Burnside-Butler Syndrome Genotype-Phenotype Associations

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The 15q11.2 BP1-BP2 deletion (Burnside-Butler) syndrome is emerging as the most common cytogenetic finding in patients with neurodevelopmental or autism spectrum disorders (ASD) presenting for microarray genetic testing. Clinical findings in Burnside-Butler syndrome include developmental and motor delays, congenital abnormalities, learning and behavioral problems, and abnormal brain findings. To better define symptom presentation, we performed comprehensive cognitive and behavioral testing, collected medical and family histories, and conducted clinical genetic evaluations. The 15q11.2 BP1-BP2 region includes the *TUBGCP5*, *CYFIP1*, *NIPA1*, and *NIPA2* genes. To determine if additional genomic variation outside of the 15q11.2 region influences expression of symptoms in Burnside-Butler syndrome, whole-exome sequencing was performed on the parents and affected children for the first time in five families with at least one parent and child with the 15q1l.2 BP1-BP2 deletion. In total, there were 453 genes with possibly damaging variants identified across all of the affected children. Of these, 99 genes had exclusively de novo variants and 107 had variants inherited exclusively from the parent without the deletion. There were three genes (*APBB1*, *GOLGA2*, and *MEOX1*) with de novo variants that encode proteins evidenced to interact with CYFIP1. In addition, one other gene of interest (*FAT3*) had variants inherited from the parent without the deletion and encoded a protein interacting with CYFIP1. The affected individuals commonly displayed a neurodevelopmental phenotype including ASD, speech delay, abnormal reflexes, and coordination issues along with craniofacial findings and orthopedic-related connective tissue problems. Of the 453 genes with variants, 35 were associated with ASD. On average, each affected child had variants in 6 distinct ASD-associated genes ($\bar{x}$ = 6.33, sd = 3.01). In addition, 32 genes with variants were included on clinical testing panels from Clinical Laboratory Improvement Amendments (CLIA) approved and accredited commercial laboratories reflecting other observed phenotypes. Notably, the dataset analyzed in this study was small and reported results will require validation in larger samples as well as functional follow-up. Regardless, we anticipate that results from our study will inform future research into the genetic factors influencing diverse symptoms in patients with Burnside-Butler syndrome, an emerging disorder with a neurodevelopmental behavioral phenotype.

Keywords: 15q11.2 BP1-BP2 deletion ; Burnside-Butler syndrome ; clinical findings ; cognition ; neuropsychiatric behavior development ; genomic characterization ; exome sequencing ; protein–protein interaction

1. Introduction

Chromosome 15 abnormalities have been reported for a number of years in the medical literature, specifically for Prader-Willi (PWS) and Angelman (AS) syndromes, the first examples of genomic imprinting in humans [1][2][3][4]. These disorders are generally due to a chromosome 15q11-q13 deletion depending on the parent-of-origin (i.e., PWS—paternal, AS—maternal). The typical 15q11-q13 deletions are classified as either Type I with deletions involving the proximal 15q breakpoint (BP1) and a distal 15q breakpoint (BP3), or Type II relating to a smaller 15q11-q13 deletion involving a second proximal breakpoint (BP2) and distal BP3. The larger Type I deletion is approximately 6 Mb and includes the *TUBGCP5*, *CYFIP1*, *NIPA1*, and *NIPA2* genes, while the smaller Type II deletion is approximately 5.5 Mb with all four genes intact [5].

Clinical and behavior differences have been reported for the past 15 years involving specific deletion classes in both PWS and AS. For example, individuals with PWS or AS having the Type I deletion, generally have more learning and behavioral problems compared to those with the Type II deletion [6][7]. Specifically, patients with PWS and larger deletions have more compulsions and maladaptive behaviors, as well as lower cognition, reading and math skills when compared to PWS patients with smaller deletions [3][5][6][8]. In AS, more impaired speech and seizure activity are noted in individuals with the larger deletion [4].

