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Unraveling *GRIA1* neurodevelopmental disorders: Lessons learned from the p.(Ala636Thr) variant

Nicolai Kohring Tvergaard[1] | Tinatin Tkemaladze[2,3] | Tommy Stödberg[4,5] | Malin Kvarnung[6,7] | Katrina Tatton-Brown[8] | Diana Baralle[9,10] | Zeynep Tümer[1,11] | Allan Bayat[1,12,13,14]

[1]Department of Clinical Genetics, Kennedy Center, Copenhagen University Hospital, Copenhagen, Denmark

[2]Department of Molecular and Medical Genetics, Tbilisi State Medical University, Tbilisi, Georgia

[3]Department of Pediatrics, Givi Zhvania Pediatric Academic Clinic, Tbilisi State Medical University, Tbilisi, Georgia

[4]Department of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden

[5]Department of Pediatric Neurology, Karolinska University Hospital, Stockholm, Sweden

[6]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

[7]Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden

[8]St George's University Hospitals NHS Foundation Trust and St George's, University of London, London, UK

[9]Wessex Clinical Genetics Service, Princess Anne Hospital, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[10]Faculty of Medicine, University of Southampton, Duthie Building, Southampton General Hospital, Southampton, UK

[11]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Kobenhavn, Denmark

[12]Department of Drug Design and Pharmacology, University of Copenhagen, Kobenhavn, Denmark

[13]Department of Epilepsy Genetics and Personalized Medicine Danish Epilepsy Centre, Dianalund, Denmark

[14]Department of Regional Health Research, University of Southern Denmark, Odense, Denmark

Correspondence
Nicolai Kohring Tvergaard and Allan Bayat, Department of Clinical Genetics, Kennedy Center, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100, Copenhagen Ø, Denmark,
Email: nicolai.kohring.tvergaard@regionh.dk and abaya@filadelfia.dk

Abstract

Ionotropic glutamate receptors (iGluRs), specifically α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs), play a crucial role in orchestrating excitatory neurotransmission in the brain. AMPARs are intricate assemblies of subunits encoded by four paralogous genes: *GRIA1-4*. Functional studies have established that rare *GRIA* variants can alter AMPAR currents leading to a loss- or gain-of-function. Patients affected by rare heterozygous *GRIA* variants tend to have family specific variants and only few recurrent variants have been reported. We deep-phenotyped a cohort comprising eight unrelated children and adults, harboring a recurrent and well-established disease-causing *GRIA1* variant (NM_001114183.1: c.1906G>A, p.(Ala636Thr)). Recurrent symptoms included motor and/or language delay, mild–severe intellectual disability, behavioral and psychiatric comorbidities, hypotonia and epilepsy. We also report challenges in social skills, autonomy, living and work situation, and occupational levels. Furthermore, we compared their clinical manifestations in relation to those documented in patients presenting with rare

heterozygous variants at analogous positions within paralogous genes. This study provides unprecedented details on the neurodevelopmental outcomes, cognitive abilities, seizure profiles, and behavioral abnormalities associated with p.(Ala636Thr) refining and broadening the clinical phenotype.

KEYWORDS
AMPAR, autonomy, developmental trajectory, epilepsy, GRIA1, natural history, outcome, syndrome, treatment

1 | INTRODUCTION

Ionotropic glutamate receptors (iGluRs) are pivotal in orchestrating excitatory neurotransmission in the brain. Among them, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) are integral components with a complex structure and functional significance.[1] AMPARs are composed of four subunits, designated GluA1-4 and encoded by *GRIA1-4*.[2] Most AMPARs form heterotetrametric complexes.[3] Each GluA1-4 subunit has three key domains: the N-terminal domain (NTD), the agonist-binding domain (ABD), and the transmembrane domain (TMD) which is comprised of four helices (M1-M4).[3] Particularly, the M3 helix forms the ion channel pore and controls gating through conformational changes upon receptor activation[3] (Figure 1A). This leads to the propelling of the excitatory postsynaptic current (EPSC), resulting in depolarization of the postsynaptic membrane and neuronal firing.[4] The M3 helix harbors a string of highly conserved amino acid residues across all GLUA1-4 subunits, designated the SYTANLAAF-motif, underlining its conserved critical role in regulating channel gating[4] (Figure 1B). Rare genetic variants in the *GRIA1-4* genes can disturb AMPAR physiology, leading to neurodevelopmental disorders (NDDs).[4–7]

