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Case Report

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Pleiotropic manifestation of pathogenic ACTB gene in Baraitser-Winter Syndrome

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Keywords

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Abstract

Actin Beta (ACTB) gene is located on chromosome 7p22.1 and encodes for an essential component of the cytoskeleton. Genetic aberrations lead to loss or gain of function variants which affects beta cytoplasmic actin protein. We present a case of Baraitser Winter Syndrome type (BWS) 1 with a missense heterogenous pathogenic variant in ACTB gene, which manifested as a large atrial septal defect, bilateral inguinal hernia and hydronephrosis, dysmorphic features and lissencephaly. The scope of this paper is to understand the pathogenomics and phenotypic expression of this heterozygous pathogenic ACTB gene mutations. And also emphasize on the exome sequencing, genetic counselling andexploring the option of preimplantation genetic testing.

Introduction

Baraitser-Winter Syndrome (BWS) is a rare developmental disorder with pleotropic manifestations affecting multiple organ systems. It is characterised by intellectual disability and distinctive facial appearance which involves trigonocephaly, bilateral ptosis. (1)It is inherited as autosomal dominant pattern whichpasses from the parent to the offspringwith complete penetrance.(2) The incidence is <1 in a million population worldwide with less than 60 cases reported in the literature. (3)The age of onset is usually in neonatal and infancy period.The BWS is associated with Actin-Beta (*ACTB*)gene that encodes for beta cytoplasmic actins. This actin protein polymerizes to form crosslinked networks, responsible for motility and contraction of the cell. Actin protein usually exists in dual forms ie. G-actin, a globular monomeric form and F-actin forms helical polymer, which are highly conserved and intrinsically flexible structures. (4)Considering the variable expression of the actin proteins, clinical manifestations lead to classification of Baraitser-Winter Syndrome into Type 1, 2 and 3.Genetic counselling including reproductive counselling is necessary to explore the futureof the next pregnancies in a family with positive child.

Case report

8 months old male African child presented to Paediatric Cardiology OPD with symptoms of increased sluggishness, failure to thrive, vomiting, generalized edema and growth retardation. The parents observed these changes since the baby was 2 months. On physical examination, umbilical hernia, hypotonia, global developmental delay was observed. Ultrasound of the abdomen shows hydronephrosis of the kidney. While the CT scan of brain showed rare brain malformation in the form of Lissencephaly. Electroencephalogram (EEG) showed normal electrical activity. Biochemical parameters showed hyponatremia, hypochloremia and decrease free T3 levels, suggestive of hypothyroidism. There was no family history of developmental disorders and the parents didn't have consanguineous marriage.

The baby was therefore recommended whole exome sequencing by next generation sequencing due to the above clinical findings. Exome sequencing was performed to sequence 20,000 genes located on the exons that reorganizes nosology for many developmental disorders. Aheterozygous missense pathogenic variant of ***(NM_001101) gene ACTB c.587G>A p (A196H)*** was detected. This missense mutation causes an amino acid change from Arginine to Histidine at position 196and is classified as Class 1 according to American College of Medical Genetics and Genomics (ACMG) guidelines. The pathogenic variant of ACTB gene is known to be involved in the pathogenesis of the Baraitser-Winter syndrome type 1.

