Precision therapy for a new disorder of AMPA receptor recycling due to mutations in ATAD1

ABSTRACT

Objective: ATAD1 encodes Thorase, a mediator of α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor recycling; in this work, we characterized the phenotype resulting from ATAD1 mutations and developed a targeted therapy in both mice and humans.

Methods: Using exome sequencing, we identified a novel ATAD1 mutation (p.E276X) as the etiology of a devastating neurologic disorder characterized by hypertonia, seizures, and death in a consanguineous family. We postulated that pathogenesis was a result of excessive AMPA receptor activity and designed a targeted therapeutic approach using perampanel, an AMPA-receptor antagonist.

Results: Perampanel therapy in ATAD1 knockout mice reversed behavioral defects, normalized brain MRI abnormalities, prevented seizures, and prolonged survival. The ATAD1 patients treated with perampanel showed improvement in hypertonicity and resolution of seizures.

Conclusions: This work demonstrates that identification of novel monogenic neurologic disorders and observation of response to targeted therapeutics can provide important insights into human nervous system functioning.

Supplemental data at Neurology.org/ng

GLOSSARY

AMPA = α-amino-3-hydroxy-5-methylisoxazole-4-propionate; AMPAR = AMPA receptor; ANOVA = analysis of variance; FDA = Food and Drug Administration; GABA = γ-aminobutyric acid; LOD = logarithm of the odds; ROH = region of homozygosity; SNP = single nucleotide polymorphism.

Clinical exome sequencing is becoming a standard of care for patients who remain undiagnosed after extensive diagnostic workup. Although exome sequencing reveals a diagnosis in 25%–40% of patients,1–3 obstacles continue to prevent genomic medicine from wide-spread use. Challenges include understanding the effect of gene variants on disease4,5 and using genomic information to improve an individual’s management.

We report an example of how these challenges can be overcome and, concurrently, describe a monogenic disorder caused by recessive loss-of-function ATAD1 mutations. Affected neonates demonstrate progressive extreme hypertonia, encephalopathy, and seizures. ATAD1 encodes Thorase, an AAA+ ATPase that internalizes postsynaptic α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors (AMPAR). AMPAR bind the major excitatory neurotransmitter, glutamate. Activity-dependent insertion and removal of postsynaptic AMPAR are integral to learning and memory.6 In ATAD1 knockout mice,7 loss of Thorase decreases internalization of AMPAR, resulting in increased postsynaptic...
receptor density, excitatory neurotransmission, excitotoxicity, and neuronal death. ATAD1 knockout mice have seizures and die between postnatal days 19 and 25. Given the similarity between mice and humans lacking functional Thorase, we designed a targeted therapeutic approach using the AMPAR antagonist, perampanel, and found that it improves behavior and survival in mice and eliminates seizures and improves tone in patients.

**METHODS** Further information can be found in the supplemental methods at Neurology.org/ng.

**Study design.** The objective of this study was to first identify the etiology of the subjects’ hypertonia and seizure disorder using exome sequencing and autozygosity mapping. Once the ATAD1 mutation was identified, the next objective was to evaluate the efficacy of the AMPA receptor antagonist, perampanel, in both a mouse model of ATAD1-associated disease and human ATAD1 patients. For mouse behavioral and imaging studies, a group size of 6 was chosen so that given an SD of 10%, an 18% difference in the mean values between the 2 groups could be detected with a power of 80%. The sample size for the human studies was determined by the number of available patients and family members. The human therapeutic trial was an open-label single-center compassionate use trial in the 2 affected patients. Because of technical limitations, the study was not randomized or blinded. Clinical improvement in the patients was measured using the Functional Status Score, a validated pediatric outcome measurement, see supplemental methods for more details.

**Standard protocol approvals, registrations, and patient consents.** Animal experiments were performed in compliance with the regulations of the Animal Ethical Committee of the Johns Hopkins University Animal Use and Care Committee. For human studies, written informed consent was obtained for the trial and for publications of photos and videos. The study was approved by the Children’s Hospital of Philadelphia Institutional Review Board. The use of perampanel was approved through a Food and Drug Administration (FDA) emergency investigational new drug application.

**Statistics.** Mouse imaging and behavioral data are graphed as mean ± SD. For statistical analysis of MRI results, distance calculations, and rest measurements, one-way analysis of variance (ANOVA) was performed followed by a Tukey post hoc test to compare mean values. For open-field analysis, a 2-way ANOVA followed by a Sidak post hoc analysis was performed. Multiplicity-adjusted p values were calculated. For survival analysis, a log-rank (Mantel-Cox) test was performed.