While developmental, cognitive, behavioral, and psychiatric abnormalities, along with seizures and cerebral malformations, have frequently been associated with *GRIA2-4*,[6–10] *GRIA1* variants resulting in NDD have only been reported twice.[4,11] In one study, exome screening of 8477 NDD patients revealed *GRIA1* variants in six patients.[11] In the other study, investigation of six patients revealed that the *GRIA1* variants lead to either loss- or gain-of-function of EPSC.[4] Symptoms of these latter six patients included cognitive and developmental impairment and unspecified behavioral problems.[4] Six of the 12 reported *GRIA1* patients, carried a recurrent gain-of-function (GoF) variant: NM_001114183.1: c.1906G>A, p.(Ala636Thr).[11,4] However, the neurodevelopmental and epilepsy phenotype were only sparsely reported, and the knowledge on natural history into adolescence and adulthood was limited.

In this study, we carried out deep-phenotyping of eight unrelated individuals between ages 3 and 34 with the recurrent GoF variant p.(Ala636Thr) as well as compare their symptoms to those documented in patients presenting with rare heterozygous variants at analogous positions within paralogous *GRIA* genes.

2 | METHODS

2.1 | Study cohort

We identified patients carrying the recurrent GoF variant p.(Ala636Thr) through Genematcher[12] or an international network of epilepsy and genetic departments. We also contacted the healthcare providers of previously published patients to collect updated clinical information. Clinical and genetic information was collected from the treating physician or parent by an online questionnaire provided through REDCap. Data included, but was not limited to, seizure history, movement disorders, developmental milestones including regression/stagnation, behavioral and psychiatric issues, broad health information (i.e., dental, surgical, urogenital findings), and information on social skills (i.e., occupation, living situation).

Developmental delay (DD) was classified as mild, moderate, severe, or profound in children 5 years or younger. Patients older than 5 years were classified as having mild, moderate, severe, or profound intellectual disability (ID). An anti-seizure medication was considered effective if the patient achieved a >50% reduction in seizures for a period of greater than 6 months. The seizure and epilepsy types were classified according to the International League Against Epilepsy Classification.[13,14] Patients were classified as having a developmental and epileptic encephalopathy (DEE) if there was evidence that seizures and/or interictal EEG abnormality negatively impacted development or intellectual disability and epilepsy (ID+E) if they had developmental impairment and seizures but no evidence of an epileptic encephalopathy. Specific epilepsy syndromes were classified according to the diagnostic criteria on the ILAE new classification.[15–17] If a particular epilepsy syndrome could not be made, then each patient was classified as DEE or ID+E.

2.2 | Ethics

The study was conducted in agreement with the Declaration of Helsinki and approved by the local ethics committees. Informed consent was received from legal guardians.

