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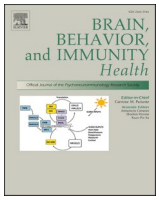

GRM7 deficiency, from excitotoxicity and neuroinflammation to neurodegeneration: Systematic review of GRM7 deficient patients★

Majid Zaki-Dizaji [a], Mohammad Foad Abazari [b,d], Hossein Razzaghi [a], Irene Shkolnikov [c], Brian R. Christie [c,d,*]

[a] Human Genetics Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[b] Research Center for Clinical Virology, Tehran University of Medical Sciences, Tehran, Iran
[c] Division of Medical Sciences, University of Victoria, Victoria, British Columbia, Canada
[d] Island Medical Program, University of British Columbia, Victoria, British Columbia, Canada

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ABSTRACT

The metabotropic glutamate receptor 7 (mGluR7) is a presynaptic G-protein-coupled glutamate receptor that modulates neurotransmitter release and synaptic plasticity at presynaptic terminals. It is encoded by GRM7, and recently variants have been identified in patients with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), developmental delay (DD), intellectual disability (ID), and brain malformations. To gain updated insights into the function of GRM7 and the phenotypic spectrum of genetic variations within this gene, we conducted a systematic review of relevant literature utilizing PubMed, Web of Science, and Scopus databases. Among the 14 articles meeting the inclusion criteria, a total of 42 patients (from 28 families) harboring confirmed mutations in the *GRM7* gene have been documented. Specifically, there were 17 patients with heterozygous mutations, 20 patients with homozygous mutations, and 5 patients with compound heterozygous mutations. Common clinical features included intellectual behavioral disability, seizure/epilepsy, microcephaly, developmental delay, peripheral hypertonia and hypomyelination. Genotype-phenotype correlation was not clear and each variant had unique characteristics including gene dosage, mutant protein surface expression, and degradation pathway that result with a spectrum of phenotype manifestations through ASD or ADHD to severe DD/ID with brain malformations. Neuroinflammation may play a role in the development and/or progression of GRM7-related neurodegeneration along with excitotoxicity. The clinical and functional data presented here demonstrate that both autosomal dominant and recessive inheritance of GRM7 mutation can cause disease spectrum phenotypes through ASD or ADHD to severe DD/ID and seizure with brain malformations.

1. Introduction

Defects in ion channels and neurotransmitter receptors have been implicated in a number of neurodevelopmental disorders (NDDs) and the purpose of the present review is to examine the role of the mGlu receptor subtype 7 (mGlu7) or Glutamate Metabotropic Receptor 7 (GRM7), in NDD's (Kumar et al., 2016; Lascano et al., 2016). Glutamate receptors (GluRs) are key mediators of excitatory synaptic transmission and plasticity in the brain, and alterations in excitatory/inhibitory signaling homeostasis can play a role in both neurodevelopment and neurodegenerative disease. Glutamate exerts its effect through two main receptor groups: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs) (Mukherjee and Manahan-Vaughan, 2013; Soto et al., 2014). Ionotropic glutamate receptors include the N-Methyl-d-Aspartate (NMDA), Amino-3- hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) and kainate receptors, are ligand-gated ion channels that promote rapid excitatory neurotransmission. The metabotropic glutamate (mGlu) receptors are class of G protein-coupled receptors (GPCRs) that bind to glutamate. They have high expression in the pre- and postsynaptic neurons to trigger intracellular signaling pathways and can regulate the function of ionotropic receptors (Fisher et al., 2018/11; Kandaswamy et al., 2014; Fisher et al.,

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* Corresponding author. Division of Medical Sciences University of Victoria Victoria, British Columbia, V8P 5C2, Canada.
E-mail address: brain64@uvic.ca (B.R. Christie).

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2020). The mGlu receptors are classified into three different groups based on their amino acid sequence homology, pharmacological profile, and type of intracellular signaling pathway. Group I include mGlu 1 and mGlu 5 that are excitatory and positively coupled to phospholipase C *via* G_q/G_{11} protein. Their stimulation leads to the formation of diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3), which induce the intracellular mobilization of Ca^{2+} ions. Group II (mGluR 2 and mGluR 3) and group III (mGluR 4, mGluR 6, mGluR7, and mGluR 8) mGluRs are inhibitory and negatively coupled to adenylyl cyclase (AC) *via* G_i/G_o proteins, and their activation inhibits cyclic adenosine monophosphate (cAMP) formation *via* interaction with $G_{\alpha i/o}$ (Niswender and Conn, 2010; Ribeiro et al., 2017).

