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Short communication

ADAM23 haploinsufficiency as a putative oligogenic contributor in an individual with focal epilepsy

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ABSTRACT

Purpose: ADAM23 is involved in neuronal excitability and interacts with LGI1, a known genetic risk factor for focal epilepsy. While *ADAM23* has been linked to canine seizures, a recent gene-burden meta-analysis first nominated it as a risk gene for epilepsy in humans. Building on these findings, our study aimed to explore the significance of truncating *ADAM23* variants in deeply phenotyped individuals with diverse seizure disorders.
Methods: We screened the exome sequencing data from 389 individuals with various seizure phenotypes for truncating variants in *ADAM23*. This report focuses on one individual harboring a heterozygous frameshift variant in *ADAM23*, selected for detailed analysis due to intriguing additional genetic findings.
Results: We identified a heterozygous frameshift variant (c.428del, p.Asn143Ilefs*26) in *ADAM23* (NM_003812.4) in a patient with drug-resistant, MRI-negative focal epilepsy accompanied by additional neurocognitive and behavioral issues. The *ADAM23* variant was inherited from an unaffected parent. Notably, the same individual carried inherited, truncating variants in two other brain-expressed, loss-of-function-intolerant genes: *TNRC6A* and *MAPK8IP3*.
Conclusion: These findings suggest that *ADAM23* contributes to epilepsy with reduced penetrance, potentially influenced by oligogenic factors. Although descriptive and hypothesis-generating, our data underscore the complexity of currently unexplored genetic contributions to epilepsy.

1. Introduction

ADAM23 encodes a cell adhesion molecule that is highly expressed in the brain and functionally involved in synaptic transmission and neurodevelopmental processes [1]. Furthermore, it is a key interaction partner of *LGI1*, which is an already well-established disease gene for focal (usually lateral temporal lobe) epilepsy [2]. Studies in animal models revealed that *Adam23* and *Lgi1* knockout mice display strongly overlapping phenotypes, with a homozygous loss resulting in lethal epilepsy and a heterozygous loss lowering the threshold for seizures [3,4]. In keeping with these preclinical observations, *ADAM23* has been identified as a common genetic risk factor for seizures in dogs (i.e., canine epilepsy), characterized by reduced penetrance [5,6]. Until recently, evidence for an association with human epilepsy was limited. However, a large-scale, biobank-based burden analysis identified *ADAM23* among the top-ranked hits, nominating heterozygous loss-of-function (LoF) variants as a novel genetic risk factor underlying common (non-lesional) epilepsies [7].

To investigate this further, we systematically screened the exome datasets of 389 individuals with various types of seizure disorders for heterozygous truncating variants in *ADAM23* to explore its potential pathogenic role in epilepsy. Herein, we report the intriguing findings identified in one individual with focal epilepsy, cognitive issues, and behavioral abnormalities.

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2. Patients and methods

2.1. Screened cohort

We screened exome sequencing (ES) data of samples that were collated through different epilepsy genetics research projects conducted at the Department of Neurology of the Medical University of Vienna, Austria (ethics committee numbers: 2051/2016, 1021/2018, 1186/2019, 1933/2024). The merged cohort comprised 389 people with various seizure disorders, including non-acquired focal epilepsy (n = 192), febrile seizures (n = 123), genetic generalized epilepsy (n = 23), developmental and epileptic encephalopathy (n = 18), lesional focal epilepsy (n = 17), and unclassified epilepsy (n = 16).

2.2. Exome sequencing

Exome sequencing was performed at the Institute of Human Genetics (Technical University of Munich, Germany) using Agilent or Twist enrichment kits and Illumina sequencing platforms. Variant analysis involved two pipelines (SAMtools and GATK HaplotypeCaller), as previously described in detail [8]. For this study, we specifically screened for heterozygous LoF (i.e., frameshift, nonsense, splice-site) variants in *ADAM23*. In the index case, we additionally performed an exploratory exome-based screen for heterozygous truncating variants in genes with a high probability of being loss-of-function-intolerant (pLI = 1), as defined by gnomAD.

2.3. Cortical expression mapping

We utilized a cortical mapping of the human brain transcriptome provided by the Allen Human Brain Atlas to visualize spatial signatures of cortical gene expression for the target genes [9].