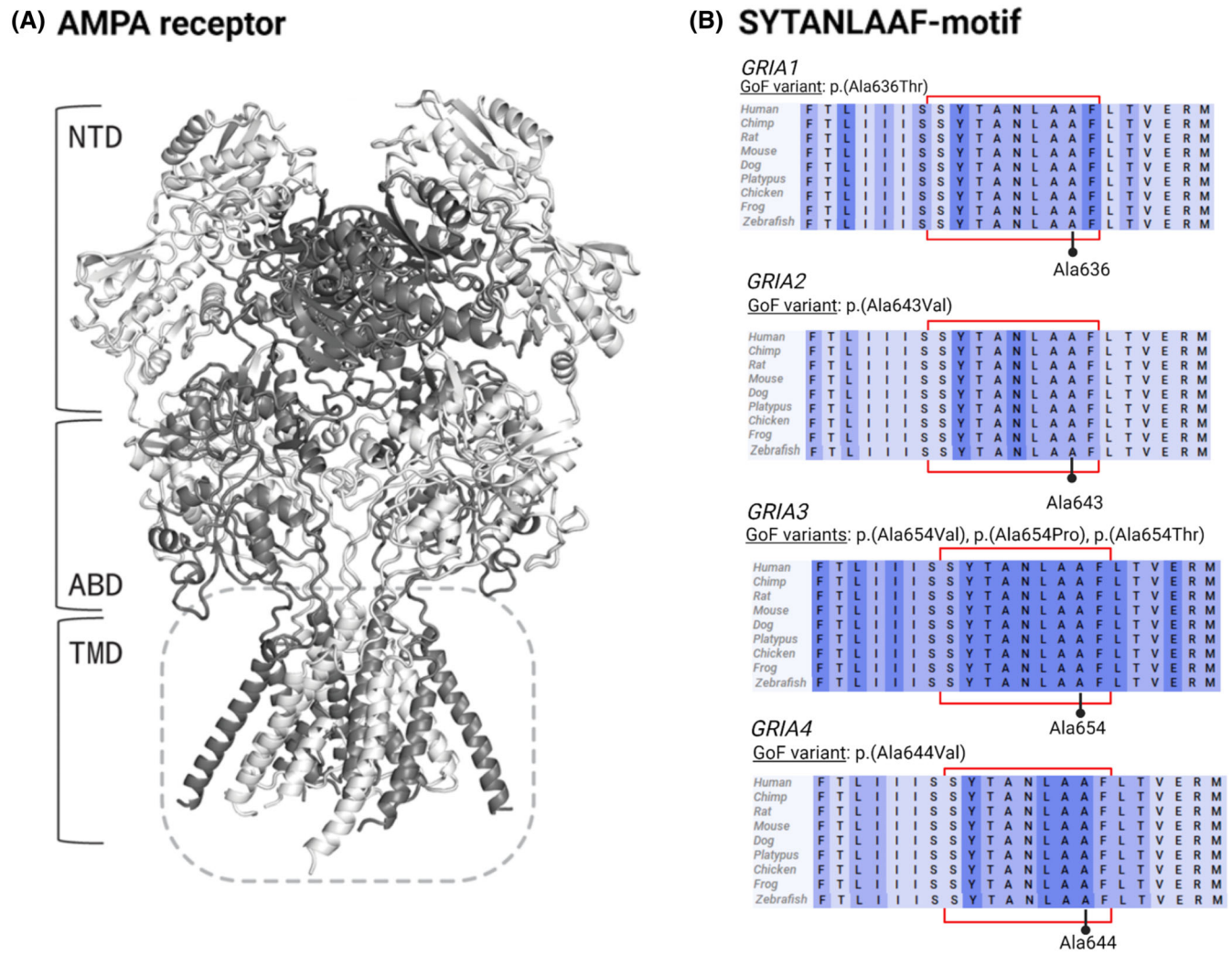

FIGURE 1 The AMPA receptor. (A) An AMPA receptor with two Glua1 subunits (white) and two Glua2 subunits (gray), constituting a heterotetrametric complex containing an N-terminal domain (NTD), agonist binding domain (ABD), and a transmembrane domain (TBD), with four helices (M1-M4). (B) Part of the M3 helix C-terminal amino acid sequence in *GRIA1-4* is visualized, with the SYTANLAAF motif boxed in red. All reported gain of function (GoF) variants found at the position equivalent to the recurrent variant p.(Ala636Thr) within the paralogous have been indicated.

2.3 | Genetic identification

The GoF variant p.(Ala636Thr) was detected through genome/exome sequencing either as trio or single sequencing followed by segregation analysis of the parents using Sanger sequencing and the variant is annotated using the transcript NM_001114183.1 (GRCh38/hg38).

3 | RESULTS

We identified eight unrelated patients (two females and six males) with the p.(Ala636Thr) variant. The mean age at time of reaching a genetic diagnosis was 6.2 years (range 2–12 years) while the mean age of patients is currently 13.4 years (range 3–34 years). Patients #4 and #5 were previously reported as "Patient Stockholm 5015-11D"[11] and "Patient Stockholm 2688-10D."[11] Further, patient #7 has also been reported previously.[4] A summary of clinical features is provided in Table 1, while Table S1 offers a complete clinical dataset.

