Case Report

9q34 & 16p13 chromosome duplications in autism

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Abstract: Epigenetic mechanisms, genetic factors, and environment influence the diversity of phenotypes developed in various diseases. Duplications in several chromosomes are well characterized in the scientific literature, but partial duplications, in some cases, present with milder forms of a disease and are yet to be understood. Fortunately, the identification of genetic diseases has now become more feasible due to several cytogenetic techniques such as microarray analysis and karyotyping. With these tools, together with other laboratory results and clinical examination, we are able to report the first case in the medical literature of double partial trisomy of chromosome 9q34 and 16p13.

Keywords: Chromosome duplication; genetic; karyotyping; microarray; trisomy 9 syndrome; chromosome 16 duplication

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Introduction

The duplication or partial trisomy of chromosome 16p13 and chromosome 9q34 has been documented in the scientific literature (1,2). The duplication of chromosome 9 (trisomy 9p syndrome) is characterized by developmental delay, hypotonia, growth delay, facial and body malformations, and intellectual disability (ID). Additionally, other congenital defects in the heart, kidneys, skull, muscles, and nervous system have been identified (3). However, these defects vary according to which area of the chromosome is affected and by the length of the duplication (1,4). *De novo* 9q34 duplication presented with frontal bossing, deep-set eyes, facial anomalies (long and narrow), micrognathia, high nasal bridge, asymmetric ears, arachnodactyly, and other congenital malformations (5). The 9;15 translocation, 9q34 duplication, and 15q21q25 deletion resulted in ID, facial anomalies, hypotonia, and cardiac and renal malformations (6).

The partial trisomy of chromosome 16 duplication is characterized by ID, facial asymmetry, developmental delay, growth deficiency, and several congenital anomalies (7). Few cases of chromosome 16 duplication have been reported, as most individuals carrying the trisomy die during their childhood (2). The "critical" area at position 16p13.1–p13.3 was not affected in our patient (7,8). To our knowledge, region 16p13.13–p13.12 has previously been mentioned as a duplication, but no studies have been directed at this area (2). However, deletions of 16p13.13 delayed degradation of the Janus kinase 2 gene protein in B-cell lymphoma, and single nucleotide polymorphisms (SNPs) have been identified in cases of multiple sclerosis (9,10). Duplications of 16p13.13–p13.12 are yet to be understood.

We report the case of a 6-year-old male patient with non-consanguineous parents, carrying two duplications in chromosomes 9 and 16 and who had been diagnosed with autism spectrum disorder (ASD). Our patient presented with a mild form of trisomy 9 syndrome, but the characteristics associated with the duplication or partial duplication of chromosome 16 were—and remain—unclear.

Case presentation

Our patient was a 6-year-old boy with developmental delay. He was the first child of healthy, non-consanguineous Puerto Rican parents. His mother's family history was remarkable for Jarcho-Levin syndrome (JLS). His mother

Table 1 This table summarizes the clinically significant findings for each of the genes involved in both partial duplications

Gene	Location	Clinical significance
Chromosome 9q34		
WDR5	9q34.2	Chemoresistance
RNU6ATAC		–
RXRA		–
MIR4669		CHD
COL5A1	9q34.3	Ehlers-Danlos syndromes
LOC101448202		–
MIR3689A		–
MIR3689C		–
MIR3689D1		–
MIR3689B		–
MIR3689D2		–
MIR3689E		–
MIR3689F		–
FCN2; FCN1		Recurrent respiratory infections, immune deficiency, poor prognosis in ischemic stroke
OLFM1		Expressed in the cortex and hippocampal retina
Chromosome 16p13		
CLEC16A	16p13.13	Diabetes mellitus, multiple sclerosis, rheumatoid arthritis, autoimmune thyroid disease, systemic lupus erythematous
SOCS1		–
TNP2; PRM3; PRM2; PRM1		Male infertility
RMI2		Bloom syndrome
LITAF		CMT disease, type 1C (AD)
SNN		–
TXNDC11		–
ZC3H7A		–
BCAR4		Breast cancer and other cancers
RSL1D1		Prostate cancer
GSPT1		–
TNFRSF17		Inflammatory bowel disease
SNX29	16p13.13–p13.12	–

CMT, Charcot-Marie-Tooth.

had no previous abortions. He was born at 39 weeks of gestation to a 21-year-old mother. He weighed 5.2 lbs. and measured 48.26 cm. There were no complications during the pregnancy. At birth, he presented with macrocephaly and mildly dysmorphic facial features, but no body malformations were noted. We received him at 13 months of age at which time he evidenced macrocephaly and developmental delay. At 13 months, he could not sit by himself, which suggested psychomotor delay. He also presented with an abnormal curvature of the spine in the cervical area, with no other joint abnormalities. The physical examination revealed decreased muscle tone (hypotonia), dysmorphic features (micrognathia and macrocephaly), and a heart murmur.