3. Results

3.1. Cohort screening and genetic findings

Our variant screening approach led to the identification of one heterozygous truncating (i.e., frameshift) variant in *ADAM23* in a male patient with non-lesional frontal lobe epilepsy and cognitive impairment. Using trio ES including *de novo* screening, we did not identify any (likely) pathogenic variants in established monogenic epilepsy-associated genes. However, an explorative variant screening revealed two additional truncating (frameshift) variants in *TNRC6A* and *MAPK8IP3* in the same individual, both of which are genes that are also highly LoF-intolerant (as reflected by a gnomAD pLI = 1). The variants in *ADAM23* and *TNRC6A* were inherited from the patient's unaffected mother, while the *MAPK8IP3* variant was inherited from the unaffected father. The index patient's younger sister, who exhibited learning difficulties but no seizures, also carried the truncating *TNRC6A* variant, but not the variants in *ADAM23* and *MAPK8IP3*. Details on all three detected truncating variants are listed in Table 1, and the cortical gene expression profiles are visualized in Fig. 1. In the remaining epilepsy cases of the screened cohort, no truncating variants in *ADAM23, TNRC6A* and *MAPK8IP3* were identified.

3.2. Clinical vignette

The reported index patient is a male individual currently aged 35 years. Pregnancy, birth and early development was reported as normal. Except for posttraumatic seizures in the paternal grandfather, the family history was unremarkable. The index patient's sister experienced learning disability but no seizures. In the patient, epileptic seizures were first noted at the age of 10 years, initially occurring up to several times daily. The patient predominantly experiences nocturnal seizures. He typically wakes up, describing a hissing sound and a sensation of fear,

Table 1
Details of the three truncating variants detected in loss-of-function-intolerant, brain-expressed genes.

Gene (transcript)	gnomAD pLI	cDNA level	Protein level	Functional impact	Zygosity	gnomAD allele count	Inheritance	OMIM phenotype
ADAM23 (NM_003812.4)	1	c.428del	p.Asn143Ilefs*26	frameshift	heterozygous	0	maternal	N/A
TNRC6A (NM_014494.4)	1	c.1027_1030dup	p.Ala344Glufs*23	frameshift	heterozygous	0	maternal	"?Epilepsy, familial adult myoclonic, 6" (#618074)
MAPK8IP3 (NM_001318852.2)	1	c.1552dup	p.Met518Asnfs*37	frameshift	heterozygous	0	paternal	"Neurodevelopmental disorder with or without variable brain abnormalities" (#618443)

Abbreviations: gnomAD, genome aggregation database; OMIM, Online Mendelian Inheritance in Man; pLI, probability of being loss-of-function intolerant.