3.1 | Neurodevelopmental outcomes

The first developmental concerns were evident in all patients prior to 24 months of life; mean age of 15 months (range 4–24 months) (Table 1). The concerns involved abnormal motor delay and/or speech delay in all patients. All patients learned to walk; average age of sitting and walking was 8 months (range 8–11 months) and 17 months (range 16–20 months), respectively. Patients #1 and #2 had neonatal hypotonia which later resolved. Patients #3–5 and #8 were reported to have a mild degree of hypotonia. Neither joint hypermobility nor increased muscle tone was reported. Out of eight patients, three had normal gross motor function while five required support for longer

TABLE 1 Clinical features of eight patients in our cohort with the recurrent p.(Ala636Thr) *GRIA1* variant.

Cohort information								
Patient number	1	2	3	4	5	6	7	8
Age	3 years	5 years	8 years	13 years	14 years	15 years	16 years	34 years
Published before	No	No	No	No	Yes (PMID: 28628100) Patient Stockholm 5015-11D	Yes (PMID: 28628100) Patient Stockholm 2688-10D	Yes (PMID: 35675825)	No
Gender	Male	Male	Female	Male	Male	Female	Male	Male
Neurodevelopment								
Age at developmental concern	12 months	8 months	12 months	20 months	4 months	24 months	18 months	24 months
Cause of concern	Non-verbal, not babbling	Unable to sit independently, late neck control	Low muscle tone and walking	Delayed walking	Head balance, neck muscle tone, plagiocephaly	Speech delay	General development, partly speech and engagement with others	Delayed motor and verbal skills
Age of sitting/walking	8/16 months	8/16 months	9/19 months	8/20 months	11/18 months	NR/14 months	8/18 months	10/18 months
First word/sentence	Non-verbal	30/48 months	48/NR months	36/44 months	24/51 months	18/36 months	NR/NR	15/24 months
Language impairment*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gait/endurance*	Normal/impaired	Normal/impaired	Normal/impaired	Normal/impaired	Normal/impaired	Normal/impaired	Normal/impaired	Unsteady/impaired
Fine motorskills*	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired
Autonomous capabilities*	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired
Neurological and neuromuscular features								
Hypotonia/hypertonia	Hypotonia	Hypotonia	Neither	Neither	Neither	Neither	Neither	Neither
Movement disorders	No	No	No	No	No	No	No	Ataxia
Cognitive symptoms and behavior								
Degree of DD	Severe DD	Moderate DD	Severe DD	Moderate	Mild	Mild	Moderate	Moderate
Degree of ID	Not applicable due to age	Not applicable due to age	Severe ID	Moderate ID	Mild ID	Mild ID	Moderate ID	Moderate ID
Behavioral issues*	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Epilepsy*								
Epilepsy	No	No	Yes	No	No	Yes	No	Yes
Seizure type	NA	NA	Unknown-onset TCS (type 1); FIAS (type 2)	NA	NA	Unknown-onset TCS	NA	Unknown-onset TCS
Age at onset of seizure	NA	NA	6 years (type 1); 7.5 years (type 2)	NA	NA	2 years	NA	10 years

TABLE 1 (Continued)

Epilepsy syndrome	No	No	ID+E	No	No	ID+E	No	ID+E
Treatment resistant	NA	NA	No	NA	NA	No	NA	Unknown
1st ASM used	*NA*	No	VPA	No	No	OXC	*NA*	No
ASM response	*NA*	*NA*	No effect	*NA*	*NA*	Seizure free (>6 months)	*NA*	*NA*
2nd ASM used	*NA*	*NA*	PER	*NA*	*NA*	*NA*	*NA*	*NA*
Response to 2nd ASM	*NA*	*NA*	Seizure free (>6 months)	*NA*	*NA*	*NA*	*NA*	*NA*
Brain MRI								
Findings*	Normal	Normal	Normal	Not performed		Abnormal	Normal	Normal	Normal
Social information								
Occupational level	Pre-school institution for children with special needs	Normal pre-school with support.	Public school with support	Public school with support	School for children with special needs	School for children with special needs	School for children with special needs	Workshop for disabled patients (assisted employment)
Living situation	Living with parents	Living with parents	Living with parents	Living with parents	Living with parents	Living with parents	Living with parents	Institutionalized with support
Children	No, too young	No, too young	No, too young	No, too young	No, too young	No, too young	No, too young	No
Romanic relationship	No, too young	No, too young	No, too young	No, too young	No	Unknown	No	No
Other clinical features								
Observations	Gastrointestinal findings*, sleep disorders	Reflux, dental findings*	Recurrent/cyclic vomiting, Slight femur rotation		Hyperopia, urogenital findings	Reflux, Skeletal findings*	Secretory otitis media, constipation	Strabismus, sleep disorders	No
Surgery								
Yes/No	No	No	No	No		Yes*	No	No	No

Abbreviations: ASM, anti-seizure medication; DD, developmental delay; ID, intellectual disability; ID + E, intellectual disability with epilepsy; MRI, magnetic resonance imaging; NA, not applicable; NR, not reported; OXC, oxcarbazapine; PER, perampanel; VPA, valproate.