**RESULTS** Identification of recessive loss-of-function ATAD1 mutations. To obtain a diagnosis in a large consanguineous Kuwaiti family with multiple neonates affected with hypertonia, seizures, respiratory failure, and death (figure 1, supplemental results), we used clinical exome sequencing and single nucleotide polymorphism (SNP)-based homozygosity analysis. The proband (individual IV-6, figure 1) was symptomatic at birth and presented to our center at age 9 months. He was nonresponsive to tactile, visual, and auditory stimuli with no spontaneous movement and extreme hypertonia. EEG at 9 months showed hypsarrhythmia, a chaotic interictal pattern suggestive of severe brain dysfunction. He did not demonstrate infantile spasms as his extreme hypertonia precluded almost all movement. Brain MRI at 2 months of life was normal, but repeat at 9 months showed marked interval reduction in cerebral volume. Prior investigations (table 1) were unrevealing.

The second patient was the proband’s 2-month old male cousin (individual IV-3, figure 1). He also
Table 1  Initial examination features and prior evaluations for patient IV-6 and patient IV-3

| Feature                                      | Patient IV-6 | Patient IV-3 |
|----------------------------------------------|--------------|--------------|
| **Initial phenotypic features**              |              |              |
| Age at initial evaluation, mo                | 9            | 2.5          |
| Age at symptom onset                         | Birth        | Birth        |
| Age at initiation of perampanel, mo          | 16           | 2.5          |
| Age at first intubation, mo                   | 1            | 3.5          |
| Dysmorphic facial features                    | No           | No           |
| Birth growth percentiles                      | 50th–75th    | Small for gestational age |
| Hypertonia                                    | Yes          | Yes          |
| Clinical seizures outside hospital            | Yes          | Yes          |
| Reactive pupils on examination                | No           | Yes          |
| Present gag reflex                            | No           | Yes          |
| Able to blink to threat                      | No           | No           |
| Able to withdraw from pain                   | No           | Yes          |
| Hyperreflexia                                 | Yes          | No           |
| Inguinal hernia                               | Yes          | Yes          |
| Scoliosis                                     | Yes          | Yes          |
| **Diagnostic evaluations**                    |              |              |
| Brain MRI at 2 mo                             | Normal       | Normal       |
| Repeat MRI (age in months)                   | Progressive volume loss (9, 20) | Normal (5) |
| Brain MR spectroscopy                         | Normal       | Normal       |
| EEG                                           | Hypsarrhythmia | Abnormal background |
| Cardiac echocardiogram                        | Normal       | Normal       |
| Renal ultrasound                              | Multicystic dysplastic left kidney | Normal |
| Muscle biopsy                                 | Normal       | Not done     |
| Serum lactate                                 | Normal       | Normal       |
| Serum CK                                      | Normal       | Normal       |
| Urine organic acids                           | Normal       | Normal       |
| Plasma amino acids                            | Normal       | Normal       |
| Plasma acylcarnitine profile                  | Normal       | Not done     |
| Alanine aminotransferase, U/L (normal 5–45 U/L) | 47           | 44           |
| Aspartate aminotransferase, U/L (normal 20–60 U/L) | 102          | 62           |
| Karyotype                                     | 46, XY       | 46, XY       |
| Early infantile epilepsy gene panel           | No mutation  | Not done     |

Abbreviations: CK = creatine kinase; MR = magnetic resonance.

had a history of hypotonia and clinical seizures at birth. On first evaluation at our center at 2.5 months of age, he had little spontaneous movement and was extremely stiff (video 1). EEG at presentation while on phenobarbital demonstrated a background lacking normal mixture of frequencies and poorly formed sharp waves but no seizures. Brain MRI was unremarkable.

Exome sequencing of patient IV-6 revealed no mutations in known disease-causing genes. However, a homozygous nonsense variant of unknown significance in ATAD1 (c.826 G>T, p.E276X) was reported (figure e-1A). His parents each carried 1 copy of the change. The variant was classed as having a potential relationship to a disease phenotype. There are no previous reports of ATAD1 mutations in humans; however, mice harboring mutations in ATAD1 have frequent seizures, hypertonia, and early death. Compound heterozygote variants of unknown significance were also found in SZT2, which causes autosomal recessive epileptic encephalopathy type 18; however, the variants did not segregate in his affected sister (IV-5) and he did not fit this phenotype (supplemental results).