The mGlu receptor subtype 7 (mGlu7) or Glutamate Metabotropic Receptor 7 (GRM7) is the most widely expressed mGlu receptor in the central nervous system (CNS), with relatively high expression in the striatum, hippocampus, thalamus, hypothalamus, amygdala, neocortex, and locus coeruleus (Ngomba et al., 2011), and peripherally in adrenal glands, stomach, and colon (Julio-Pieper et al., 2010; Scaccianoce et al., 2003; Boccella et al., 2020). The mGlu7 is usually a presynaptic receptor with a widespread expression on L-glutamate and GABAergic neurons, and acts to inhibit neurotransmitter release both constitutively and in an activity-dependent manner (Kandaswamy et al., 2014; Fisher et al., 2020; Fisher et al., 2021/01). *GRM7* gene mapped to chromosome 3p26.1 (Bjarnadóttir et al., 2005) and has 15 transcripts, six of which are predicted to be protein coding. Among the 15 existing variants of the mGluR7, the mGluR7a and mGlu7Rb isoforms, who differ in their C-terminal domain, are the most widespread in the CNS (Boccella et al., 2020; Seebahn et al., 2011). The other isoforms of the receptor have been observed at the peripheral level in tissues such as the testis, trachea, uterus, and salivary glands (Schulz et al., 2002). The mGluR7 is the most highly conserved receptor subtype among all mGluRs across mammalian species (Ferraguti and Shigemoto, 2006). Transcript variant 1 (mGluR7a) of this gene (ensembl: ENST00000357716.9, RefSeq: NM_000844) contains 10 exons, 10 coding exons, transcript length of 4149 bps, and translation length of 915 residues.

Polymorphisms in *GRM7* gene have been reported to be associated with major depressive disorder (MDD) (Niu et al., 2017; Dattilo et al., 2022), attention deficit hyperactivity disorder (ADHD) (Zhang et al., 2021), Alzheimer (Squillario et al., 2020), schizophrenia (Ganda et al., 2009; Zhang et al., 2018; Azari et al., 2019; Mazdeh et al., 2019; Liang et al., 2020), age-related hearing impairment (ARHI) (Friedman et al., 2009; Newman et al., 2012; Luo et al., 2013; Matyas et al., 2019; Chang et al., 2018), noise-induced hearing loss (NIHL) (Yu et al., 2018), autism spectrum disorder (ASD) (Noroozi et al., 2016/06), bipolar disorder (BP) (Kandaswamy et al., 2014), and migraines (Cox et al., 2012). Eli et al., in 2011 demonstrated heterozygous deletion of the *GRM7* gene in 3p26.1 locus to be associated with ADHD (Elia et al., 2011). Although genetic disorders of glutamate receptors are rare (<1%), several cases presenting with neurodevelopmental disorders have been identified with homozygous and heterozygous *GRM7* gene mutations (Fisher et al., 2020; Fisher et al., 2021/01; Song et al., 2021). This review, focuses on the clinical phenotypes and genotypes of patients with GRM7-associated disorders in order to achieve a comprehensive view of this disease, explore co-presentation of neuropsychiatric disorders with GRM7 alterations, and provide a better prognostic feature of the disease. Single nucleotide polymorphism (SNP) association studies are out of scope of this review.

2. Material and methods

2.1. Search strategy

A comprehensive search up to May 1, 2024, limited to articles written in the English language, was performed using PubMed, Web of Science, and Scopus databases, applying the following search terms: ("GRM7" or "metabotropic glutamate receptor 7" or "mGlu7" or "mGluR7") and ("mutation" or "variant") and ("neurodevelopmental disorder or neurodegeneration disorder"). Reference lists of all full-text articles and major reviews identified in this search were hand-searched for additional studies.