*Means that the answer and/or question topic is elaborated in Table S1.

distances despite being able to walk shorter distances independently; among these five patients, four had normal gait while one had an unsteady gait. While none of the patients reported regression in hand function, fine motor skills were impacted across the board: seven could eat with utensils, five could put on clothes, but only one could button a shirt or pants, and just three could use a zipper. Additionally, three patients could use scissors, four could brush teeth, one could write, one could draw, while a single patient had no purposeful hand usage (Table S1).

While only #1, presently at the age of 3 years, remains nonverbal, it is noteworthy that all other patients exhibited delayed speech acquisition (Table S1). The mean age at which initial words were spoken was 28 months, with a variation spanning from 15 to 48 months. For those who progressed to speaking in sentences, the average age was 31 months, with a range of 24–51 months. Among those with language abilities, verbal syntax manifested in various forms: two patients displayed normal syntax accompanied by dysarthria, three spoke in short sentences with dysarthria, one communicated through short sentences without dysarthria, while another utilized simple words without dysarthria (Table S1). Only a single patient (#7) had learned to communicate with sign language. Verbal regression was only reported in #8 around the age of 2 years; this patient is currently 34 years old and communicates using short sentences.

All patients exhibited cognitive impairment ranging among mild ($n = 2$), moderate ($n = 4$), and severe ($n = 2$) (Table 1). No cognitive regression was reported (Table S1).

A brain magnetic resonance imaging was available in seven patients and was found to be normal in six. Patient #5 was diagnosed with an abnormal corpus callosum and also a spinal stenosis; he later underwent decompression by laminectomy (age not reported) (Table S1).

3.2 | Seizures, epilepsy syndromes, and seizure outcomes

An epilepsy diagnosis was reached in 3/8 patients (37.5%) with mean age of 6 years (range 2–10 years) at time of seizure onset (Table 1). Seizure types at onset were unknown-onset bilateral tonic–clonic seizures as none of them were caught on EEG. Despite treatment initiation, they occurred either monthly or annually; they presented either during sleep ($n = 1$) or while awake ($n = 1$) and could be triggered by fever/infection ($n = 1$). One patient (#3) subsequently developed focal nonmotor seizures with impaired awareness during the follow-up period. This seizure type was observed weekly and there were no reported triggers. Epilepsy syndromes were classified as ID+E rather than DEE.

Seizure freedom was achieved in 2/3 patients (66%). The antiseizure medications that reached at least 50% seizure reduction included perampanel (#3) and oxcarbazepine (#6). None of the patients underwent vagal nerve implantation or were treated with ketogenic diet.

3.3 | Behavioral and psychiatric outcomes

A wide variety of behavioral problems were reported in seven patients; difficulty in making friends ($n = 7$), autism spectrum disorder (ASD) ($n = 7$), difficulty in understanding social situations ($n = 6$), attention deficit hyperactive disorder (ADHD) ($n = 6$), limited interests and repetition ($n = 5$), sensory seeking behavior ($n = 3$), sensory avoiding behavior ($n = 3$), anxiety ($n = 3$), obsessive compulsive disorder ($n = 2$), loss of interest in things that used to interest them ($n = 2$), sudden onset of reduced activity ($n = 1$). Mood swings were common and included episodes of rage ($n = 4$), high levels of frustration ($n = 3$), occasional aggressive outbursts toward others ($n = 3$), or self-damaging behavior ($n = 1$). Of the six patients diagnosed with ADHD, two were based on formal neuropsychological testing while four were based on clinical assessment (Table S1). For the ASD diagnoses, four were based on formal testing, while one was based on clinical estimate.

