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Case Report

Further phenotypic expansion of 15q11.2 BP1-BP2 microdeletion (Burnside-Butler) syndrome

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Abstract. We report a 10-year-old Caucasian male identified with copy number variation detected by microarray analysis including a maternally inherited 15q11.2 microdeletion involving 4 genes, paternally inherited 13q12.2 microdeletion with 10 genes, and a de novo 2q14.3 duplication involving four genes. He had a history of speech delay, cognitive deficits, attention deficit hyperactivity disorder and a posterior lenticonus cataract removed at 5 yr of age. The genes on chromosomes 2 and 13 are not known to be involved with cataract formation, which lends further support for a role of the 15q11.2 region and additional evidence for phenotypic expansion of the 15q11.2 BP1-BP2 microdeletion (termed Burnside-Butler) syndrome.

Keywords: Microarray analysis, motor and language delay, congenital cataracts, dysmorphic features

1. Introduction

The proximal long arm of chromosome 15 contains five common breakpoints (BP1, BP2, BP3, BP4, and BP5). Deletions involving the typical proximal BP1 breakpoint and distal BP3 breakpoint in the 15q11-q13 region or proximal BP2 and distal BP3 breakpoints are best known to cause both Prader-Willi syndrome (PWS) and Angelman syndrome (AS), depending on the parent of origin (a paternal deletion in PWS and a maternal deletion in AS) [1, 2]. Hence, the classical 15q11-q13 deletion seen in PWS and AS is flanked by either the proximal BP1 or BP2 breakpoints and the more distal BP3 breakpoint. This acrocentric chromosome contains about 4% of the genome and has a cluster of low copy DNA repeats, which are located at the common 15q11-q13 breakpoints and mediate deletions or duplications. These clustered DNA repeat regions allow chromosome 15 mis-pairing at meiosis and subsequent non-allelic homologous recombination [3, 4]. Individuals with PWS and AS with the larger type 1 deletion involving breakpoints BP1 and BP3 are reported with a more severe phenotype than individuals with the smaller type 2 deletion involving BP2 and BP3 [5–8].

The genomic region between breakpoints BP1 and BP2 spans approximately 500Kb and contains four genes (*NIPA1, NIPA2, CYFIP1,* and *TUBGCP5*) that are evolutionarily conserved and biallelically

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expressed [9]. Three of these genes (*NIPA1, NIPA2,* and *CYFIP1*) are implicated in central nervous system development and/or function and become candidates to study for developmental/behavioral abnormalities when deranged. The best-studied gene in this region is *NIPA1,* which is associated with spastic paraplegia [10, 11] then followed by *CYFIP1* which encodes a protein found in synaptosomal extracts. The *CYFIP1* gene product interacts with *FMRP*, the protein produced by the *FMR1* gene, which is responsible for the Fragile X syndrome. Fragile X syndrome is the most common cause of familial intellectual disability and primarily affects males [12]. Disturbed expression of these genes due to copy number changes appear to impact on behavioral and neurological function in affected individuals and particularly in those with PWS having the type 1 or type 2 15q11-q13 deletion [5–13].

To more thoroughly address an association of genes located between breakpoints BP1 and BP2 in the 15q11-q13 region, Burnside et al. [14] summarized patients presenting primarily due to developmental/behavioral problems for genetic services and testing at a large commercial laboratory. They found 146 of approximately 17,000 patients (or 0.86%) studied with microarray analysis had a copy number alteration of the 15q11.2 BP1-BP2 region. Of the 146 unrelated individuals (69 with a deletion and 77 with a duplication) clinical information was available on 56 with a microdeletion, and 49 with a microduplication. They proposed that this genomic area was a susceptibility region for neurological dysfunction including developmental motor and language delay, behavioral problems, autism, seizures and mild dysmorphic features [14–17]. Hence, the 15q11.2 BP1-BP2 microdeletion/microduplication (termed Burnside-Butler syndrome) was established and characterized.

To further expand the phenotype, Wong et al. [18] reported two unrelated patients with unique findings not previously observed in this cytogenetic syndrome, one individual had a proximal esophageal atresia and distal tracheoesophageal fistula (type C), while the second patient presented with congenital cataracts. They suggested that the tracheoesophageal findings and congenital cataracts may be included in the phenotypic spectrum of the 15q11.2 BP1-BP2 microdeletion or Burnside-Butler syndrome. More recently, Usrey et al. [19] reported two unrelated patients with congenital arthrogryposis and the 15q11.2 BP1-BP2 microdeletion by microarray analysis not seen previously in this syndrome. We will now describe a second patient with cataract formation to further support the clinical observation by Wong et al. [18] with this cytogenetic syndrome.

2. Case report

Our patient was a 10-year-old Caucasian male with copy number variation detected by microarray analysis using a 180K oligonucleotide array performed by CombiMatrix Diagnostics (Irvine, CA). Microarray findings included a maternally inherited 15q11.2 microdeletion, a paternally inherited 13q12.12 microdeletion, and a *de novo* 2q14.3 duplication. He had a past medical history of speech delay, attention-deficit/hyperactivity disorder, and bipolar disorder not otherwise specified. Additionally, he was found to have a congenital history of posterior lenticonus cataract of the right eye, diagnosed at 1 yr of age. Posterior lenticonus cataracts are known to be associated with certain genetic conditions, including Alport syndrome and oculocerebrorenal Lowe syndrome [20, 21]. Our patient did not have features seen in these rare, single-gene conditions. Our patient's eye condition was first medically managed by giving phenylephrine drops twice daily and patching 8 h a day. However, opacity of the cataract gradually increased over time and became amblyogenic. His vision was at best corrected to 20/60, at which time surgical intervention was recommended. Extracapsular cataract extraction occurred at 5 yr of age. He has done well since.

