The Link between Genetic Abnormalities in the Monogenic Disorders and the Behavioral Phenotype of Polygenic Disorders Has Yet To Be Addressed in Research

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Neurodevelopmental disorders occur worldwide without geographic boundaries. Angelman syndrome, Fragile X syndrome (FXS), Prader-Willi syndrome, Tuberous Sclerosis Complex, Velo-craniofacial syndrome and Williams syndrome, are caused by a known location(s) on a specific chromosome(s) are monogenic disorders. Conversely, Attention-deficit and hyperactivity disorder (ADHD), Autism spectrum disorders (ASD), Bipolar disorder, Rett syndrome, Obsessive compulsive disorder, Schizophrenia and Tourette syndrome are likely caused by unknown common variants of many genes, on many chromosomes, each contributing a subtle effect [polygenic disorders].

Monogenic disorders follow the Mendelian inheritance (autosomal dominant, recessive, X-Linked) which is largely caused by single major genes, the genes involved in these Mendelian disorders could effectively be characterized by linkage analysis and other molecular techniques once the pattern of transmission was established as consistent with a particular genetic model [1]. Conversely, polygenic disorders do not follow the simple Mendel inheritance. They are complex (polygenic) due to imprinting, mitochondrial inheritance, genetic heterogeneity, variable clinical expression, age of onset, and incomplete penetrance. The predisposition of polygenic disorders is determined by a complex interaction of multiple genetic and environmental factors. Therefore, the exact patterns of transmission, the extent of genetic heterogeneity, the specific number of susceptibility loci, and the degree of the interaction between loci in these disorders are unknown.

The link between genetic abnormalities in the monogenic disorders and the behavioral phenotype of polygenic disorders has yet to be addressed in research. A better understanding of the overlap of polygenic characteristics in specific chromosomes known for the monogenic disorders will improve our understanding of the behavioral phenotype of monogenic and the neurobiology/genetics of polygenic disorders. So, the use of genetics, brain morphological and behavioral phenotypes of monogenic disorders as a way forward in the genetic search for polygenic disorders.

Autism has a heterogeneous symptoms’ profile and developmental mechanisms [2,3]. Autism shares many of the phenotypic features with FX [4], however, FX genetics’ are not as complex. Given the apparent phenotypic resemblance between autism and FX, it is imperative to examine the extent to which these disorders share brain biomarkers. In other words, autism and FX may provide a model for understanding how specific genetic factors can influence neuroanatomy, cognition and behavior.

Autism is a behaviorally defined disorder characterized by clinical and genetic heterogeneity affecting the cognitive, social, and emotional domains. The lack of successful therapy, genetic heterogeneity, and the increasing incidence make it one of the most challenging neurodevelopmental disorders. Conversely, FXS, which shares most of the autism behavioral/cognitive phenotype, is genetically defined. Fragile X is the most common single gene cause of autism, responsible for 2% to 6% of all cases of autism, it is clinically recommended that all individuals diagnosed with autism or ASD should have the FX DNA test when etiology of their autism is not known. Approximately 30% of males with FXS have full autism as determined by the standardized criteria of autism diagnostic observation scale (ADOS) and Autism diagnostic interviews revised (ADI-R). Among the remaining patients with FXS, of those who do not meet the criteria for ASD diagnosis, the majority have one or more autistic features, such as hand flapping, poor eye contact and tactile defensiveness [5].

The basis for incomplete penetrance of autism (30%) or PDD-NOS (30%) among individuals with FXS is not yet known. However there is evidence that patients with additional medical disorders that affect the CNS, such as seizures or additional genetic problems, have an increased risk for autism compared with patients with FXS alone [6]. FMR1 mutations that control the growth and maturation of cells and synapses increase risk for autism, but are not strict determinants of autism [7]. Diminished or absent production of the FMR1 protein could lead to aberrant brain development and function. Such a mutation intersects with developmental pathways that influence physical development, cognitive ability and behavior.

For those with both FXS and autism, there is a spectrum of involvement of with significant heterogeneity, both cognitively and behaviorally, with IQ values ranging from severely intellectually impaired to normal, particularly in females. However, there is a strong association between low IQ and autism diagnosis in both males and females with FXS [5]. The cause of this heterogeneity is related to background genetic effects and environmental effects that influence IQ, social abilities, anxiety, ADHD and additional features that are components of FXS phenotype [8].

The absence of FMRP in individuals with FXS has significant consequences in the translation of too many proteins. Because FMRP usually suppresses translation, its absence leads to broad translational upregulation in the hippocampus [9]. Zang et al. [10] have demonstrated linkage between FMRP and many proteins that are related to autism. There is also evidence for up-regulation of mammalian target of rapamycin (mTOR) pathway in the hippocampus of the knockout (KO) mouse and in studies of humans with FXS [11]. The mTOR pathway is dysregulated in several other genetic disorders associated with autism as tuberous sclerosis [12].

Genes known to be causes of ASD interact with the translational
pathway defective in FXS, and it has been hypothesized that there will be substantial overlap in molecular pathways and mechanisms of synaptic dysfunction between FXS and ASD [13]. It was suggested that the difference between the 2 groups in the medial prefrontal and anterior cingulated cortices thickness may entail an altered social cognitive style [14]. Functional MRI studies directly differentiating between social indifference (autism) and social avoidance (fragile X) are needed to further characterize the spectrum of social abnormalities between these 2 groups. Synaptic dysfunction may be a key neural substrate for cognitive and behavioral impairments in FXS.

The detection of molecular and neurobiological similarities between FXS and ASD, so targeted treatments developed for FXS may also target subgroups of ASD, and clinical trials in FXS may serve as a model for the development of clinical trial strategies for ASD and other cognitive disorders. Better understanding of the bases of ASD will require the integration of multidisciplinary data from FXS and other genetic disorders. Individuals diagnosed with autism or ASD are recommended to FX DNA test when etiology of their autism is not known.

Developing countries are facing an alarming gap between innovations in childhood learning and developmental disabilities (LDD) research and their delivery to communities. This gap is now attaining public health significance. On one hand, they prioritize the control and eradication of infectious diseases and reproductive, maternal health. On the other hand, LDD research receives scant attention and almost no funding from donor agencies that specialize in addressing the problems of developing nations. We recommend establishing a scientific-public collaboration to develop and apply global health knowledge for evidence-informed policy and practice.

References