3.4 | Education, work, residence, and autonomy

All seven children lived with their parents, whereas the only adult patient (#8) was fully institutionalized. The adult patient participated in a workshop tailored for people with disabilities. Patients #4–8 were older than 12 years; however, none of them were reported to have a boy or girl friend. All seven children are currently enrolled in educational institutions where they received additional support as needed. This support varied, including attendance at a regular preschool with support ($n = 1$), a preschool for children with special needs ($n = 1$), a regular public school with support ($n = 2$), or a specialized school for children with special needs ($n = 3$). The cohort reported autonomous abilities such as independently reading ($n = 2$), counting ($n = 2$), having friends ($n = 1$), crossing the road safely ($n = 1$), and taking the bus ($n = 1$). Additionally, four patients (aged 3, 5, 8, and 14 years) remained completely dependent on others (Table S1).

3.5 | Additional outcomes

Sleep disorders were reported in two patients and included nocturnal awakening ($n = 2$) and head banging or body rocking while falling asleep ($n = 1$) (Table S1). Extra-neurological features were rare, these included reflux, constipation, and vomiting in five patients, and hyperopia, strabismus, high palate, secretory otitis media, enuresis, slight femur rotation, and hypoplastic atlas causing cervical spinal stenosis reported in one patient, respectively (Table S1). No autoimmune, cardio-vascular, or pulmonary findings were reported.

4 | DISCUSSION

We carried out clinical examination of eight unrelated patients with the heterozygous p.(Ala636Thr) variant in *GRIA1*. Recurrent symptoms

included delayed motor and/or speech development, mild-to-severe cognitive impairment, muscle hypotonia, and epilepsy. This study enabled us to deep-phenotype the motor skills (gait, endurance, and hand function), speech (verbal syntax and pronunciation), behavioral and psychiatric comorbidities, and sleep. It also offers the first delineation of social skills, levels of autonomy, the epileptology, living and work situation, and occupational levels. While this paper primarily focuses on a recurrent variant, it marks a significant milestone in *GRIA*-related research by establishing a novel standard for clinical data collection and evaluation. Notably, it stands as a pioneering study to thoroughly characterize not only patient symptoms but also natural history including living conditions, occupational levels, and levels of independence. This meticulous approach not only enriches our understanding of the variant but also opens new avenues for comprehensive investigation in this field.

We also compared our cohort with the six patients carrying the same variant already reported in the literature[4,11] and were able to further delineate the phenotypical spectrum as well as strengthen previously reported associations (Table 1). Although borderline ID has been reported once in the literature,[11] most suffer from moderate to severe ID/DD which is supported by our findings as only two of our patients suffer from mild ID. Seizures have only been reported once before[11] with onset at age 2 years, although, there were no description of the seizure semiology. We have previously reported that patients with *GRIA3* GoF variants present with seizures before their first birthday (median 1st month of life) while seizures associated with LoF *GRIA3* variants occur later than 1st year of life (median 16 months of life).[5] We found that *GRIA1*-related epilepsy is a recurrent feature that occurred on 3/8 (38%) patients with average age of onset around age 6 years (range 2–10 years). This underlines that patients with *GRIA1*-NDDs should be monitored for seizures beyond the first years of life. Interestingly, seizures in our cohort were treatable and 2/3 patients with epilepsy are currently seizure free while #8 has annual bilateral tonic–tonic seizures but is currently not on anti-seizure medication (Table 1 and Table S1).