The emerging 15q11.2 BP1-BP2 microdeletion (Burnside-Butler) syndrome (BBS) encompasses the region between the PWS/AS chromosome 15q deletion breakpoints and includes the *TUBGCP5*, *CYFIP1*, *NIPA1*, and *NIPA2* genes. This microdeletion was consistently reported in early studies of patients presenting with unexplained behavioral, cognitive, and/or psychiatric problems [9][10][11]. Ho et al. [12] later summarized the results of ultra-high microarray single nucleotide polymorphism (SNP) analysis and found this microdeletion to be the most common cytogenetic finding observed in over 10,000 consecutive patients studied and presenting for genetic services with features of ASD or other neurodevelopmental disorders. Furthermore, a systematic literature review by Cox and Butler [10] found over 200 individuals reported with this microdeletion and grouped the clinical findings into five categories: (1) developmental, speech, and motor delays (73%, 67%, and 42% of cases, respectively); (2) dysmorphic ears and palatal anomalies (46%); (3) writing and reading impairment, memory problems, and verbal IQ scores ≤ 75 (50–60%); (4) general behavior problems, unspecified (55%); and (5) abnormal brain imaging, including a smaller brain surface with a thicker cortex (43%).

Notably, the four genes encoded in the 15q11.2 BP1-BP2 region are syntenic, bi-allelically conserved, and functionally predicted to interact with each other along with seven other genes (i.e., *IGFBP2*, *CFHR1*, *CFHR3*, *MNS1*, *SPG20*, *BMPR2*, and *SPAST*) recently reported and analyzed via in silico studies and STRING functional interactions network [13]. Rafi and Butler [13] also found that the encompassed four protein-coding genes showed 11 nodes and 34 edges. Network nodes represent proteins with splice isoforms or post-translational modifications collapsed into each node for all proteins produced by a single protein-coding gene. Edges represent protein–protein associations that jointly contribute to a shared function. These genes are at the center of our focus on genomics and clinical findings in individuals with the 15q11.2 BP1-BP2 deletion.

2. Discussion

This study is the first of its kind to characterize phenotypic, behavioral, and cognitive measures combined with exome sequencing in families with the 15q11.2 BP1-BP2 deletion. An initial goal was to determine if the sequences of one or more of the four genes in the 15q11.2 BP1-BP2 region showed a variant inherited from the parent with the intact (non-deleted) chromosome. When disturbed, the four genes in the 15q11.2 region are associated with cognitive impairment, speech and/or motor delay, dyslexia, and psychiatric/behavioral problems (e.g., attention deficit hyperactivity disorder (ADHD), autism, schizophrenia, or psychosis). The cardinal disease associations for the four contiguous genes in the 15q11.2 BP1-BP2 region are: *NIPA1*—Spastic Paraplegia 6; *NIPA2*—Angelman syndrome and Prader-Willi syndrome; *CYFIP1*—fragile X syndrome and autism; and *TUBGCP5*—Prader-Willi syndrome. The four genes are individually associated with PWS, ASD, schizophrenia, epilepsy, and Down syndrome. Collectively, all four genes have been associated with up to 75% of patients with ten distinctive neurodevelopmental disorders [13].

The addition of newly reported findings including ataxia, poor coordination, seizures, and congenital anomalies including palatal, heart, and ear defects along with structural brain disturbances [11] which are also associated with the four genes in the 15q11.2 BP1-BP2 region raises the question of whether these genes interact with other genes, their biological processes or molecular functions. These related genes may play a role in the clinical presentation causing core features of Prader-Willi and Angelman syndromes as additional clinical structural differences are seen in those with the four genes deleted in the typical 15q11-q13 Type I deletion seen in these syndromes. For example, dysfunctional variation in the *NIPA1* and *NIPA2* genes could impair the function of magnesium transport as both genes encode magnesium transporters [14][15]. Their biological processes and molecular functions could regulate axonogenesis and axon extension via relationships with bone morphogenetic protein (BMP) and signaling pathways, regulations of cellular and developmental growth, and interaction with the *FMR1* gene causing fragile X syndrome [13]; all pertinent and relevant to the reported variable clinical phenotypes seen in this microdeletion syndrome. We used whole-exome sequence data to identify other genes outside of the deleted region with possibly damaging variants to help detect genetic effects underlying expression of symptoms in the affected child bringing the family to medical attention. Detailed physical examinations and family pedigrees were performed, for the first time, by an experienced clinical geneticist trained as a dysmorphologist to characterize the phenotype and review of systems on each subject. In addition, cognitive and behavior testing, including motor assessments for ataxia or balance disturbances of each family member, were performed using various validated techniques and tests by experts in the field. These studies were the major outcome measures for comparison with the genomic data and analysis for similarities among our families with the 15q11.2 BP1-BP2 deletion.

