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Glutamate receptor mutations in psychiatric and neurodevelopmental disorders

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Abbreviations: PNDD, psychiatric and neurodevelopmental disorders; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; BD, Bipolar Disorder; SCZ, Schizophrenia; ID, Intellectual Disability; AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl-D-Aspartate; mGluR, metabotropic G-protein coupled glutamate receptor; mEPSC, mini excitatory post synaptic currents.

Alterations in glutamatergic neurotransmission have long been associated with psychiatric and neurodevelopmental disorders (PNDD), but only recent advances in high-throughput DNA sequencing have allowed interrogation of the prevalence of mutations in glutamate receptors (GluR) among afflicted individuals. In this review we discuss recent work describing GluR mutations in the context of PNDDs. Although there are no strict relationships between receptor subunit or type and disease, some interesting preliminary conclusions have arisen. Mutations in genes coding for ionotropic glutamate receptor subunits, which are central to synaptic transmission and plasticity, are mostly associated with intellectual disability and autism spectrum disorders. In contrast, mutations of metabotropic GluRs, having a role on modulating neural transmission, are preferentially associated with psychiatric disorders. Also, the prevalence of mutations among GluRs is highly heterogeneous, suggesting a critical role of certain subunits in PNDD pathophysiology. The emerging bias between GluR subtypes and specific PNDDs may have clinical implications.

Background

Most psychiatric and neurodevelopmental disorders (PNDD) have a strong heritable component.[1] Twin studies have proved that neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD),[2] autism spectrum disorders (ASD),[2] as well as psychiatric conditions like Schizophrenia[3] (SCZ) and Bipolar Disorder[4] (BD) have an important genetic background. Nevertheless, until very recently, causal genes have only been found in the context of Intellectual Disability (ID). Classical genetic studies have failed to identify genes with high penetrance in PNDD, thus indicating that the genetic background of these disorders is highly heterogeneous.

Recent developments in DNA analysis and sequencing, such as next-generation sequencing, SNP arrays, exome sequencing or analysis of copy number variations (CNVs),[5,6] allow to study the whole genome of large cohorts of affected individuals, enabling the analysis of CNS disorders with highly heterogeneous genetic etiology. Several of these studies have focused on PNDDs, uncovering new genes with potential roles in these disorders. Interestingly, many of the genes identified are involved in synaptic physiology,[7] pointing towards synaptic dysfunction as an important contributing factor in many of these disorders.

Although numerous psychiatric conditions have traditionally been ascribed to unbalances in monoaminergic systems, it is also accepted that alterations in the glutamatergic system are involved in these disorders. In particular, an important group of genes expressed at the synapse identified in the context of PNDDs encode for glutamate receptor subunits. Glutamate receptors (GluRs) mediate excitatory synaptic transmission and plasticity in the brain.[8] GluRs comprise three families of ionotropic receptors: AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), NMDA (*N*-methyl-D-Aspartate) and Kainate; as well as three groups of metabotropic receptors (mGluRs I-III). Ionotropic receptors are found as tetramers of various subunits: 4 *GRIA* genes code for AMPA subunits, 7 *GRIN* genes code for NMDA subunits and 5 *GRIK* genes code for Kainate subunits.[8] Finally, metabotropic receptors, which are G-protein coupled receptors, are coded by 8 *GRM* genes.[9] Functionally, ionotropic GluRs are specialized on different aspects of synaptic transmission. While NMDA receptors act as coincident detectors of postsynaptic membrane depolarization and glutamate release, AMPA receptors mediate fast transmission in excitatory synapses. Kainate receptors also participate in synaptic transmission and plasticity. On the other hand, metabotropic receptors modulate excitatory signaling.[8,9]

In this review we discuss recently identified mutations in GluR subunits in the context of PNDDs, including large genomic

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rearrangements directly affecting these genes or point mutations predicted to be deleterious. Linkage and association studies of natural variation, such as SNPs or microsatellites, have not been included in this work as these have a less direct implication in disease.

Mutations in AMPA Receptor Subunits

Of all four genes coding for AMPA receptor subunits,[8] only mutations in *GRIA2* and *GRIA3* have been related with PNDDs (**Table 1**). Alterations in these two genes have been associated with some cases of ASD,[10,11] but have mainly been found concomitant with ID.

Although chromosomal deletions encompassing *GRIA2* had been described for individuals with mental and developmental retardation (*see ref. 12 for review*), only recent studies have identified specific mutations in *GRIA2* in the context of ID,[12,13] suggesting that *GRIA2* haploinsufficiency might cause ID.

