such as FKBP6, ELN, LIMK1, FZD9, TBL2, WBSCR22, WBSCR27, WBSCR28, STX1A, CLDN3, CLDN4, LAT2, ABHD11, RFC2, CLIP2, GTF2IRD1, GTF2I, TRIM50 or EIF4H (Fig.3).

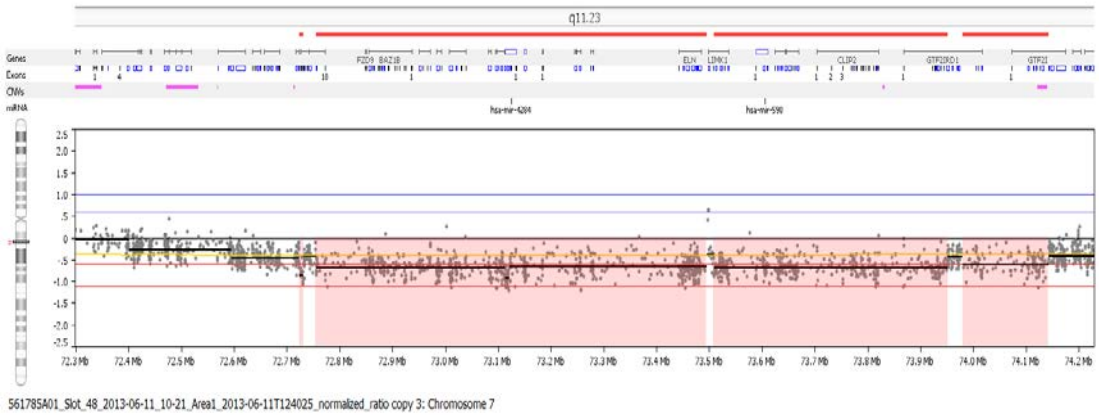

Fig.3. Genes content of the deleted regions

Discussion

Since 1993, *7q11.23 region* is known as the WBS region. It was reported that CNVs (microdeletions / microduplications) located in this region are responsible for the WBS complex phenotype characterised through multi-system involvement and variable expressivity [4].

The main clinical features reported as pathognomonic signs for WBS are distinctive facial characteristics (broad forehead, short upturned nose, long philtrum, or small jaw), cardiovascular abnormalities (supravalvular aortic stenosis, pulmonary artery stenosis, coarctation or aortic arch hypoplasia, ventricular septal defects, tetralogy of Fallot or atrioventricular canal persistence), connective tissue anomalies, growth and endocrine problems, neurological impairment (hyperreflexia, cerebellar dysfunction, strabismus, sensorineural hearing loss, hypotonia or brain malformations) and characteristic neurocognitive and behavioral phenotype (mild-moderate ID, impaired capacity to reorient in the environment and detect social threats, high sociability, strong verbal abilities associated with lack of depth in understanding, anxieties, depression, autism, sleep difficulties, attention deficit) [4-6,12-36]. The present case showed many clinical signs reported as being specific for WBS, namely severe cardiovascular anomalies (coarctation of the aortic arch associated with pulmonary artery stenosis and patent ductus arteriosus), transient hypercalcemia, strabismus, growth difficulties, particular behavior and distinctive facial dysmorphic features like broad forehead, flat nasal bridge, short upturned nose, long philtrum, wide mouth with full lips and small jaw.

The clinical assessment togheter with the results of the genetic testing indicate that is the first case of classic WBS clinically diagnosed and genetically confirmed through aCGH in the South-West region of Romania. The most widely used genetic method to confirm the clinical diagnoses of WBS is FISH with *elastin* gene as probe performed on metaphase chromosomes. This technique is not very expensive, but has several important disadvantages: does not detect the exact size and genes content of the detected CNVs (microdeletion / microduplication), is labor-intensive and time-consuming and it cannot be used in the cases harboring atypical CNVs [4]. Conversely, methods like qPCR, MLPA (multiplex ligation-dependent probe amplification) or aCGH that detect small CNVs through DNA analysis are very sensitive, mapp the size of the microdeletion / duplication, offer valuable information regarding the affected genes (aCGH) and allow the processing of multiple samples from different patients within the same run [37-39]. Thus, aCGH testing of our patient detected three microdeletions located in the *7q11.23* region and also provided information regarding their size, the breakpoints