2.2. Study selection

The articles were first reviewed based on the title and abstract to determine which studies were appropriate for inclusion and all full articles were assessed for eligibility criteria: written in English, conducted on human subjects, reporting at least one patient with GRM7-associated NDDs diagnosis, and detailed description of clinical features associated with genetic mutations. Those patients appearing in more than one publication were identified, and the duplicate data were removed. Studies using congress abstracts, and articles in languages other than English were excluded. When necessary, the corresponding authors of the selected published reports were contacted.

2.3. Data extraction

After collection of data by two researchers in the last steps, data were collected from each article: publication year, mutation type, inheritance, clinical symptoms, disease type of the patients. Two reviewers performed the selection process independently, while a third reviewer was consulted to resolve disagreements between the two reviewers.

3. Results

3.1. Study characteristics

Overall, 92 articles were evaluated, that 65 articles were excluded due to the duplication and irrelevance of the title and abstract. There were 15 articles that fulfilled the inclusion criteria and were subsequently used for data extraction. A total of 63 patients were reported in these 15 articles and after removing overlapping cases, 42 unique patients remained for data analysis (Fig. 1, Table 1s).

3.2. Epidemiologic characteristics of patients

In the current study, we evaluated 42 patients (17 males, 13 females, and 12 with unknown gender). These patients were geographically distributed; Europe with 12, Tunisia with 6 patients, United States, Saudi Arabia, UAE, and Turkey each with 3 patients, Iran, France and Syria each with 2 patients and South Korea, China each with 1 patient. The 24 of 25 patients with available consanguinity data, were born to consanguineous parents.

3.3. Molecular finding

The human *GRM7* gene contains 10 coding exons that encode a 915-amino acid protein, mutations are located throughout the gene and there do not seem to be any mutation hotspots (Fig. 2). In this study from 42 reported patients (28 families) with a confirmed mutation in the *GRM7* gene, 17 patients (16 families) had heterozygous mutations (Table 1), 20 patients (8 families) had homozygous mutations, 5 patients (3 families) had compound heterozygous mutation (Table 2). In other words, 17 patients showed an autosomal dominant inheritance and 25 of them presented an autosomal recessive inheritance. The 26 unique mutations in the *GRM7* gene have been reported, that consist of 11 missense (42%), 2 nonsense (8%), 9 large deletion (35%), 3 large duplication (12%), 1 indel-frameshift (4%).

3.4. Clinical findings

Different presentations are observed in patients with different types of mutations in the *GRM7* gene. In monoallelic mutations, symptoms are

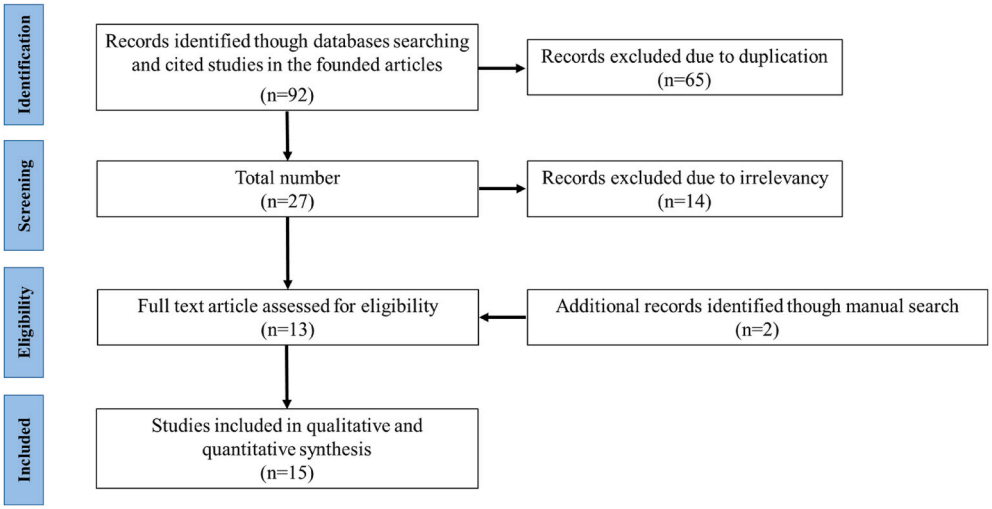

Fig. 1. Study selection flow chart. We used PubMed, Web of Science, and Scopus databases for the initial search. After removing duplicate patient records and records that proved to be irrelevant (n = 13), two additional studies were added as a result of searching the reference lists of papers that met the inclusion criteria.