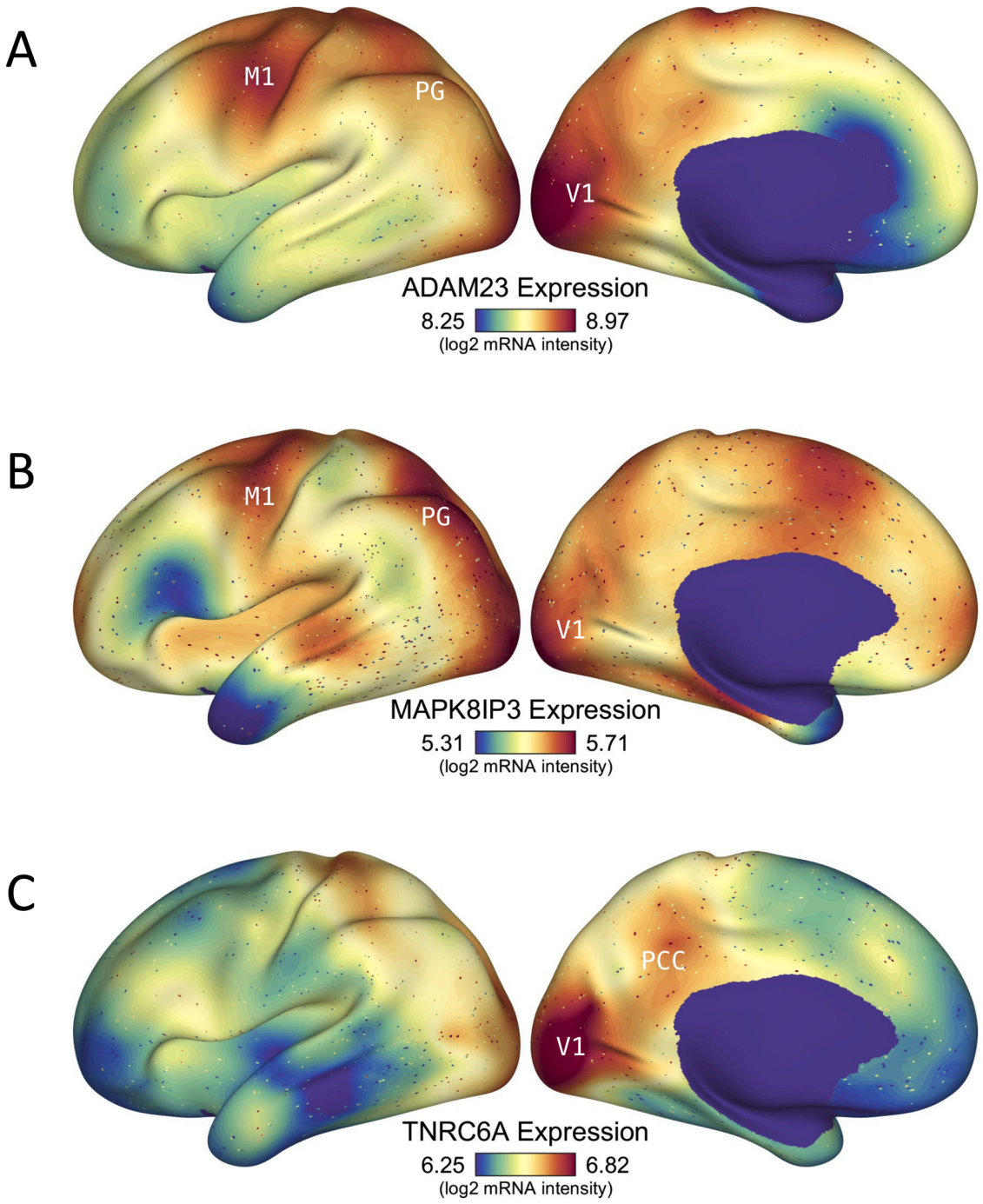

Fig. 1. Cortical gene expression for ADAM23, MAPK8IP3, and TNRC6A. ADAM23 (A) and MAPK8IP3 (B) show a high expression in the visual (V1), parietal cortex (PG), and motor cortex (M1). TNRC6A (C) shows a high expression in the visual cortex, particularly in V1, and posterior cingulate cortex (PCC).

followed by loss of consciousness and a bilateral tonic-clonic seizure. On average, the patient experiences status epilepticus 1-3 times per year. Since epilepsy onset, neurocognitive and behavioral issues with aggressive behavior have been noted.

Neuropsychological assessment revealed impairments in attention, language, memory, and visuospatial functions, along with mild depressive tendencies. Intellectual performance was significantly below average with an IQ of 67. Brain MRI revealed mild and unspecific periventricular leukoencephalopathy but no epileptogenic lesions. Long-term video EEG monitoring showed left frontal spikes, generalized spikes, and bifrontal slowing. Ictal EEG showed no clear pattern at onset, but a rhythmic bifrontal activity after seizure onset, together suggesting MRI-negative frontal lobe epilepsy.

Multiple anti-seizure medication (ASM) regimens since childhood (including oxcarbazepine, levetiracetam, valproate, phenytoin, topiramate, lamotrigine, lacosamide, carbamazepine, zonisamide) did not lead to sustained seizure control. Since then, he continued to experience multiple seizures per week. Due to severe treatment resistance, the patient underwent vagus nerve stimulation at the age of 20 years, resulting in a reduction in seizure frequency. At the last follow-up visit, seizure frequency was 1-3 per month, with status epilepticus or seizure clusters still occurring 1-3 times per year. Given the knowledge of the interaction potential, it was decided to maintain a combination of valproate, perampanel, primidone, and cenobamate as the current treatment regimen,

as this was found to be the most favorable option for the patient.