Although rare heterozygous variants in *GRIA2-4* have been recognized as causative factors in NDDs for several years,[5–7] the association of *GRIA1* with a Mendelian disorder has emerged only recently.[4,11] The recurrent GoF variant p.(Ala636Thr) greatly alters the receptor sensitivity toward Glu, leading to a 25-fold reduced half-maximally effective concentration (EC_{50}).[4] The Ala636 residue is the third alanine in the SYTANLAAF-motif of the M3 helix that undergoes conformational changes during channel gating (Figure 1C).[4] Specifically, in silico models show that Ala636 exhibits nearly identical conformation across all four subunits when the gates are in their closed state.[4] This consistency is maintained by strong hydrophobic interactions with the side chains of the adjacent subunit, revealing the substitution of alanine with threonine as a destabilizing factor in closed-gate configurations, most likely due to additional bulk and polarity.[4] Given the high conservation of the SYTANLAAF-motif across all subunits, it is alluring to explore whether any pathological variation at this position, along with their associated phenotypes, have been reported in the paralogs (*GRIA2-4*). In *GRIA2-4*, the third alanine residue in the SYTANLAAF-motif is Ala643, Ala654, and Ala644, respectively.[5–7] Indeed, pathological GoF variants at these positions have been established in *GRIA2* (p.(Ala643Val)),[6] *GRIA3* (p.(Ala654Val), p.(Ala654Pro), p.(Ala654Thr)),[5] and GRIA4 (p.(Ala644Val))[18] (Figure 1B). In *GRIA2-4*, the GoF variants increase glutamate potency (decreased EC_{50}), much like the recurrent variant p.(Ala636Thr) in GRIA1.[5,6,18] Table 2 compares the phenotypes reported in NDD patients with these analogous variants. While patients with the GoF *GRIA1–4* variants share common phenotypic characteristics such as ID/DD, abnormal body tone, epilepsy, and behavioral issues, there are evident distinctions. Notably, *GRIA3* variants manifest a particularly severe phenotype characterized by neonatal-onset, treatment-resistance seizures, heightened risk of early mortality, and limited or absent verbal and/or motor skills (Table 2). Muscle hypertonia and hyperekplexia have so far exclusively been linked to the three *GRIA3* variants,[5] whereas patients with the paralogous *GRIA* variants typically display reduced body tone (Table 2).

Knowing whether a variant leads to gain- or loss-of-function may enable precision therapy, as the anti-seizure medication, perampanel, is a specific negative modulator of AMPAR.[6] Indeed, perampanel has previously been administered to a patient with the analogous variant p.(Ala643Val) in *GRIA2*.[6] A combination of ketogenic diet and perampanel successfully suppressed seizure activity in the patient and also lead to improved body tone and milestones.[6] Further, perampanel is currently prescribed to our patient #3 who has been seizure free for 6 months since treatment initiation. Although encouraging, further studies involving more patients are necessary to elucidate the genuine effect of such treatment endeavors. As conducting large randomized controlled studies is not feasible for rare genetic disorders, N-of-1 trials have been proposed as a valid alternative for such cohorts.[18] These trials involve systematically alternating between periods of treatment and no treatment in single or small number of patients. By doing so, they allow for the comparison of treatment efficacy within the same individual, thereby minimizing the effects of individual variation and providing personalized evidence for treatment effectiveness. Therefore, future N-of-1 trials are crucial for defining the efficacy of perampanel treatment of patients with GoF *GRIA1-4* variants, including the recurrent variant p.(Ala636Thr).

5 | CONCLUSION

In conclusion, this study investigates clinical symptoms of *GRIA1*-related NDDs, specifically focusing on patients carrying the recurrent GoF variant p.(Ala636Thr). Our cohort is the largest retrospective study of patients carrying this variant, expanding the understanding of the clinical spectrum and the natural history into adulthood. Key findings include a spectrum of neurodevelopmental challenges such as

TABLE 2 Comparative analysis of symptoms between patients in this cohort harboring the recurrent heterozygous p.(Ala636Thr) *GRIA1* variant and published patients manifesting rare heterozygous variants at analogous positions within paralogous *GRIA* genes.