Table 1
Reported pathogenic human GRM7 variants with autosomal dominant inheritance and associated clinical features.

Patients/ origin	Mutation (hg38, NM_000844.4)	Mutation type	Size	Location	Deleted/ Duplicated Genes	Zygosity	Sex	Clinical Features	References Year
6 European	7167266–7180549	large deletion	~13 kb	Intron 2	GRM7	Het	–	ADHD	Elia et al. (2011) 2011
1 USA	c.1865G > A (p. R622Q)	Missense	–	–	–	Het	Male	ASD	(Iossifov et al., 2014; Sanders et al., 2012) 2012
1 European	7036492–7127766	large deletion	91 kb	Intron 1	GRM7	Het	–	ASD	Gai et al. (2012) 2012
1 European	7047942–7156028	large deletion	108 kb	Intron 1-2 Exon 2	GRM7	Het	–	ASD	Gai et al. (2012) 2012
1 European	7048735–7156028	large deletion	107 kb	Intron 1-2 Exon 2	GRM7	Het	–	ASD	Gai et al. (2012) 2012
1 UK or Irish	7260663–7541916	large deletion	281 kb	Intron 2-7 Exon 3-7	GRM7	Het	–	BP	(Kandaswamy et al., 2014; McQuillin et al., 2011) 2014
1 UK or Irish	6984586–7090756	large deletion	106 kb	Intron 1	GRM7	Het	–	BP	(Kandaswamy et al., 2014; McQuillin et al., 2011) 2014
1 UK or Irish	7330848–7716421	large duplication	385 kb	Intron 4-8 Exon 5-8	GRM7, GRM7-AS1	Het	–	BP	(Kandaswamy et al., 2014; McQuillin et al., 2011) 2014
1 China	7179403–7482865	large deletion	303 kb	Intron 2-5 Exons 3–5	GRM7	Het	Male	ASD, hyperactivity	(Liu et al., 2015/04; Yang et al., 2019) 2015
1	7215827–7401195	large deletion	185 kb	Intron 2-4 Exons 3-4	GRM7	Het	Female	Global developmental delay	(Fisher et al., 2018/11) 2018
1	6167984–6939430	large duplication	771 kb	5′ UTR And Exon 1	GRM7, GRM7-AS2, GRM7-AS3	Het	Male	ID, behavioral abnormality	(Fisher et al., 2018/11) 2018
1	7467977–7836719	large duplication	368 kb	Intron 7-9 Exons 8-10	GRM7, GRM7-AS1	Het	Male	ID, microcephaly	(Fisher et al., 2018/11) 2018

not syndromic and include ADHD, ASD, BP, DD, ID, microcephaly and behavioral abnormality (Table 1). In contrast in biallelic forms symptoms are syndromic and include seizure, DD, ID, microcephaly, hypotonia and etc. (Table 2). In biallelic form, mutation is contingent with early-onset– nearly under 1 year–and with seizure symptoms among primary presentations.

4. Discussion

The association of glutamate receptor mutations with psychiatric and neurodevelopmental disorders have been established (Soto et al., 2014; Niswender and Conn, 2010). Recently several reports documented association between GRM7 mutations and neurodevelopmental abnormalities including seizures, microcephaly, ASD, and hypotonia (Fisher

