

Toward Individualized Treatments for Neurodevelopmental Disorders Targeting Metabotropic Glutamate Receptor (mGluR) Genes Impacted by Copy Number Variants



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Abstract

Development of novel therapeutics for neurodevelopmental and neuropsychiatric disorders has long been hampered by heterogeneity among phenotypes, and a lack of understanding of the molecular etiology of relevant disorders. Data from genomic studies, including copy number variants (CNVs) can give us insight into mechanisms and possible treatment targets. Studies from our group and others have identified rare disease-associated CNVs in metabotropic glutamatergic receptor (mGluR) genes in attention deficit hyperactivity disorder (ADHD), autism, and other neuropsychiatric disorders. These studies indicate that a sub-cohort of respective disease populations may be defined by genomic markers, and may respond preferentially to individualize treatment-in this case by targeting the mGluR network. We review relevant studies, including a recent clinical trial, with the objective of delineating potential next steps in translational development.

Keywords: mGluR; Metabotropic glutamate receptor; Neuropsychiatry; ADHD; Autism; Copy number variant; CNV; NFC-1; Fasoracetam; Translation; Attention deficit hyperactivity disorder; Glutamate metabotropic receptor; Monohydrate; Philadelphia; Variant; Monohydrate; Compulsive disorder; Biomarkers; Therapy; Disorder; Participants; Duplication syndrome

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; CHOP: Children's Hospital of Philadelphia; CNV: Copy Number Variant; FMR1: Fragile X Mental Retardation 1; GFIN: Gene Family Interaction Network, GRM: Glutamate Metabotropic Receptor; LTD: Long Term Depression; Mecp2: Methyl CpG binding protein 2; mGluR: metabotropic Glutamate Receptor; NFC-1: Fasoracetam monohydrate; OCD: Obsessive Compulsive Disorder; TDC-1: Tuberous Sclerosis Complex-1

Introduction

Rare Variants as Therapeutic Targets: In the genome era, the "traditional" discovery model has been to leverage large datasets to generate array/sequence data to identify risk loci in disease cases versus controls. This has powered numerous important discoveries across the medical spectrum [1]. However, for neurodevelopmental and neuropsychiatric conditions in particular, the heterogeneity of phenotypes and co morbidity of disorders has hampered discovery and validation of biomarkers [2]. A parallel approach has been to define cohorts based on genomic profile, with (individually) rare variants in (broader) functional networks informing therapeutic intervention.

A recent study of approximately 14,000 individuals sequenced 202 drug-targeting genes, including dopaminergic,

adrenergic, glutamatergic, histaminergic and cholinergic receptor genes-considered potential drug targets, found that 95% of relevant variants were rare (>0.5% population frequency), with 74% found in only one or two individuals [3]. This finding substantiates the strategy of focusing on rare variants as sources for therapeutic targets. The studies below focus specifically on our work with rare variants in the mGluR network, but are broadly applicable to other networks.

Discussion

Attention deficit hyperactivity disorder (ADHD)

ADHD is the most common neurobiological disorder in children, with a prevalence of ~6-8% [4-6], and ~4.5% in adults [7]. Pharmacotherapeutic treatment, typically by way stimulants

achieves amelioration of symptoms in 75-90% of individuals, comparatively high versus other major neurobiological conditions⁸. Nevertheless, with the prevalence of ADHD exceeding 15 million individuals in the United States alone, it is clear that huge numbers who are unresponsive to therapy, while stimulants have been associated with a wide range of common and rare adverse effects [8,9].

A 2011 study from our group compared CNVs in ADHD cases (~3,500) and controls (~12,000), identifying significant enrichment among cases for CNVs directly encoding mGluRs (GRM1, GRM5, GRM7, and GRM8), or involved in the GRM network¹⁰ which includes ~279 genes. In total, GRM-network genes were identified in 11.3% of cases versus 1.2% of controls, with a “core” gene subset (n=79) showing 10-fold enrichment [10]. Evidence from several sources highlight a role of glutamatergic systems in the etiology of ADHD and associated phenotypes. In rats, deleting the code mGluR gene, GRM5, and pharmacologic inhibition of the protein mGluR5 increases spontaneous locomotor activity in rats [11]. In mice, knock-out of GRM7 [12] and GRM8 [13], produces a similar phenotype. Neuroimaging studies have shown increased glutamatergic signalling in fronto-striatal pathways in children with ADHD, as well as autism spectrum disorder and obsessive-compulsive disorder (OCD)-though importantly this effect may be relevant to only a subset of relevant patients. To follow-up on these findings, we initiated a clinical trial of NFC-1 (fasoracetam) - a small synthetic molecule and mGluR activator- in adolescents with ADHD.