Laboratory studies revealed high ammonia levels (148 ug/dL) and a lactate (18.8 mg/dL) to pyruvate (0.4 mg/dL) ratio of 47. Total and free carnitine levels were 68 and 50 umol/L (ratio =0.74) respectively. Therefore, he was treated for a metabolic disorder. We also ordered a karyotype analysis, which showed a normal 46, XY male karyotype with normal G-banding. Due to the child's developmental delay, a magnetic resonance imaging was performed, the results of which showed that his ventricles, basal cisterns, and cerebral sulci all were prominent in size; no other abnormalities were seen. At 3 years of age, the child was clinically stable, but mental disability persisted. He was diagnosed with ASD after a psychological consultation.

Now 6 years of age, the patient is responsive and alert but is unable to verbalize. He also can walk normally and does not present body dysmorphic features, but mild hypotonia continues. His ears are symmetric but slightly larger than his parents', measuring 5.5 cm; he has a head circumference of 54 cm. A microarray analysis was performed to determine whether the boy suffered from a genetic disease.

Results

A microarray analysis of peripheral blood sample showed approximately 982 kb duplication of the long arm of chromosome 9 (9q34.2 to 34.4) and approximately 1.6 Mb duplication of the short arm of chromosome 16 (16p13.13 to p13.12). Refer to *Table 1*.

Chromosome 9 duplication

Partial duplications of genes *WD repeat domain 5* (*WDR5*) and *olfactomedin 1* (*OLFM1*) were identified, but the

expressions of the proteins have not been analyzed, and therefore it is unclear whether their expression was affected by their partial duplication. In addition, complete duplications of genes *RNA*, *U6atac small nuclear* (*U12-dependent splicing*) (*RNU6ATAC*), *retinoid X receptor alpha* (*RXRA*), *microRNA 4669* (*miR4669*), *collagen type v alpha 1 chain* (*COL5A1*), *LOC101448202*, *microRNA 3689C* (*miR3689C*), *microRNA 3689D1* (*miR3689D1*), *microRNA 3689B* (*miR3689B*), *microRNA3689D2* (*miR 3689D2*), *microRNA 3689E* (*miR3689E*), *microRNA 3689F* (*miR3689F*), *ficolin 2* (*FCN2*), and *ficolin 1* (*FCN1*) were also identified.

Chromosome 16 duplication

Partial duplications of *C-type lectin domain containing 16A* (*CLEC16A*) and *sorting nexin 29* (*SNX29*) were identified, but their expressions were not submitted for analysis, and it is unclear whether their expressions have been affected by the partial duplication. In addition, complete duplications of genes *suppressor of cytokine signaling 1* (*SOCS1*), *transition protein 2* (*TNP2*), *protamine 3* (*PRM3*), *protamine 2* (*PRM2*), *protamine 1* (*PRM1*), *RecQ mediated genome instability 1* (*RMI1*), *lipopolysaccharide induced TNF factor* (*LITAF*), *stannin* (*SNN*), *thioredoxin domain containing 11* (*TXNDC11*), *zinc finger CCCH-type containing 7A* (*ZC3H7A*), *breast cancer anti-estrogen resistance 4* (*BCAR4*), *ribosomal L1 domain containing 1* (*RSL1D1*), *G1 to S phase transition 1* (*GSPT1*), and *TNF receptor superfamily member 17* (*TNFRSF17*) were also identified.

Discussion

To our knowledge, none of the duplications discussed herein have been studied, or reported on in any medical or scientific publication. By analyzing the clinical relevance of each duplicated gene and observing the patient's progress, we attempted to estimate and/or hypothesize the function of the gene or genes being analyzed. However, for genes *RNU6ATAC*, *LOC101448202*, *SNN*, *TXNDC11*, and *ZC3H7A*, no clinically relevant information was found.

WDR5 is expressed in greater quantities in the testes. Its overexpression has been linked to poor breast cancer prognosis and has been shown to promote both cancer-cell proliferation and chemo-resistance in bladder cancer (11,12). *WDR5* has been shown to regulate bone growth *in vivo* (13).

RXRAs are located in the nuclei of various cells. *RXRA* has been shown to interact with vitamin D receptors to make a complex that interferes with *RXRA* chromatin localization and resists the inhibitory effects of 1α,25-dihydroxyvitamin D3. It is also being studied as a cancer therapy (14). Microduplication in 9q34.2–34.3 (*RXRA*'s location) was associated with congenital heart defects in 13 out of 25 patients (15).

Mutations in the *COL5A1* gene are associated with Ehlers-Danlos syndromes and with life-threatening vascular abnormalities. However, only a small percentage of patients show vascular abnormalities (16). Our patient did not have any indications of a collagen disease.

Noncoding miRNAs have been described in the literature as regulators of several cellular mechanisms (17). Overexpressed *miR569* has been identified in ovarian cancer (18). Additionally, Alzheimer's disease, has been associated with the overexpression of hippocampal *miR-34c*, and mice lacking *miR9-2* and *miR9-3* have shown defects in mesencephalic structures (19,20). Our patient presented duplications in *miR4669*, *miR3689A*, *miR3689C*, *miR3689D*, *miR3689B*, *miR3689D2*, *miR3689E*, and *miR3689F*. To our knowledge, these ncRNAs have yet to be understood. Mutations in *miR3689* are is a possible marker for B-cell acute lymphoblastic leukemia (21). We hypothesize that the duplication of one or more of these ncRNAs might be involved in brain development, as our patient was diagnosed with ASD. We also hypothesize that the overexpression of these genes was involved in the regulation of the other genes that were duplicated in this child, as he did not present the typical signs of 9q34 duplication syndrome.