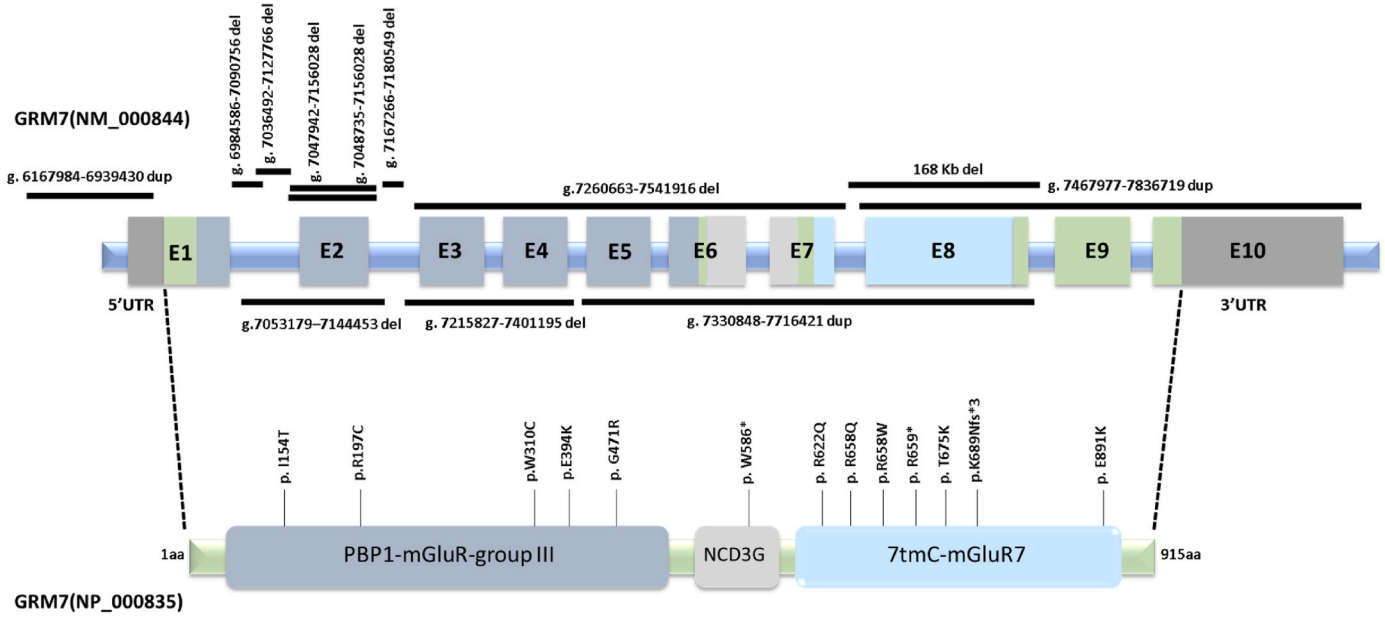

Fig. 2. Graphical illustration of *GRM7* gene structure and protein domains with locations of published genetic mutations in patients with GRM7 deficiency. Mutations in *GRM7* occurred throughout the length of the gene, without hotspots. Large deletions and duplications are indicated with line. E: exon, PBP1_mGluR_-groupIII: Ligand-binding domain of the group III metabotropic glutamate receptor; 7tmC_mGluR7: metabotropic glutamate receptor 7 in group 3, member of the class C family of seven-transmembrane G protein-coupled receptors, NCD3G: Nine Cysteines Domain of family 3 GPCR (from NCBI, Structure, Conserved domains).

Table 2
Reported pathogenic human GRM7 variants with autosomal recessive inheritance and associated clinical features.