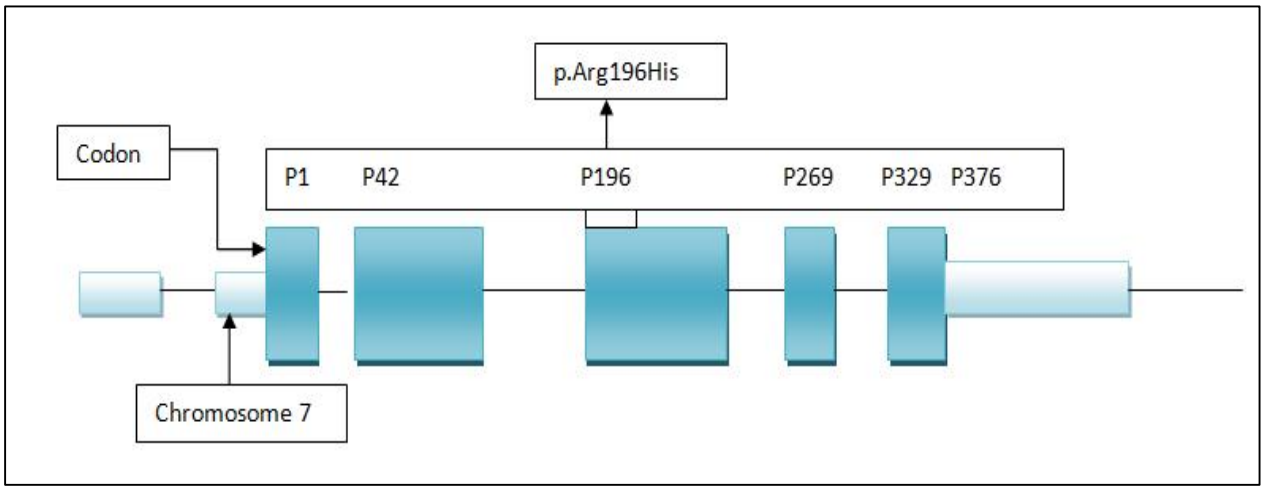

Figure 1: The following diagram represents the mutation spectrum of the given patient who is diagnosed with*gene ACTB c.587G>A p (A196H*) mutation

Discussion

The Baraitser–Winter cerebrofrontofacial syndrome (OMIM #243310, #614583) is associated with missense mutations in the cytoplasmic beta- and gamma-actin genes *ACTB* and *ACTG1* .(5) It was first reported by Baraitser and Winter in 1988 in a female child with the affected siblings with a different condition.(1)

The *ACTB* gene provides direction for making a protein called beta (β)-actin, which is part of the actin protein family. Proteins in this family are arranged into a matrix of fibers called the actin cytoskeleton, which makes up the structural framework inside cells.(6).There are six types of actin; four are present only in muscle cells, where they are involved in the tensing of muscle fibers (muscle contraction). The other two actin proteins, β-actin and gamma (γ)-actin (produced from the ACTG1 gene), are found in cells throughout the body. These proteins play important roles in determining cell shape and controlling cell motility. β-actin may also be involved in relaying chemical signals within cells.The syndrome can be classified into three different subtypes with regard to the different types of molecular genetic testing, which involve BWS Type 1 , BWS type 2 and BWS type 3.(6)

Pathogenic *ACTB* variant are associated with de novo autosomal dominant Baraitser-Winter syndrome type 1 is caused due to mutations in the ACTB gene which is present of chromosome 7.(7) Phenotypically, it is characterized by the combination of hypertelorism, broad nose with large tip and prominent root, ridged metopic suture, arched eyebrows, sensorineural deafness, shoulder girdle muscle bulk and progressive joint stiffness, rarely lissencephaly or neuronal heterotopias. They also show a cleft lip and palate and hallux duplex.(3)

Baraitser–Winter syndrome type 2 is a rare complex genetic condition with craniofacial, muscular, and visceral involvement due to missense mutations in ACTG1 and with dysregulation in the function of cytoplasmic actin, there are a wide range of effects in cranial neural crest derivatives during development. *ACTG1* gene encrypts for the cytoskeletal protein γ-actin, which functions in non-muscle cells and is abundant in the auditory hair cells of the cochlea. Autosomal dominant missense mutations in *ACTG1* are also associated with DFNA20/26, a disorder that is typically characterized by post-lingual progressive hearing loss. (8)

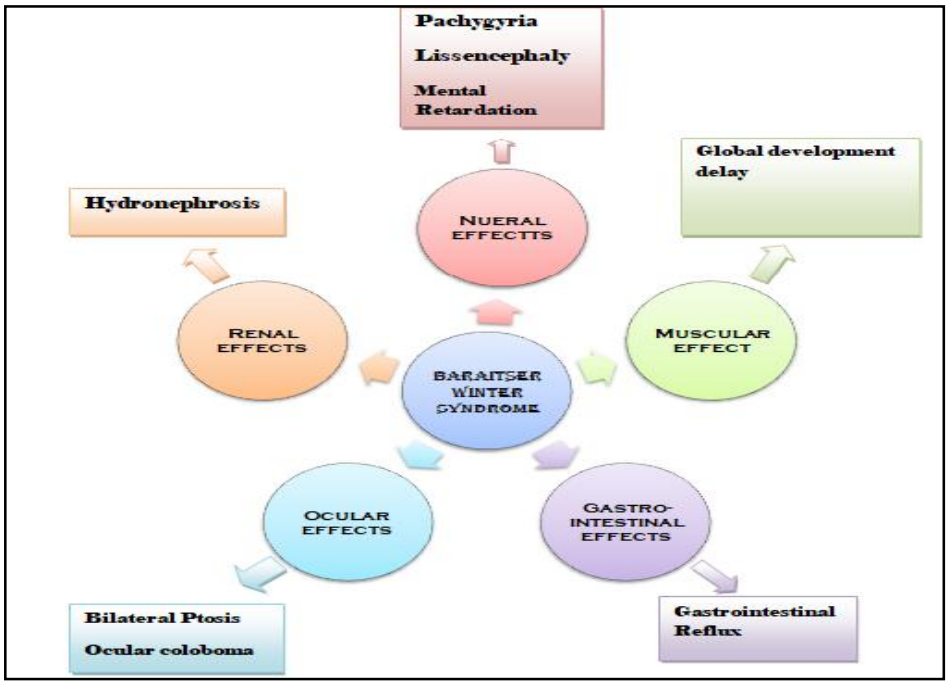

Figure 2: Clinical Symptoms of Baraitser Winter Syndrome.