FCN1 and *FCN2* are involved in the immune response (22-24). *FCN1* is expressed in granulocytes and monocytes and is released in secretory granules. It has been hypothesized that an increase of *FCN1* might promote neutrophil adhesion, aggregation, and migration and consequently cause tissue damage. *FCN2* levels decrease after ischemic stroke (25). There is a correlation between developing type 1 diabetes at an early age and SNP in *FCN1*, while SNP in *FCN2* is associated with pulmonary disease (23,24,26). *FCN2* has been shown to enhance phagocytosis, and low levels of this protein are related to immune deficiency and recurrent respiratory infections (22,24,27). Our patient did not present problems with his immune system.

OLFM1 is mainly expressed in the cortex and hippocampal retina, and is associated with neurogenesis, cell-cycle regulation, and tumorigenesis (28-30). In animal models, the overexpression of *OLFM1* causes excessive

migration of the neural tube, enlargement of the neural tube, and thickening of the optic tectum (31-33). The inhibition of *OLFM1* causes ocular problems, such as reduced eye size and poor extension of the optic nerve (33). In mice, *OLFM1* interacts with schizophrenia-1-gene protein (34). These findings together with the phenotype observed in our patient could suggest that *OLFM1* might also be related to ASD development in humans. However, more studies should be done to substantiate this claim.

There have been several genome-wide association studies that have related *CLEC16A* to the development of several diseases, such as systemic lupus erythematosus, multiple sclerosis, type one diabetes, juvenile arthritis, alopecia, rheumatoid arthritis, primary adrenal insufficiency, and biliary cirrhosis (35-43). *CLEC16A* is important for autolysosome function in Purkinje cells, and homozygous mutations in this gene cause neurodegenerative disease that manifests as motor impairment (44). Mice lacking *CLEC16A* presented with low levels of B cells and immunodeficiency (45).

The *SOCS1* protein interacts with IFN-alpha receptor 1 and the TNF-gamma receptor to inhibit STATs activation. *SOCS1* can also attenuate Toll-like receptor-mediated modulation of T-cell response. Its overexpression might protect against multiple sclerosis and tumor development because of its *JAK/STAT* attenuation effects (46).

Transition nuclear protein two gene mutations have been associated with reduced and abnormal sperm and, consequently, infertility (in mice) (47). Another study identified SNPs in the *TNP2* genes of infertile human males (48). *PRM1* and *PRM2* SNPs have been strongly associated with male infertility because of their essential function in sperm maturation (49). *PRM3* has also been associated with sperm production (50). Duplications of these genes still need to be understood, but because of the role that these duplications have in chromatin condensation, it is possible that having increased levels of these proteins might lead to hyper-condensed chromatin.

Mutations in *RecQ*-mediated genome instability proteins 1 and 2 have been identified in a mild form of Bloom syndrome in a twin study (51). Xu *et al.* [2008], also associated *RMIs* with Bloom syndrome.

LITAF is a 161-amino acid protein that is associated with the highly hereditable Charcot-Marie-Tooth (CMT) type C disease (52,53). Our patient did not present any psychomotor delay during his first years of life.

Genetic abnormalities in BCAR4 have been implicated in breast cancer. The prognosis of patients with BCAR4 is worse when *BCAR4* levels are highly elevated compared to those with lower levels of *BCAR4* (54). High *BCAR* expression is also associated with poor prognosis in prostate cancer (55,56).

Li *et al.* [2016] associated the overexpression of RSL1D1 with poor prognosis in prostate cancer and postulated it as a possible biomarker of the disease.

Tumor necrosis factor superfamily 17 is involved in immune responses and B-cell maturation. This gene has been posited as being a marker for inflammatory bowel disease (57).

The grandmother of our patient had had two spontaneous abortions; both fetuses had been diagnosed with JLS. This syndrome is associated with the *MESP2* gene, an abnormality in 9q34 (58). However, while our patient did not present a duplication in *MESP2*, this data could suggest that the family carries an anomaly in chromosome 9. A microarray analysis of gene expression should be performed on the mother to determine if she carries a mutation in chromosome 9. Finally, the phenotype presented by our patient could be associated with genetic factors, epigenetic changes, environmental influences, or a combination of these. The duplication in chromosome 16 might have a protective effect on the duplication in chromosome 9 or vice versa. Duplications in chromosome 16 are commonly lethal mutations, but patients that survive their presence have overlapping phenotypical features that are similar to those found in trisomy 9 syndrome. However, due to the lethality of trisomy 16 a well-established diagnosis has yet to be developed.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/acr.2020.03.07). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the parents of the patient for the publication of this case report.

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