mGluR: It is based Clinical Trial In January 2018, we published the results of a five-week Phase Ib Trial of NFC-1 in adolescents with ADHD [6]. This was the first such trial to use the compound-previously developed as an Alzheimer’s therapeutic-in the United States. Participants were selected based on their status as carriers of mGluR risk variants -over 200 patients were screened for mGluR mutations using a SNP array, and 30 were selected based on the presence of a disruptive CNV within/near one or more mGluR network genes. NFC-1 was shown to be safe and well-tolerated. In response to escalating dosages of NFC-1, patients also improved on clinical measures, as assessed by global improvement and severity scales, and ADHD symptom scales. Further, improvements were most pronounced in participants with a CNV in one of 79 Tier-1 genes (n=17)-those genes identified as core to the mGluR network, and least pronounced for those with Tier-3CNVs (n=6)-i.e. CNVs in related gene networks that interact with the mGluR network⁶. Response was also dose-dependent, with larger doses associated with a greater clinical response. Acknowledging the small sample size (n=30) and potential alternative mechanisms of action, these results do suggest that a subset of ADHD cases have deficit(s) in a glutamatergic network that may benefit from individualized treatment. By using a subset of the mGluR network genes related to the best NFC-1 responders in clinical trials, a diagnostic panel could be developed to test those with ADHD and identify those that would respond to mGluR-related compounds such as NFC1.

Given the relatively high comorbidities between ADHD and other neuropsychiatric disorders, we can consider whether such an approach may apply to related disorders. Glutamatergic system abnormalities have been associated with a range of neuropsychiatric disorders schizophrenia [14], anxiety [15], depression [16] autism [17], as well as disorders of the central nervous system [18]. These are discussed below.

Autism spectrum disorder (ASD)

ASD has long been associated with CNVs, and a landmark study by Sebat et al. [19] was important to establishing CNV-based discovery-in this instance identifying a significant difference in the rate of large de novo CNVs between sporadic cases (~10%), multiplex families (~3%) and controls (~1%). In the following decade, studies have catalogued CNVs in ASD and related disorders, with the glutamatergic system prominent across several large studies [20].

Fragile X syndrome is highly comorbid with ASD [21], and ~30% of affected individuals have an ASD phenotype [22,23]. Screening for the causal mutation the 5’ untranslated region of the Fragile X mental retardation 1 (FMR1) gene is systematic for children with ASD symptoms. This mutation decreases expression of the Fragile X mental retardation protein (FMRP) [24-26], which represses mRNA translation associated with downstream activation of mGlu1 and mGlu5. Rodent models of FXS have disrupted long-term depression and long-term activation, associated with abnormal glutamatergic synaptic plasticity and neuronal growth [27,28]. Importantly, mGlu5 agonists have been shown to reverse phenotypic deficits in Fmrp knockout mice [29,30], prompting several clinical trials. Fenobam was tested in an open-label pilot study for the treatment of FXS (no significant adverse effects were observed) [31], and mavoglurant, another mGlu5 negative modulator, improved behavioral symptoms in FXS in two phase IIb trials; however, primary outcome measures (parental observations) were not achieved [32].

Other ASD-related phenotypes also involve glutamatergic dysfunction. Rett Syndrome, caused by loss-of-function mutations in the transcription factor, methyl CpG binding protein 2 (Mecp2) [33]. Knockout or mutation of the Mecp2 gene in mice leads to impairments in glutamatergic neurotransmission, including disrupted long-term potentiation in the hippocampus and NMDA receptor expression [34]. MECP2-Duplication syndrome, another monogenic ASD subtype, but characterized by over expressed Mecp2 protein, has essentially the opposite phenotype. Fisher et al. [35] recently showed that the mGlu7 protein expression is upregulated in the hippocampus of Mecp2-Tg1 mice, though notably this did not translate to a functional increase in mGlu7 activity at SC-CA1 synapses. Tuberous Sclerosis, in whom ASD is present in up to 3.8% of cases [36,37], shows similar evidence of glutamatergic-network dysfunction, and mice with an inactive tuberous sclerosis complex-1 (Tsc1) gene in glia have disrupted astrocyte glutamate transporters with impaired regulation of ionotropic glutamate receptors.

Rodent models show impaired mGlu-mediated long-term depression (LTD) [38,39], and pretreatment of hippocampal slices with the mGlu5 positive modulator CDPPB restored LTD to wild type levels, and normalized protein synthesis [39].