2.1. Clinical and Neuropsychiatric Behavior Developmental Findings

We did not identify consistent patterns of cognitive impairments across individuals with 15q11.2 BP1-BP2 microdeletion syndrome. General cognitive, academic, and receptive vocabulary abilities were relatively intact with only one participant, Subject 11, not able to complete standardized IQ testing, showing indications of intellectual/developmental delay. Similarly, verbal memory abilities appeared to be unaffected across the majority of participants, though 3/10 participants showed mild deficits in suggesting that more selective issues in verbal memory and learning may impact a subset of individuals with the 15q11.2 BP1-BP2 microdeletion. Similarly, multiple participants (4/10) showed executive deficits characterized by a reduced ability to flexibly shift response sets. These participants were largely nonoverlapping with those showing verbal memory issues indicating that these cognitive effects may be relatively distinct across individuals with 15q11.2 BP1-BP2 deletion syndrome. Several children had a history of learning problems reported by parents, school records, or neuropsychological evaluations.

Our results suggest that individuals with 15q11.2 BP1-BP2 deletions have increased risk for ASD. The prevalence of ASD in the general population is estimated to be 1 in 54 (1.8%) [16]; however, in our sample, we found that 3/6 (50%) of affected children met testing standards for a diagnosis of ASD and 2/5 (40%) of affected parents demonstrated elevated autistic traits (one additional child, Subject 3, and one additional parent, Subject 10, scored just below the cutoff for the ADOS-2 and BAP-Q, respectively). Consistent with high rates of ASD and ASD-related traits in our sample, we observed high rates of repetitive behavior in a majority of our participants with 5/6 affected children and 3/5 adults demonstrating severity of repetitive behavior that is comparable to similarly aged persons with ASD [17]. Of note, our sample of 15q11.2 BP1-BP2 deletion carriers (parents) may actually underrepresent the prevalence of ASD in the population of these carriers since persons who are parents and those who volunteer to participate in research and travel significant distances are likely to represent a cohort with relatively mild symptoms. Notably, all of the affected children were observed to have variants in multiple genes that were associated with ASD or found on the intellectual disability testing panel.

One limitation to classification of ASD in this sample is the use of only one observational diagnostic tool (the ADOS-2), rather than using a combination of clinical observation, parent interviews and strict DSM-V criteria to confirm diagnosis; however, scores on the ADOS-2 combined with scores on the Vineland and RBS-R strongly indicate elevated rates of ASD and ASD-related traits in our sample. Similar to findings from studies of individuals with idiopathic ASD, the majority of our participants (9/11) showed adaptive functioning abilities below the mean for their age. These findings suggest that the 15q11.2 BP1-BP2 deletion confers increased risk for ASD and functional impairments independent of selective impacts on cognitive abilities.

Most of the individuals in this sample presented with at least one dysmorphic feature, some of which were present across multiple families. Five had abnormal ear findings such as broad, soft, fleshy, or overfolded ears. The child of Family C also had a smooth upper lip and philtrum. In the case of Family E, both the father and child had a broad, round face as well as broad hands. Flat feet were present in three individuals. Both the mother and child of Family B had small upper incisors. Six of the participants had eye findings demonstrating ptosis including both affected individuals from Family C and the father of Family E. The connective tissue finding of mild scoliosis was observed in two unrelated individuals whereas kyphosis was found in one other participant. Hyperextensibility or instability of various joints was a common feature, with unrelated individuals demonstrating a positive Beighton hyperflexibility score of at least six out of nine showing hypermobile joints. The 6-year-old child of Family A had a history of ankle instability and wore leg braces. Leg asymmetry was also found in two unrelated individuals. Pectus carinatum was seen in one individual while four participants had loose, soft skin, and two unrelated individuals had birth marks. Two unrelated affected children had a reported history of delayed wound healing.