Patients/ origin	Male/ female	DNA (hg38, NM_000844.4)	Protein	Mutation Type	Age onset	Zygosity	Clinical Features	References
2 USA	1 m, 1f	c.1972C > T/ c.2024C > A	p.R658W/p. T675K	Missense	1 day-1 mo	Com Het	DD, ID, microcephaly, axial hypotonia, peripheral hypertonia, seizure, thin corpus callosum, hypomyelination, cerebellar atrophy	(Marafi et al., 2020; Charng et al., 2016) 2016
4 Saudia Arabia	2 m 2f	c.461 T > C	p. I154T	Missense	4 mo–8 mo 1 mo–4 mo	Hom	DD, ID, microcephaly, axial hypotonia, peripheral hypertonia, hyper reflexia, seizure, cerebral atrophy, thin and shortened corpus callosum, cerebellar atrophy, hypomyelination	(Fisher et al., 2021/01; Marafi et al., 2020; Charng et al., 2016) 2016
2 Syria	1 m, 1f	c.1757G > A	p. W586*	Nonsense	3 weeks	Hom	DD, ID, microcephaly, seizure	(Marafi et al., 2020; Reuter et al., 2017) 2017
3 UAE	2 m, 1f	c.1973G > A	p. R658Q	Missense	1 w, 3 mo, 5 mo	Hom	DD, ID, microcephaly, seizure, axial hypotonia, cerebral atrophy, thin corpus callosum, cerebellar atrophy, bilateral hippocampal atrophy, conductive hearing loss	Marafi et al. (2020) 2020
1 Turkey	1 m	c.2671G > A	p. E891K	Missense	2 mo	Hom	DD, ID, microcephaly, seizure, thin corpus callosum, axial hypotonia, peripheral hypertonia, hyper reflexia, unilateral hearing loss	(Marafi et al., 2020) 2020
1 Turkey	1 m	c.1975 C > T	p. R659*	Nonsense	2 days	Hom	DD, ID, microcephaly, axial hypotonia, peripheral hypertonia, hyper reflexia, cerebral atrophy, thin corpus callosum, cerebellar atrophy, global hypomyelination	Marafi et al. (2020) 2020
6 Tunisia	3 m, 3f	c.1411G > A	p. G471R	Missense	3 mo–16 mo	Hom	DD, ID, microcephaly, seizure, cerebral atrophy, thin corpus callosum	Jdila et al. (2021) 2021
1 South Korea	1f	c.589C > T/ c.1972C > T	p. R197C/p. R658W	Missense	4 mo	Com Het	ID, DD, epilepsy	Lee et al. (2022) 2022
2 **French**	1 m, 1f	168 Kb deletion (exon 8) c.1180G > A	p.E394K	Large del/ Missense	5–10 mo	Com Het	Microcephaly, axial and peripheral hypotonia, seizure, infantile spasms, hand and head action tremor, thin corpus callosum	(Januel et al., 2024) 2024
2 Iran	1 m, 1f	c.2067 delA	p. K689Nfs*3	Deletion-frameshift	–	Hom	Microcephaly, Epilepsy, neurodevelopmental delay, spasticity, dysmorphic features	Januel et al. (2024) 2024
1 Turkey	1f	c.930G > C	p.W310C	Missense	10 d	Hom	Epilepsy, neurodevelopmental delay, Microcephaly, axial hypotonia, peripheral hypertonia and spasticity, thin corpus callosum	Januel et al. (2024) 2024

et al., 2021/01; Song et al., 2021; Marafi et al., 2020; Liu et al., 2015/04). Here we reviewed clinical and genotype features of 42 reported patients with GRM7-associated disorders. Roughly, consanguinity and family history were present in all patients with available data and these factors may be indicators in the suspected patients (Song et al., 2021; Marafi et al., 2020).

Typically, biallelic mutation of GRM7 cause syndromic severe neurodevelopmental abnormalities, in contrast monoallelic mutation led to non-syndromic neurological abnormalities like ASD, ADHD. Of the reported patients, 59% represented autosomal recessive inheritance and 41% showed autosomal dominant inheritance. However, GRM7-associated monoallelic variants (susceptible variants) are frequent and their number continuously increased. All of the reported patients with monoallelic variants (except one) showed deletion or duplication variants. The GRM7 locus seems to be a hotspot for copy number variations (CNVs) associated with psychiatric and behavioral disorders (Table 1), nicotine dependence (Begum et al., 2016), early-onset obesity (Serra-Juhé et al., 2017) and cancer (Ribeiro et al., 2022). A review of the DECIPHER database revealed multiple cases of patients showing deletions or duplications involving GRM7, although most of these also affected other genes (Fisher et al., 2018/11; Freitas and Niswender, 2023). In our study, we specifically reported on deletions or duplications solely within the GRM7 gene.