The patient was the product of an uncomplicated pregnancy, without evidence of exposure to infections, diseases, or teratogens. He was delivered vaginally at term, weighing 2,890 g (15th percentile). There were no postnatal complications. He met most developmental milestones on time or early, with the exception of speech, in which he would leave out the beginning or ending of words, or sometimes, entire words. At the age of 3 yr, his hearing evaluation was normal. Consequently, he was placed in a high-risk pre-kindergarten program, where he was engaged in an individualized education plan for speech and attended speech therapy sessions. At age 7 yr, he was evaluated at a child health and developmental center where the Wechsler intelligence scale for children, fourth addition, testing and Vineland II adaptive behavior scale were administered. His cognitive testing results were variable, scoring at the 32nd percentile for verbal comprehension, 21st

percentile for perceptual reasoning, 4th percentile for working memory, and 1st percentile for processing speed. Behavioral testing revealed adaptive behavior and communication skills to be below average. Daily living skills and social skills were moderately low. He had an ongoing tendency to exhibit aggressive behaviors toward family members. He socialized poorly with his peers.

Family history revealed that his younger, 8-year-old brother had the same chromosome 13 and 15 deletions inherited from the parents. He also had speech delay, but was otherwise healthy. He had a younger half-sister who did not have any chromosomal abnormalities or medical conditions. His 32-year-old mother had a history of mild learning disability, requiring an individualized education plan in the school setting during childhood. His 36-year-old father had a history of speech delay. Both parents were employed. Consanguinity was denied.

A physical examination done at 10 yr of age revealed microcephaly (head circumference: 49.3 cm; <3rd percentile), speckled irides bilaterally, a replacement lens in the right eye secondary to cataract removal, over folded ears bilaterally, mild pectus excavatum and inverted nipples bilaterally. He had transverse palmar creases bilaterally and clinodactyly of the 3rd and 4th toes. He had no other dysmorphic features and was otherwise healthy.

3. Discussion

Chromosomal microarray testing, confirmed by fluorescence in situ hybridization (FISH), revealed a 350Kb deletion (at 20,290,385–20,640,325 bp from pterminus) of maternal origin, del(15)(q11.2q11.2) (RP11-80H14-). Loss of genetic material of the 15q11.2 region included the four highly conserved genes: *CYFIP1, NIPA1, NIPA2* and *TUBCGP5*. His developmental delays, autistic features, behavioral disturbances, attention deficit hyperactivity disorder, and mild dysmorphic features are all characteristic of the 15q11.2 BP1-BP2 microdeletion or Burnside-Butler syndrome, associated with derangement of genetic material between breakpoints BP1 and BP2 on chromosome 15. Additional array findings included a paternally derived 1.3 Mb deletion (at 22,385,973–23,818,065 bp), del(13)(q12.12q12.12) (RP11-88F2-), including *C1QTNF9, C1QTNF9B, C1QTNF9B-AS1, LINC00327, MIPEP, MIR2276, SACS, SGCG, SPATA13* and *TNFRSF19*, and a de novo copy number gain at 2q14.3 (at 127,551,174-127,799,009 bp), including *BIN1* (partial), *CYP27C1*, *ERCC3*, and *MAP3K2* (partial). An online Mendelian inheritance in man (OMIM) gene search did not identify any of the missing or duplicated aforementioned genes on chromosomes 2 or 13 to be associated with congenital cataracts, these copy number variants (CNVs) playing a role in the phenotype cannot be entirely ruled out [22]. However, the cataract formation seen in our patient and the report of congenital cataracts by Wong et al. [18] in a patient with the same 15q11.2 BP1-BP2 microdeletion or Burnside-Butler syndrome is further evidence of expanding the phenotype in persons with this cytogenetic microdeletion syndrome.

Studies to target rare CNVs and their contributions to complex developmental pathways and phenotypes are ongoing including a recent report of global CNV burden to the risk of sporadic congenital heart disease (CHD) [23] whereby 12 patients with CHD had 15q11.2 microdeletions from a large CHD cohort ($n = 2{,}256$). The microdeletion encompassed the four genes between breakpoints BP1 and BP2 generating an odds ratio of 8.2 ($P = 0.02$). In addition, a recent genome-wide association study of large rare CNVs in Alzheimer's disease was reported among Caribbean Hispanics [24]. A nominal association was found between Alzheimer's disease and a 470Kb duplication of the 15q11.2 region including the four genes of interest. The dosage increase for *CYFIP1* and *NIPA1* genes was confirmed by quantitative PCR. Hence, clinical heterogeneity is associated with chromosome 15 aberrations involving the 15q11.2 BP1-BP2 region and influences clinical outcomes and incomplete penetrant phenotypes.

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