Similar to the ADHD approach outlined above, our group has used a CNV-based network approach to define Gene Family Interaction Networks (GFINs) for ASD17. Leveraging data from several large studies [40-43], we compared CNVs in 6,742 cases and 12,544 neurologically-normal controls. Among the top GFINs was the mGluR pathway, with relevant CNVs in 5.8% of European-derived cases ($P < 2.40 \times 10^{-9}$). Genes with the most significant CNV regions contributing to this overall network significance included all but one of the eight members of the GRM family-GRM1, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8. Other large CNV studies have identified genes in glutaminergic signalling pathway as ASD-associated [41], [44-49], as well as single nucleotide polymorphisms [50,51] and CNV duplications [52] of GRM8 have been reported. These results further implicate rare defects in mGluR signalling beyond monogenic cases (e.g. fragile X and tuberous sclerosis). This is supported by an exome sequencing study by Iossifov et al. [53], demonstrating that loss-of-function mutations were more common in individuals with ASD compared to controls, with relevant mutations overlapping significantly with proteins that interact with the fragile X protein, FMRP. Interestingly, seven of the children in the five-week ADHD Phase Ib Trial of NFC-1 in adolescents with ADHD [6] reported above, had ASD comorbid symptoms and demonstrated robust response to NFC1-1 [6].

Our group recently analyzed five major psychiatric disease cohorts, including 7849 cases and 10,799 controls, in a systematic manner to promote comparability of results, and more importantly to understand the degree to which the shared CNV loci may similarly or differently impact the development of neuropsychiatric disorders [54]. This is the first large-scale CNV meta-analysis across a spectrum of neuropsychiatric disorders. The study found individually rare highly penetrant variants contribute to a common mGluR network variant which is significantly enriched in ADHD and ASD cases-and in those with related comorbidities. This emphasizes a common genetic component involved in the pathogenesis of neuropsychiatric disorders.

Tourette syndrome (TS)

TS is a childhood-onset neurodevelopmental disorder characterized by multiple motor and phonic tics. In addition to tics, patients with TS often experience other neurobehavioral symptoms such as hyperactivity and impulsivity, difficulties with reading and schoolwork, obsessive-compulsive thoughts, and repetitive behaviours. It has been estimated that 90% of patients with TS suffer from comorbid neuropsychiatric disorders, most commonly ADHD and OCD, but also conduct disorder, anxiety and ASD [55-57]. In a recent meta-analysis of TS and ADHD, there is support for a shared genetic basis between the disorders

[58]. Evidence for a shared genetic basis has also been reported between TS and OCD, as well as TS and ASD [59-62].

Treatment of neurobehavioral disorders associated with TS, such as ADHD and OCD, may be complicated as some medications are contraindicated in patients with TS. Consequently, new treatments are needed to treat the spectrum of symptoms of TS, including tics and neurobehavioral disorders. In a recent ADHD clinical trial with NFC-1, an mGluR activator, two of the 30 ADHD clinical trial participants had tics that subsided while the participants were administered NFC-1. The tics re-appeared when NFC-1 was withdrawn at the end of the study. This suggests that other TS subjects with mGluR mutations may similarly respond to NFC-1.

Based on the enrichment of mGluR network genes, the promising clinical trials in ADHD, and the high co-morbidity of ADHD with TS, a pilot study of 95 adolescent patients diagnosed with TS was completed by our group. All subjects had recurrent tics of sufficient duration to meet diagnostic criteria for TS. All 95 subjects were subsequently evaluated for CNVs that are disruptive to mGluR signalling. Among 95 genotyped adolescents with TS, 28 (~29%) had mutations in one or more mGluR network genes. Given the control frequency of patients with CNVs in mGluR network genes is ~1.2% [63], the data suggests that a high proportion of patients with TS might have this pathway disrupted and may be responsive to therapy that reverses the consequences of these mutations. This provides a compelling case for the potential of diagnostics and treatments focused on modulation of mGluR gene networks for treating patients with TS and particularly TS with co-morbidities also associated with mGluR network variants.

Conclusion

Cumulative evidence indicates a shared genetic etiology of neurodevelopmental and neuropsychiatric diseases. Evidence by our group and others has shown enrichment in mGluR network CNVs in ~5-30% of subjects with polygenic neuropsychiatric disorders such as ADHD, ASD, and TS. In addition, glutamatergic-network dysfunction is involved in monogenic disorders with neuropsychiatric phenotypes. These data suggest that mGluR network genes may serve as critical hubs that coordinate highly-connected modules of interacting genes, many of which may harbor CNVs and are enriched for synaptic and neuronal biological functions. The identification of shared structural variants underlying neuropsychiatric disorders helps refine the genetic basis for co-morbidity and co-occurrence among individuals or families. This has the potential to aid the development of common therapeutics for shared genetic targets such as mGluR across different neurodevelopmental and psychiatric diseases.

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Conflict of Interest

- a. Heather Hain has no economic or other conflict of interest to declare.
- b. Joseph Glessner has no economic or other conflict of interest to declare.
- c. John Connolly has no economic or other conflict of interest to declare.
- d. Hakon Hakonarson was founder and equity holder in NeuroFix Therapeutics LLC developing NFC-1, which is now owned by Aevi Genomic Medicine Inc.

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