GRIA3 was first identified as a candidate gene for X-linked ID in 1999, in a female with a balanced translocation directly involving this gene.[14] Since then, several other *GRIA3* mutations have been associated with ID, including complete[15,16] or partial duplications,[17,18] mutations on its 5'UTR[19] and a whole gene deletion.[20] Interestingly, both duplications and deletions of *GRIA3*, translate into a diminished or absent synthesis of GluA3 protein. Partial duplications would cause either reduced *GRIA3* transcripts or aberrant protein levels ultimately contributing to ID. Missense *GRIA3* variants[20] have also been found linked to ID and, with the exception of the G833R mutation (see **Table 1**) these individuals express *GRIA3* at normal levels. Nevertheless, when functionally tested GluA3 variants displayed altered channel function either in homomeric combination or in heteromers with normal GluA2.[20]

GluA3 is normally present at synapses together with GluA2 contributing to the normal cycling of AMPA receptors.[8] From the studied individuals with ID, it can be inferred that the lack of GluA3 is not crucial for neuronal viability. In fact, synaptic targeting and function of these receptors are not significantly altered in GluA3 KO mice.[21] Remarkably, long-term potentiation (LTP), widely thought to be the cellular basis of learning processes,[22] is abnormal in these animals. Nevertheless, in humans, the lack of GluA3 could impair normal neuronal wiring or stabilization of activated synapses during development.

AMPA receptor auxiliary subunits, TARPs and CNIHs,[23] control receptor function by modulating channel trafficking and kinetics. It is interesting to note that a mutation affecting *CACNG2* (TARP γ-2) has been described in an individual with moderate ID.[24] This mutation caused a decreased association with AMPA subunits, altering the receptor trafficking and reducing mEPSCs in hippocampal neurons. Finally, *CNIH2* deletion has also been found in a boy with mild ID.[25] Thus, it is noteworthy that malfunctions of AMPA receptor auxiliary can also be associated with ID.

Mutations in NMDA Receptor Subunits

NMDA subtype of ionotropic GluRs play a pivotal role in neuronal communication. These receptors are composed of two obligatory subunits (GluN1) and two variable ones, which consist of either GluN2(A-D) or GluN3(A,B).[26] Of the variable subunits, GluN2B expression starts very early in development and is critical for synaptogenesis and neuronal survival in cortical brain areas, thus making it a candidate factor in neurodevelopmental disorders. Indeed, *GRIN2B* is the most frequently mutated *GRIN* gene (see **Table 1**) in PNDDs, being mainly related to ID.[27-30] Specific *GRIN2B* gain-of-function mutations have also been associated with ASD, supporting the hypothesis of an imbalance between excitatory and inhibitory neurotransmission in ASD etiology,[31,32] as well as in West Syndrome with severe developmental delay.[27] *GRIN2A* gene codes for GluN2A subunit, which is broadly expressed in adult brain. *GRIN2A* de novo mutations[30] and microdeletions[33] have also been associated with ID, indicating the viability of GluN2A haploinsufficiency. A different group of *GRIN2A* mutations have also been associated with ASD.[34,35] Likewise, a rare *GRIN2A* de novo mutation was recently associated with schizophrenia,[31] although the role of GluN subunits with SCZ is under debate.[36] Although less frequently, mutations in *GRIN1* gene, the obligatory NMDA receptor subunit, have also been identified. A mutation in *GRIN1* has been found to cause non-syndromic intellectual disability (NSID), an observation functionally validated using cellular models.[24]

Interestingly, regarding *GRIN2C*, *GRIN3A* and *GRIN3B*, only rare truncating mutations affecting both healthy individuals and ASD/SZ patients[31] have been reported. In contrast, no truncating mutations were found in *GRIN1*, *GRIN2A*, *GRIN2B* and *GRIN2D* genes, suggesting a more critical function of these genes during neurodevelopment and the lethality of the putative loss-of-function. Taken together, these recent reports suggest that de novo mutations of NMDA receptor subunits are frequently associated with ID, although some specific mutations are also associated with psychiatric diseases.

Mutations in Kainate Receptor Subunits

Previous classic genetic association studies suggested linkages to mood disorders for some of the kainate receptor-encoding genes, mainly *GRIK2* and *GRIK3* (*see ref. 37 for review*). More recently, CNVs in *GRIK2* were found enriched in, but not exclusive of, children with ID, indicating limited pathogenic burden.[38] Interestingly, a complex loss-of-function mutation in *GRIK2* was found to co-segregate with NSID.[39] This *GRIK2* mutation involves various deletions and inversions spanning exons 7 to 11, resulting in loss of the first ligand-binding domain, the adjacent transmembrane domain, and the putative pore loop of GluK2. Moreover, GluK2 mutants showed complete absence of currents despite normal cell surface expression. This study strongly indicates that loss of GluK2 protein can cause severe-to-moderate cognitive impairment in humans.