and genes affected by the deletions: *ELN, LIMK1, FZD9, TBL2, WBSCR22, WBSCR27, WBSCR28, STX1A, CLDN3, CLDN4, LAT2, ABHD11, RFC2, CLIP2, GTF2IRD1, GTF2I, TRIM50* and *EIF4H*, details that would not have been revealed if only FISH evaluation had been performed. This results revealed that the microdeletions carried by our patient are located in the genome region commonly affected in WBS. It also shown evidences that the deletions involved the elastin gene (*ELN*) which may partly explain the severe cardiac anomalies identified in this case. Since 1993, has been established that haploinsufficiency of *ELN* that comprises 33 exons is responsible for the cardiovascular and connective tissue abnormalities identified in WBS [10,40]. *FKBP6, BAZ1B* and *WBSCR22* are other genes contained in the deleted region, strongly expressed in the cardiovascular structures, that might explain the pathogenesis of the described cardiac deffects. Duplication of *FKBP6* gene, component of the synaptonemal complex, was reported to be associated with congenital hearth deffects [41]. Furthermore, knock-out animal studies showed that hetero-/homozygous deletions of the *BAZ1B* gene are associated with cardiac anomalies like multiple atrial and muscular ventricular septal deffects or hypertrophy of both ventricles. These data outline the important role of *BAZ1B* gene in the normal development and function of the hearth [4]. Recently, it was shown that the haploinsufficiency of this gene might be also involved in the neurodevelopmental impairment and specific dysmorphism described in patients diagnosed with WBS [42,43]. There are no data available in the literature regarding the association of *WBSCR22* gene mutations with cardiovascular abnormalities.

Another gene affected by the microdeletion detected in our case was LIM kinase 1 (*LIMK1*) that is mainly expressed in the central nervous system and involved in organization of the actin cytoskeleton by modulating actin depolymerization [4]. Based on the fact that actin remodeling was associated with the formation and maintenance of memory and learning [44], *LIMK1* impairment by the microdeletions reported in our case could partly explain the abnormal neurobehavioral phenotype identified characterised through stereotypes, repetitive play and impaired detection of social threats [45,46]. These clinical findings might be also explained by the functonal impairment of *FZD9, STX1, GTF2I, GTF2IRD2* or *EIF4H* genes contained in the affected genomic region. These genes are highly expressed during the development and differentiation of central and peripheral nervous system structures [4,47,48]. Accordingly, several studies linked the *GTF2I* (*general transcription factor IIi*) gene with the pathogenesis of autism spectrum disorders described in WBS [49-51]. Haploinsufficiency or genetic variations such single nucleotide polymorphisms (SNPs) of *GTF2I* were reported to be associated with the cognitive-behavioral phenotype of WBS [49,52]. Furthermore, experimental studies showed that the transmembrane cell surface receptor encoded by the *FZD9* gene is involved in hippocampus development and defects of this gene are associated with learning and memory disorders [43,53]. Our clinical report sustains the hypotheses raised by previous studies that the genes mentioned above gene might be candidate genes responsible for the development of the WBS neurocognitive profile, namely the autistic-like features. Also, other genes (*TBL2, CLDN3, CLDN4, LAT2, ABHD11, RFC2, CLIP2 or TRIM50*) located in the region affected by the microdeletions detected in our case was shown to have important roles in the development and functions of the nervous system or other organs [4,54]. Thus, all these findings could explain the complex phenotype described in our patient diagnosed with WSB.

In summary, we describe a typical case of WBS genetically confirmed through aCGH testing. The result of the aCGH testing also contributed through the detection of the affected genes to establish a proper follow-up of the patient, mainly focused on the prevention of possible severe complications related to the severe cardiovascular phenotype identified such as sudden dearth or portal hypertension [55] or to the defects of the tumor suppresor genes contained in the deleted region (*BCL7B, CLDN3* or *CLDN4*) [4,56,57] that could threaten the patient's life.

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Ioana Streață and Simona Șerban-Șoșoi contributed equally to this work.

F. Mixich and M. Ioana contributed equally to this work.

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