After studying several reports, Winter suggested that Baraitser Winter syndrome type 3 (BWS3) had frontal agyriaepachygyria or polymicrogyria, coarse traits, hypertelorism, congenital ptosis, macroblepharon, arched eyebrows, broad nasal root and bridge, long philtrum, macrostomia, thin upper lip, high arched palate, micrognathia, low-set and posteriorly rotated ears with abnormal, pinnae, and short-webbed neck are the characteristic traits of BWS3. DNA investigations reveal that c.586C>T mutation (p.Arg196Cys) in ACTB leads to the BWS3. Mental retardation, trigonocephaly, loose skin, bifid thumbs or halluces, limitation of movement in large joints, narrow thoraxwith dysplastic nipples, and genitourinary anomalies were also described. (9)(10)(11)

The present study describes a case of autosomal dominant Baraitser winter syndrome type 1, which is heterozygous pathogenic variant identified in the *ACTB* gene. The patient was found out to have ***ACTB, c.5867G>A p.Arg196His*** missense pathogenic mutation class 1. This variant causes change in amino acid from arginine to histidine at position 196. Clinically, this gene is associated with rare developmental disorder affecting multiple organ systems. The common symptoms are intellectual disability, distinctive facial appearance which involves trigonocephaly, bilateral ptosis. The supplementary presence of malformations and ocular colobomata are also suggestive of this syndrome. Other features include moderate low stature, fixed tightening of muscle or skin, congenital cardiac disease and genitourinary malformations .(11) The most common brain disorder in association with Baraitser-Winter syndrome is pachygyria, which is an area of the brain that has an unusual smooth surface with fewer folds and grooves.(3) The present case showed umbilical hernia, hypotonia, global developmental delay, hydronephrosis of the kidney and rare brain malformation in the form of Lissencephaly. A congenital heart defect in the form of ostiumsecundum atrial septal defect with deficient rims shunting left to right, dilated right atrium and right ventricle, laminar mitral valve inflow and no tricuspid regurgitation. It was also found out that the patient had a bilateral superior vena Cava, left SVC to dilated coronary sinus. The biventricular function was observed to be normal.

Exome sequencing is tested with next-generation sequencing, it is now practical to sequence large amounts of DNA, for instance all the pieces of an individual's DNA that provide instructions for making proteins. Massive parallel sequencing or massively parallel sequencing is any of several high-throughput viewpoints to DNA sequencing using the theory of massively parallel processing or second-generation sequencing. These pieces, called exons, are thought to make up 1 percent of a person's genome. All together, the exons in a genome are known as the exome, and the method of sequencing them is known as whole exome sequencing. This method allows discrepancy in the exonic region of any gene to be identified, rather than in only a select few genes. Because most known mutations that cause disease occur in exons, whole exome sequencing is thought to be an efficient method to identify possible disease-causing mutations.(12)

The genetic counseling is recommended to family members of patients with this abnormality. In this patient, pre implantation genetic testing was offered to prevent the further birth of future progeny. Genetic counseling is mandatory and it provides knowledge about genetic conditions might affect you or your family. The objective of genetic counseling is to expand understanding of genetic diseases, discuss disease management options and explain the risks and benefits of testing. Counseling sessions focus on giving vital, unbiased information and non-directive assistance in the patient's decision-making process.(13)

Conclusion

BWS amusingly portrays how new molecular diagnoses are reconceiving and expanding the clinical spectrum of what we previously consider as distinct syndromes, and how NGS technologies, by deciphering the molecular basis of clinically defined entities, will reorganize nosology for many developmental disorders.

Baraitser winter syndrome is a rare autosomal dominant disease which is cause due to mutation in the ATCB gene which is characterised by intellectual disability and distinctive facial appearance which involves hypothyroidism, trigonocephaly, bilateral ptosis. According to our literature BWS is an extremely rare case of a complex developmental autosomal dominant disorder with craniofacial, visceral and muscular involvement. Although the criteria for diagnosis are hard, the facial phenotype seems most relevant and reliable handle at all ages.

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