EXPLORING THE ROLE OF WFS1 VARIANTS IN BIPOLAR DISORDER

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Background: Bipolar Disorder (BPD) is an exceptionally heritable psychiatric illness. Methods for identifying the underlying genetic variations associated with BPD have primarily included Genome Wide Association Studies (GWAS). While this method has identified genomic loci linked to the disorder, these loci contribute only a small percentage of BPD's heritability in any single individual. Furthermore, these studies have failed to lead to a better understanding of BPD's pathophysiology.

Materials/Methods: We have enrolled 26 individuals with juvenile onset BPD and performed a detailed family history revealing that > 50% of these individuals have a first degree relative with BPD. DNA was collected from these individuals along with respective family members, array Comparative Genomic Hybridization (aCGH) performed on all probands, and exome sequencing of all affecteds from each family. By exome sequencing these families, we have identified several genes with potentially deleterious variants segregating with BPD in multiple families. We discovered variants in WFS1 segregating with BPD in five families. In order to investigate the role WSF1 in BPD, we are creating drosophila harboring loss-of-function mutations in wsf1, the Drosophila homolog of WSF1. We will then express the human orthologue, WFS1, via the GAL4/UAS system with the pan-neuronal elav-GAL4 and pan-glial repo-GAL4 drivers. We will express either wild-type WFS1 or WFS1 harboring one of the BPD associated variants.

Results: Previous studies have revealed knockdown of wsf1 in neurons and glial cells cause age-dependent behavioral deficits, and neurodegeneration, revealing loss of wsf1 causes neuronal dysfunction.

Conclusions: This work highlights the use of cross-species studies in discovering the pathophysiology associated with neuropsychiatric disorders.