A *GRIK4* variant with an insertion-deletion in the 3'UTR region (which results in increased GluK4 levels) was found to confer protection against bipolar disorder.[40] Moreover, this *GRIK4* variant increased hippocampal activation during face processing,[41] suggesting a link between kainate receptor-mediated excitation in the hippocampus and Bipolar Disorder.

So far, the subfamily of kainate glutamate receptors is the one for which less mutations have been identified in the context of PNDDs. However, collectively taken, these results support the notion that mutations leading to up- or down-regulation of kainate subunits can cause learning disabilities and modulate mood disorders.

Mutations in Metabotropic Receptor Subunits

Currently, a limited number of papers report deleterious mutations related to PNDDs in *GRMs* (see **Table 1**). Of these, two perform *GRM1* exon sequencing in SCZ and BD,[42,43] another sequenced the *GRM3* gene in a cohort of individuals with BD[44] and one perform a genome-wide copy number variation (CNV) association study[45] on attention deficit hyperactivity disorder (ADHD). Finally, a mutation in the Kozak's sequence of *GRM3* assocaited with SCZ has also been reported .[46]

It is important to highlight that, as it happens with genes giving susceptibility to psychiatric diseases,[1] none of the reported mutations supports for a causal role in disease. In most cases, *GRMs* mutations are observed in both cases and controls. Quite surprisingly, this is even the case for whole gene deletions or duplications.[45] The small number of mutations identified for *GRMs* make it still difficult to conjecture on their relevance to disease.

Nevertheless, a striking observation can be made: there is no report implicating *GRM* mutations in neurodevelopmental disorders such as ID or ASD. Despite the extensive literature on the role of these receptors, especially *GRM1* and *GRM5*, in Fragile X-Syndrome and ASD,[47,48] deleterious mutations on *GRMs* have so far been found only in the context of psychiatric disorders, such as SCZ, BD or ADHD.

Closing Remarks

Recently developed DNA analysis tools are allowing for the rapid uncovering of GluRs mutations in the context of PNDDs. This can be seen by the exponential increase in the number of papers reporting GluR mutations in most recent years. Based on this, we expect that new GluR mutations will be identified in the future, hopefully allowing for a better understanding of GluR etiological contribution to PNDDs. Although the number of studies reporting GluR mutations in PNDD is so far restricted, some initial conclusions can be drawn. These will need to be examined in the light of future studies.

In the first place, mutations of subunits of some receptor subtypes are related to certain disease types but not to others. In this regard, mutations in AMPA subunits have only been found in the context of ID and ASD, both neurodevelopmental disorders. Similarly, mutations in genes coding for AMPAR auxiliary proteins are also related with ID. Along these lines, mutations in NMDA subunits are mostly linked to ID and ASD. In stark contrast, mutations in metabotropic receptors are only related to psychiatric disorders. Accordingly, the data available would suggest that mutations in ionotropic glutamate receptors predispose towards neurodevelopmental disorders, while mutations in metabotropic receptors would predispose towards psychiatric disorders. One can also draw a parallel between the extent of mental disability and the contribution to neurotransmission of the affected receptor type. Thus, loss-of-function mutations in AMPA and NMDA subunits are frequently found in patients with ID. This is consistent with their important role in neuronal development, fast transmission, and synaptic plasticity. On the other hand, the abundance of *GRM* mutations in individuals with psychiatric disorders is consistent with the more modulatory role of mGluRs. The occurrence of ID in carriers of a mutant GluK2 suggests that tuning of neuronal network activity by kainate receptors can have profound effects on cognitive abilities.

Secondly, mutation rates amongst GluR are very heterogeneous in PNDDs. Indeed, while some genes accumulate many potential deleterious mutations, no mutations have been found in others. Amongst AMPA subunits, for instance, *GRIA1* and *GRIA4* have not been found mutated in the context of PNDD, while twelve different mutations have been described for *GRIA3*. Similarly, few mutations are found in *GRIN1* as compared to *GRIN2A* or *GRIN2B*. Remarkably, the spectrum of mutations in NMDA subunits concentrates in particular coding regions, namely, the extracellular and pore-forming domains. This observation suggests that impaired ion selectivity and conductance of NMDA receptors is closely linked to developmental defects, while the role of its intracellular tail might have a less critical role in disease. There are several potential explanations as to why some GluR genes do not appear mutated in relation to disease; they might play indispensable biological functions, thus leading to lethality even in heterozygosity, or other molecules could compensate for their dysfunction.