Neurological problems were also present in several children. Two were diagnosed with epilepsy, one had non-essential tremor, and the child of Family D had gross hypotonia. The mother and child of Family D were both found to have decreased deep tendon reflexes, whereas the child of Family B had increased deep tendon reflexes. Ataxia was seen in the child of Family E. Motor delay was also relatively common, with four affected children showing delayed motor milestones. Motor deficits in affected individuals were also evident in our tests of postural control. While this test does not have normed scores or clinical cutoffs, group averages and effect sizes indicate that both children and adults with the 15q11.2 BP1-BP2 microdeletion show increased variability of postural sway relative to non-affected controls. This is consistent with findings of increased variability of motor behavior in neurodevelopmental disorders including Prader-Willi syndrome [18], ASD [19][20], and fragile-X associated disorders [21], and involvement of ataxia-related genes in 15q11.2 BP1-BP2. Of note, all affected children had PDVs in genes evidenced to cause ataxia, epilepsy, comprehensive cardiovascular defects, and neuronal migration disorders. In addition, many children had PDVs in genes involved in connective tissue disorders, cerebral cortical malformations, micro/macrocephaly, and congenital malformations with craniofacial defects that are included on the clinical cleft palate DNA testing panel.

2.2. Protein–Protein Interactions and Functions Related to NIPA1, NIPA2, CYFIP1 and TUBGCP5 Genes in the 15q11.2 BP1-BP2 Region

Of particular interest are the genes that had either a de novo variant, or a variant inherited from the parent without the deletion that encode proteins that interact with products of the four genes in the 15q11.2 BP1-BP2 region. As reported by Rafi and Butler [13] when examining the protein–protein interactions of the four genes in the 15q11.2 BP1-BP2 region, the predicted biological processes can be summarized as follows: regulation of cell growth, magnesium ion transmembrane transport, regulation of axonogenesis, regulation of plasma membrane bounded cell projection organization, positive regulation of axon extension, regulation of cellular response to growth factor stimulus, regulation of developmental growth, positive regulation of cell projection organization, mitotic spindle organization, regulation of BMP signaling pathway, and positive regulation of plasma membrane bounded cell projection assembly.

Notably, NIPA1 protein was observed in our previous study to interact with 11 other proteins. Five (45%) of the 11 proteins were members of the BMP superfamily, three (27%) were BMP receptors and TGFB1 (9%) protein, indicating that three-fourths of the NIPA1 interacting proteins are important for developmental bone morphogenesis or multifunctional proteins that control proliferation, differentiation, and other functions in many cell types. The NIPA2 protein interacted with 19 other proteins with three (16%) involved with the BMP protein superfamily, three (16%) proteins interact with BMP receptors, ACVR1, TGFBR1, and six members of the SMAD superfamily of proteins (42%); all playing a role as intracellular signal transducers and transcriptional modulators activated by TGFB, thereby impacting bone morphogenesis and its related functions. Specifically, the Spastin protein, encoded by *SPAST,* was observed to interact with both NIPA1 and NIPA2. A variant in *SPAST* was found in Subject 9. This child had hypotonia and history of fine and gross motor delay as well as autism. Spastin severs polyglutamylated microtubules and likely has a role in axon growth and branching [22][23]. Mutations in both *SPAST* and *NIPA1* have been identified as causes of hereditary spastic paraplegia, a condition which causes progressive weakness and spasticity of the legs [24][25]. De novo variants in *SPAST* are evidenced to be associated with ASD with comorbid spastic paraplegia [26].