Although generally GRM7 related patients especially non-deletion/duplication cases exhibit similar features (Table 2), each variant has unique characteristics including response to antiepileptic drugs, degradation pathways, and mutant protein surface expression (Song et al., 2021; Marafi et al., 2020). In addition, each variant may change *GRM7* gene dosage differently that leading to various phenotype manifestations through ASD or ADHD to severe DD/ID with brain malformations (Song et al., 2021). Of note, overexpression of mGluR7 in the prefrontal cortex attenuates autistic behaviors in mice (Wang et al., 2021a). This gives rise to a potential mechanism by which associated polymorphisms or heterozygous mutations in GRM7 show phenotypic expression (Noroozi et al., 2016/06; Liu et al., 2015/04; Palazzo et al., 2016; Yang and Pan, 2013; Noroozi et al., 2019; Iossifov et al., 2014; Sanders et al., 2012; Gai et al., 2012). GRM7 variants severely reduce protein expression, so it is expected that GRM7 related phenotypes are due to loss-of-function of the mGlu7 receptor (Song et al., 2021). Thus, heterozygous carriers remain largely asymptomatic. It is posited that heterozygous GRM7 mutations may cause disease only in the presence of other confounding genetic or environmental factors and as consequence of mGluR isoform mutation variation (Lüffe et al., 2022) (Fig. 3).

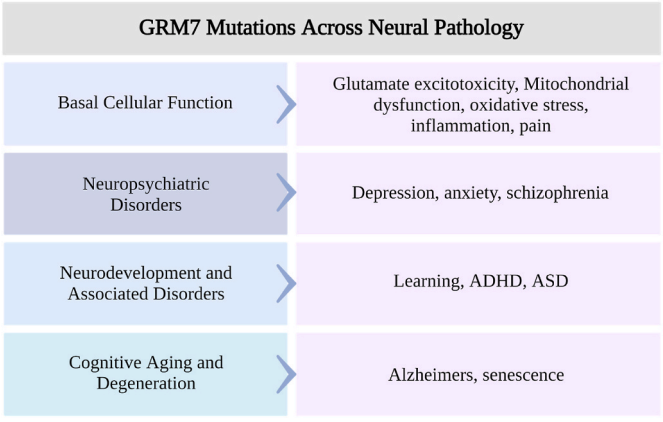

Fig. 3. Mutations in GRM7 abolish its normal physiological function and cause various neuropsychiatric, neurodevelopmental and neurodegeneration disorders. GRM7 deficiency may exert its harmful effect though disturbance of excitatory/inhibitory neural signaling homeostasis, and consequently glutamate-mediated excitotoxicity by impaired mitochondrial functions, oxidative stress and neuroinflammation.

In line with previous studies, our data show that the most common clinical features in these GRM7 related patients include intellectual-disability, seizure/epilepsy, microcephaly, behavioral abnormality, developmental delay, peripheral hypertonia and hypomyelination (Table 2). GRM7-knock-out mice also showed impairment in associative learning (cognitive function), social behavior, motor coordination, epilepsy, depression, and anxiety (Fisher et al., 2020). These behavioral phenotypes overlap with the phenotypic characteristic of human NDDs (Fisher et al., 2020; Song et al., 2021; Palazzo et al., 2016). Human and mouse GRM7 proteins are highly homologous (99.5% identical), but the GRM7-knock-out mice don't show any brain malformation, such as cortical atrophy or microcephaly, which is observed in patients with the GRM7 mutations (Song et al., 2021). It is possible that GRM7 may be less important for early neuronal development in mice than it is in humans and that mutant-GRM7proteins in humans may transmit detrimental signals during early neurodevelopment.

Neurodegenerative disorders have common pathological mechanisms, such as protein aggregation, inflammation, oxidative stress (OS) and excitotoxicity. However, it is not clear whether inflammation is the primary cause of illness or secondary for progression and severity of neurodegeneration (Rauf et al., 2022/05). Neuroinflammation plays a significant part in the development and/or progression of several neurodegenerative diseases (Guzman-Martinez et al., 2019). Excitotoxicity consequential to overstimulation of glutamate receptors causes mitochondrial dysfunction, oxidative stress, and production of pro-inflammatory factors (Nisar et al., 2022). Excitotoxicity is among key drivers of the neurodegeneration due to disturbance of excitatory/inhibitory (E/I) neural signaling homeostasis. Collectively, these events cause ATP depletion and ultimately lead to neuronal cell death (Nisar et al., 2022). MGluR activity may confer neuronal resilience to inflammation-induced glutamate excitation (Woo et al., 2021). Recently Woo et al. (2021) demonstrated Group III mGluRs to be implicated in chronic inflammatory, demyelinating and neurodegenerative disease of the CNS such as multiple sclerosis (MS) through mGluR-mediated neuronal calcium flux (Woo et al., 2021).