4. Discussion

Although preclinical data have repeatedly implicated *ADAM23* in seizure pathophysiology [3,4], the first genetic evidence in humans emerged only recently from a large biobank-based case-control analysis. In this work, *ADAM23* ranked among the top candidates, alongside well-established epilepsy genes. It has been proposed that *ADAM23* may be particularly relevant to common, non-lesional forms of epilepsy [7].

Motivated by these findings, we conducted a targeted screen for truncating *ADAM23* variants in previously sequenced epilepsy cohorts together comprising 389 cases. This identified one patient with focal epilepsy and cognitive impairment, carrying a maternally inherited heterozygous frameshift variant in *ADAM23*.

Notably, recent evidence suggests that individuals with presumably monogenic disorders, including epilepsies, often harbor multiple deleterious variants in evolutionarily constrained genes [10]. Indeed, in our case, additional truncating variants were identified in two other LoF-intolerant genes (pLI = 1). The second maternally inherited variant was a frameshift mutation in *TNRC6A*. This gene encodes a component of a cytoplasmic ribonucleoprotein complex involved in the regulation of mRNA silencing, stability, and translation [11]. While intronic repeat expansions in *TNRC6A* have been linked to familial adult myoclonic epilepsy, these are associated with mRNA toxicity rather than haploinsufficiency [12]. Despite its constraint against truncating variants, no monogenic disorder has so far been associated with truncating *TNRC6A* variants. Furthermore, a paternally inherited variant was found in *MAPK8IP3*, which encodes a component of the axonal transport machinery that plays a critical role in neuronal function and maintenance [13]. Both *de novo* missense and truncating variants in this gene have been linked to neurodevelopmental phenotypes with structural brain abnormalities [14,15]. The presence of recurrent missense variants and the fact that (predictably) truncating variants are only found in the N-terminal region of the gene rather argue against a classical LoF mechanism.

Due to the lack of well-established gene-disease associations we did not yield a monogenic epilepsy diagnosis in our case. Nonetheless, the presence of three inherited truncating variants in brain-expressed genes supports a hypothesis of oligogenic epilepsy. This aligns with recent findings implicating *ADAM23* in human epilepsy and suggesting a role of multiple deleterious variants in constrained genes underlying an oligogenic architecture [7,10].

Our index case had been diagnosed with non-lesional (non-acquired) focal epilepsy, but the phenotypic spectrum associated with *ADAM23* variants remains to be defined. Notably, *LGI1*, whose protein product interacts closely with ADAM23, is a well-established disease gene associated with autosomal dominant lateral temporal lobe epilepsy [2]. This functional link may support a role for *ADAM23* in focal epilepsy, although current evidence is limited. Most recently, biallelic variants in both *LGI1* and *ADAM23* were reported to cause early-infantile epileptic encephalopathy [16], suggesting that these (functionally connected) genes may contribute to a shared phenotypic spectrum ranging from non-lesional focal epilepsy in the heterozygous state to severe developmental and epileptic encephalopathy when biallelically affected.

The main limitation of our report is that it describes only one individual with *ADAM23* haploinsufficiency. Although our approach was guided by recent findings from a large-scale study using a case-control design [7], our interpretation of an oligogenic pathogenesis should be regarded as hypothesis-generating. The absence of additional cases with truncating *ADAM23* variants in our cohort precludes statistical assessment of variant burden. Another limitation is the absence of functional evidence for a causal relationship between the three variants and the phenotype. Given the involvement of three brain-expressed genes, gene-gene interactions may also play a role.

Taken together, future research efforts should focus on large-scale, genome-wide sequencing studies through multinational consortia to identify additional cases with truncating variants in *ADAM23*. Such efforts may also help establish whether these variants are enriched in epilepsy cases compared to healthy controls. In parallel, functional studies using experimental models are needed to elucidate the consequences of such variants, including potential gene-gene interactions that may contribute to the phenotype in our case.

To conclude, our gene-specific screening approach identified a unique genetic constellation suggesting a putative oligogenic contribution of *ADAM23, MAPK8IP3*, and *TNRC6A* in a patient with focal epilepsy. While our findings are inherently hypothesis-generating and descriptive in nature, they highlight the complexity of unexplored genetic contributions to epilepsy.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT (version GPT-4) for language optimization. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

All authors declare that they have no conflict of interest related to this article.

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