The CYFIP1 protein is also reported to interact with other proteins having a wide range of activity with functions related to cytoskeleton organization and actin filament binding with cell-matrix adhesion, MAP kinase signal transduction of cell growth, survival and differentiation, stimulation of glucose uptake, intracellular protein breakdown and tissue remodeling with mediation of translational repression [27]. We observed that five additional genes with either a de novo or non-deleted parent inherited variant in the affected child encode proteins that interact with CYFIP1. *GOLGA2* encodes a protein that acts as a membrane skeleton that maintains the structure of the Golgi apparatus. Mouse models of this gene indicate its involvement in brain morphology and the development and quantity of neurons [28][29]. Loss of this gene also resulted in ataxia in mice [28]. Subject 2 had a PDV in this gene as well as a disturbed motor phenotype, ASD, and neuropsychiatric behavior developmental phenotypes. *MEOX1* encodes a mesodermal transcription factor that plays a key role in somitogenesis, specifically sclerotome development. *MEOX1* is involved in overall organism development in humans [30] and mutations in mice result in evidence of congenital neurological disorders [31]. Subject 7 had a de novo PDV in *MEOX1* along with connective tissue defects, congenital malformations, epilepsy, and neuropsychiatric behavior developmental phenotypes. Finally, *FAT3* encodes an atypical cadherin protein and may play a role in the interactions between neurites derived from specific subsets of neurons during development. While *FAT3* was not included in any of the disease association categories we directly evaluated, missense mutations in this gene are associated with the neurodevelopmental disorder, Hirschsprung disease (https://www.ncbi.nlm.nih.gov/clinvar/RCV000201304.1/). Both Subjects 2 and 3 had a PDV in this gene and evidence of a neurodevelopmental phenotype and should be monitored for gastrointestinal issues.

2.3. Identified Gene Variants with Potential Clinical Significance

As the first effort to identify variants in the four 15q11.2 BP1- BP2 genes in this microdeletion syndrome, we analyzed the non-deleted alleles in affected patients and assessed family members as well, using whole-exome sequencing in order to compare the genomic data of related genes with clinical, cognitive, and behavioral data. Some of these variants are identified by the gene panels as potentially contributing to multiple phenotypes in our subjects, as in the case of *MLC1*, which was a candidate for macrocephaly and motor delay in Subject 9 and for contribution to epilepsy in Subject 7. All variants passing inclusion criteria for possibly damaging the gene in which it is located, and the corresponding evidence for clinical significance of having a variant in the gene, can be found in Supplemental Table S1 (could be downloaded in https://www.mdpi.com/1422-0067/22/4/1660).

Other particular genes of interest with PDVs include numerous genes of the collagen or COL group which code for proteins that make up various subtypes of collagen. Disturbances in these genes are known to cause several connective tissue disorders [32]. For example, in addition to the stop-loss variant in the connective tissue disorder gene *FLCN*, Subject

5—who had significant joint hyperextensibility—inherited a frameshift in *COL5A3* from the parent with the deletion. Additional missense variants in collagen-encoding genes, *COL21A1* and *COL6A2*, were inherited from the non-deleted parent in Subject 7, who had joint hyperflexibility. Specifically, variation in *COL6A2* is associated with Ullrich congenital muscular dystrophy 1 (https://omim.org/entry/254090) (accessed on 6 February 2021). Subject 9 had an inframe deletion in *COL4A3* and a missense variant in *COL6A6* that was inherited from the deleted parent. While no joint hyperflexibility was noted, this patient had flat feet which may reflect collapse of connective tissues of the midfoot. Dysfunction in collagen proteins may also manifest as other symptoms. *COL4A3*, for instance, is implicated in disorders resulting in renal failure (https://omim.org/entry/120070) (accessed on 6 February 2021) and Subject 9 was also noted to have a history of constipation. Furthermore, variation in *COL6A6* has been implicated in skin disorders [33]. Subject 11, also without joint hyperflexibility, had the same missense variant identified in *COL6A6* and had birthmarks noted on the thigh and forehead.

Finally, *CDK19* gene is another candidate explaining clinical findings in Subject 11 who had a de novo missense variant in this gene. A disturbance in this gene has been associated with bilateral congenital retinal folds, microcephaly, and intellectual disability [34]. Of these findings, intellectual disability was present in Subject 11.

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