It follows that neuroinflammation plays a significant part in the development and/or progression of GRM7 related neurodegeneration along with Excitotoxicity. The effects of mGluR7 activation may be site and condition dependent (healthy versus pathological). For instance, mGluR7 activation in the dorsal striatum can inhibit neuropathic pain but facilitate pain under normal conditions (Boccella et al., 2020). Like groups I and II, Group III mGluRs have an emerging role in prognosis and developing of cancer (Lange et al., 2021/06) and inflammatory phenotype in microglia (Barker-Haliski and White, 2015). GRM7 have a putative role in inhibiting cancer progression and exhibited a strong negative correlation with genes associated with immune response and inflammasomes in glioma (Belotti et al., 2022). GRM7 deficiency and consequently glutamate-mediated excitotoxicity may exert its effect through impaired mitochondrial functions and oxidative stress (Olloquequi et al., 2018). Although it is thought neuroinflammation typically affects the severity and progression of neurodegenerative and psychiatric disorders (Lyman et al., 2014), stimulation of peripheral Group III mGluRs (Zhang et al., 2009) or specifically GRM7 (Wang et al., 2021b) reduce hyperalgesia though modulating inflammatory process. Thus, it may be assumed mGluRs like GRM7 directly/indirectly implicated in neuropathogenesis through modifying neuroinflammation.

There is no effective treatment for CNS pathologies, including neurodevelopmental and neurodegenerative diseases in which the Glutamate/GABA balance is disturbed with linked excitotoxicity. The different and heterogeneous locations of mGluRs in the CNS could provide individualized treatment options by selectively targeting different receptor subtypes. Because of its heterogeneity, the mGluR7 family of receptors are promising targets for neuroprotective therapy (Domin, 2022). *In vivo* and *in vitro* studies in mice have also revealed that the activation of Group III mGluRs exerts neuroprotective effects, partly through homeostasis of glutamate levels (Bruno et al., 2000). Rett

syndrome is associated with low levels of mGluR7 mRNA, and potentiation of GRM7 activity reduces symptom severity in mouse models of autistic behavior (Wang et al., 2021a) and Rett syndrome (Gogliotti et al., 2017). Likewise, activation of mGluR7's can provide protection for the cholinergic basal forebrain neurons in Alzheimer's disease through the modulation of NMDA signaling (Gu et al., 2014). GRM7 SNPs (rs141134664, rs57521140, and rs73809055) have also been associated with treatment outcomes (eg, risperidone) in patients with schizophrenia (Zhao et al., 2022). Altogether GRM7 seems to be a potential target for variety of neuropathological conditions (Freitas and Niswender, 2023).

The study is restricted to English language papers, which may result in the exclusion of potentially relevant literature. Additionally, the limited number of patients with GRM7 variants prevented a comprehensive quantitative assessment, raising the possibility of drawing inaccurate conclusions. In the future, by including a broader representation of patients with GRM7 variants from diverse populations, the reliability of these findings could be enhanced.

5. Conclusion

In summary, the clinical and functional data presented here indicate that both autosomal dominant and recessive inheritance of GRM7 mutations can cause disease phenotypes contingent with ASD or ADHD, to severe DD/ID and seizures with neuroanatomical malformations. This suggests that further investigations are needed to determine how heterozygote mutations, that produce varying reductions in GRM7 expression, may increase the risk of disorders such as ASD and ADHD, and potentially contribute to other neuropathological conditions.

CRediT authorship contribution statement

Majid Zaki-Dizaji: Writing – original draft. **Mohammad Foad Abazari:** Writing – review & editing, Writing – original draft. **Hossein Razzaghi:** Writing – original draft. **Irene Shkolnikov:** Writing – review & editing, Writing – original draft. **Brian R. Christie:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100808.

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