Interestingly, we do not see an increased number of mutations in GluR subunits expressed early in development, which a priori, should be more relevant to neurodevelopmental disorders. For instance, a similar number of mutations has been found for *GRIN2B*, which starts to be expressed early in development, and for *GRIN2A*, that is expressed post-natally.[49] In contrast, no mutations have been described for *GRIA4*, also highly expressed during development.[50] Nevertheless, this observation should be taken cautiously as mutations in developmental genes could cause lethality and also because gene expression data, mostly obtained from rodent species, might not be completely valid for humans.

Although the etiopathology of PNDDs is complex and multigenic, a growing set of genetic and functional evidences indicate the contribution of glutamate receptors in these damaging disorders. The following years will be crucial to understand whether the different receptor subunits are associated with certain PNDDs or not, as well as their interaction with genetic background and environmental factors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Table 1. Contribution of glutamate receptor subunit mutations to psychiatric and neurodevelopmental disorders

Mutated gene	Neurological disorder	Mutation	Altered function(s)	Reference
GRIA2	ASD	Deletion	Haploinsufficiency	10
	ID	Complete deletion	Haploinsufficiency	12
	ID	Truncation	Haploinsufficiency	13
GRIA3	ID	Interruption by breakpoint translocation t(X;12)(q24;q25)	nd	14
	ASD and ID	Complete duplication	nd	15
	ID	Complete duplication	nd	16
	ASD	Partial tandem duplication (4 exons)	nd	11
	ID	Partial tandem duplication (5 exons)	Reduced transcripts	17
	ID	Partial tandem duplication (12 exons)	Aberrant transcripts with premature termination codon	18
	ID	Duplication 874-bp upstream GRIA3	Absence of transcripts	19
	ID	Complete deletion	nd	20
	ID	R450Q	Accelerated receptor desensitization kinetics	20
	ID	R631	Decreased channel function	20
	ID	M706T	Decreased channel function	20
	ID	G833R	Protein miss-folding and degradation	20
CACNG2	ID	V143L	Altered binding to AMPARs, reduced AMPARs expression, decreased mEPSCs	24
CNIH2	ID	Complete deletion	nd	25
GRIK2	NSID	Deletion and inversion	Abolished channel function	39
GRIK4	BD	Insertion-deletion	Overexpression	40
GRIN1	NSID	E662K	nd	24
	NSID and Epilepsy	S560dup	Decreased channel function	24
	SCZ	A968T, 3669C- > T (silent)	nd	31
	ID	Microdeletions	nd	33
GRIN2A	ID	L649V, P522R	nd	30
	ASD	Copy number variation	nd	35

ID, intellectual disability; NSID, non-syndromic ID; ASD: autism spectrum disorder; BD, bipolar disorder; SCZ, schizophrenia; ADHD, attention deficit hyperactivity disorder; *copy number variation study with average CNV size of 62Kb

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Table 1. Contribution of glutamate receptor subunit mutations to psychiatric and neurodevelopmental disorders (continued)

Mutated gene	Neurological disorder	Mutation	Altered function(s)	Reference
GRIN2B	West syndrome with dvpt delay	N615I, V618G	Reduced Mg2+ blockade and increased Ca2+ permeability	27
	ID with focal epilepsy	R540H	Mild changes of channel function	27
	ASD	L825V	nd	31
	ID	c.411+1G > A, 2360–2A > G, T268SfsX, R682A Translocation breakpoints disrupting GRIN2B	nd	28
	ID	P553L	nd	30
	ASD with ID	Single-base substitution at Exon10 3¢ splice site	nd	34
	ASD	S34GInfsX25, C456Y, W559X, 2172–2A > G	nd	32
	ID	Micorodeletions of GRIN2B locus	nd	29
GRIN2C	ASD	W18X (truncation)	nd	31
GRIN3A	SCZ	Q508X, E227X	nd	31
GRM1	SCZ	F122L, A683E, P970L, P1015A	Low Inositol Phosph.	43
	SCZ	P1014S	Low Membrane Expr.	43
	ADHD	Duplication (8 cases 2 controls)	nd	45
	SCZ	L575V, L602M, I604M	nd	42
	BP	T548M	nd	42
GRM3	BP	Kozak sequence variant (19 cases, 4 controls)	Altered expression (predicted)	44
	SCZ	Haplotype in intron 2	Lower glutamate levels (MRI)	46
GRM5	ADHD	Deletion (10 cases 1 control)	nd	45
GRM7	ADHD	Deletion (6 cases)	nd	45
GRM8	ADHD	Deletion (8 cases)	nd	45

ID, intellectual disability; NSID, non-syndromic ID; ASD: autism spectrum disorder; SCZ, schizophrenia; ADHD, attention deficit hyperactivity disorder; BP, bipolar disorder; *copy number variation study with average CNV size of 62Kb

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