Cohort information						
Gene	*GRIA1*	*GRIA2*	*GRIA3*	*GRIA3*	*GRIA3*	*GRIA4*
c.DNA position	c.1906G>A	c.1928C>T	c.1960G>C	c.1960G>A	c.1961C>T	c.1932C>T
Protein position	p.(Ala636Thr)	p.(Ala643Val)	p.(Ala654Pro)	p.(Ala654Thr)	p.(Ala654Val)	p.(Ala644Val)
Published before	No	PMID 36161652	PMID 38038360	PMID 38038360	PMID 38038360	PMID 29220673
Number of patients	8	1	1	1	1	1
Inheritance	De novo (6) Unknown (2)	De novo (1)	De novo (1)	De novo (1)	De novo (1)	De novo (1)
Functional effect of variant	GoF	GoF	GoF	GoF	GoF	GoF
Age	13.4 y (range 3–34 y)	32 mo	3.5 y (deceased)	9 y	5 mo (deceased)	4 y
Neurodevelopment						
Age at first developmental concern	15 mo (range 4–24 mo)	6 mo	NR	NR	NR	13 mo
Age of sitting	8 mo (range 8–11 mo)	12 mo	Non-ambulant	>1 y	NA	15 mo
Age of walking	17 mo (range 16–20 mo)	Non-ambulant	Non-ambulant	26 mo	NA	20 mo
First words	28 mo (range 15–48 mo)	Nonverbal	Nonverbal	3 y	Nonverbal	17 mo
Present verbal ability	Normal with dysarthria (2) Short sentences (4) Simple words (1) Nonverbal (1)	Nonverbal (1)	Nonverbal (1)	Can say long sentences but mostly they are short and repetitive (1)	Nonverbal (1)	Nonverbal (1)
Impaired fine motorskills	8/8	1/1	NR	NR	NR	NR
Developmental regression	1/8 (lost words around 24 months)	Yes	NR	NR	NR	NR
Neurological and neuromuscular features						
Muscle hypotonia	2/8	Yes	No	No	No	Yes
Muscle hypertonia	No	No	Yes	Yes	Yes	No
Movement disorders	1/8 (ataxia)	Unknown	Hyperekplexia, reflex nonepileptic myoclonia, tremor	NR	Hyperekplexia, reflex nonepileptic myoclonia	Clumsy gait
Hyperekplexia	No	Unknown	Yes	Yes	Yes	No
Cognitive symptoms and behavior						
Degree of global developmental delay	Mild (2) Moderate (4) Severe (2)	Profound (1)	Profound (1)	Moderate (1)	Severe (1)	Moderate–severe
Behavioral issues	8/8	Unknown	Crying spells, irritability	AO, ASD, reduced attention span	NR	ADHD, stereotypic hand movements, AO, ASD

TABLE 2 (Continued)

Formal ADHD diagnosis		No	No	Yes (48 mo)	No		NR	Yes (36 mo)		
Formal ASD diagnosis		Yes	No	Yes (age unknown)	NA		Yes (51 mo)	Yes (36 mo)		
Epilepsy										
Epilepsy diagnosis	3/8			Yes	Yes		No	No	Yes	
Age at onset of seizure	6 y (range 2–10 y)			9 mo	10 d		NA	NA	13 mo	
Seizure type	Unknown-onset TCS (3) FIAS (1)			Epileptic spasms syndrome, FTS, FIAS	FTS. FBTCS with apnea		NA	NA	NR (febrile seizures, status epilepticus)	
Treatable seizure	2/3 (one patient seizure free on PER, another seizure free for 10 years and off ASM			Almost seizure free on PER	Yes (partial seizure free on a combination of LMT, VPA, and CLZ)		NR	NR	Yes (partial seizure free with only febrile seizures)	
Brain MRI										
Abnormal brain MRI		1/8	Unknown	Normal (1 mo)		Normal (3 y)		Normal (8 d)		Normal
Other clinical features										
Sleep disorders	2/8; nocturnal awakening (2), head banging and body rocking while falling asleep (1)			Unknown	Yes	Yes (long wakefulness, nocturnal awakening)		NR		NR

Abbreviations: ADHD; AO, aggressive outburst; ASD, autism spectrum disorder; ASM, anti-seizure medication; attention deficit hyperactive disorder; CLZ, clonazepam; d, days; FBTCS, focal to bilateral clonic–tonic seizure; FBTCS: focal to bilateral tonic clonic seizures; FCS, focal clonic seizure; FIAS, focal impaired awareness seizure; FTS, focal tonic seizure; GoF, gain-of-function; LMT, lamotrigine; mo, months; MRI, magnetic resonance imaging; NA: not applicable; NR, not relevant; OXC, oxcarbazepine; PER, perampanel; TCS, tonic–clonic seizure; VPA, valproate; y, years.

cognitive and/or DD, absent or delayed speech, diverse behavioral and psychiatric comorbidities, epilepsy, and a significant reliance on external support. Our study not only broadens the clinical phenotype associated with *GRIA1*-related NDDs, but also underlines the potential therapeutic interventions for patients carrying the recurrent variant p.(Ala636Thr).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Zeynep Tümer https://orcid.org/0000-0002-4777-5802

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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