SNP analysis confirmed that the family was consanguineous (table e-1). Patient IV-6 was found to have a de novo 1.25 Mb duplication of 17p13.3 (for more details, see supplemental results). Overlapping duplications have been reported with variable phenotypes including mild dysmorphic features, learning disability, hypotonia, autism spectrum disorder, and mild brain abnormalities. This duplication was not present in affected individuals IV-3 or IV-5. Furthermore, given the extreme hypertonia and early respiratory failure seen in individual IV-6, we did not feel that this could fully explain his phenotype.

Homoyzogosity mapping revealed that the patient (IV-6), his deceased affected sister (IV-5), and affected cousin (IV-3) shared only one region of homozygosity (ROH) that was not shared with any unaffected relative (III 1–4 and IV-1, 2, and 7). This 6.5 Mb shared ROH (chr10:83,619,940–90,095,915, hg19 coordinates) contained 28 protein-coding genes, 14 of which are associated with a known disease phenotype (tables e-2 and e-3). ATAD1 is located in this shared ROH, while SZT2, the other candidate gene identified through exome sequencing, is not. Molecular analysis confirmed that all affected family members were homozygous for the p.E276X variant, while unaffected family members were not (figure 1). Multipoint genetic linkage analysis of 8 SNPs as markers in this region demonstrated a logarithm of the odds (LOD) score of 3.7 (table e-4), while the LOD score calculated directly using only the ATAD1 p.E276X variant was 3.5. An LOD score ≥3.3 has been shown to correspond to a genome-wide significance level of <0.05.

The effect of the p.E276X variant on ATAD1 expression was investigated in lymphoblastoid cells derived from the patient and an unaffected control. ATAD1 messenger RNA expression was decreased by 78% in p.E276X cells. This degree of reduction is consistent with nonsense-mediated decay, as noted by the absence of Thorase protein on Western blotting (figure e-1B). Investigation of ATAD1 variation in control populations revealed that in the Exome
Aggregation Consortium (exac.broadinstitute.org/gene/ENSG00000138138) database, only 3 loss-of-function variants were observed in the gene, while the expected number of loss-of-function variants is 14.9. This suggests selection against loss-of-function mutations in ATAD1.

Evaluation of perampanel as a therapeutic approach. Given that the p.E276X variant tracked with disease, decreased ATAD1 expression, and that ATAD1 knockout mice died of seizures, we concluded that this mutation was likely pathogenic. ATAD1 mutations increase AMPA receptor–mediated excitatory signaling due to impaired receptor recycling.7 Considering this mechanism of disease, we hypothesized that perampanel,14,15 a noncompetitive AMPAR antagonist could have therapeutic benefit. Therefore, we investigated the efficacy of perampanel in ATAD1+/− mice. Perampanel dosing in mice was based on prior studies8 and a dose escalation study (figure e-2).

Perampanel response in mice. Ex vivo brain MRI of ATAD1+/− mice (figure 2A) demonstrated a volume reduction in all areas examined as compared to controls. Perampanel treatment did not show significant prevention of volume loss; however, there was a trend toward improvement (figure 2B). Loss of ATAD1 was also associated with increased T2-signal intensity throughout the brain, which is indicative of brain pathology with increased fluid content (figure 2C). Perampanel improved whole-slice signal intensity in ATAD1+/− animals by 30.3% (95% confidence interval 11.3%–59.5%); further analysis of individual brain regions revealed improvement of signal intensity in the thalamus and striatum (figure 2D).

On open-field activity testing, ATAD1+/− mice showed both an abnormal activity pattern as compared to wild-type mice (figure 3, A–H) and decreased spontaneous movements as measured by the distance traveled and the total rest time (figure 3, I and J). Perampanel corrected these behavioral deficits, while phenobarbital, an antiepileptic that targets γ-aminobutyric acid (GABA) receptors rather than AMPA receptors, did not. ATAD1+/− mice

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**Figure 2** Perampanel improves brain MRI differences in ATAD1+/− mice

(A) Representative ex vivo brain MRIs of wild-type and ATAD1+/− perampanel-treated and perampanel-untreated mice. (B) Untreated ATAD1+/− mice (light blue bars) demonstrated volume reduction in all brain areas measured as compared to ATAD1+/− mice (black bars). Perampanel therapy (dark blue bars) was associated with a trend toward normalization of brain volumes. (C) Whole-slice T2 MRI signal intensity was significantly increased in ATAD1+/− mice. This change was reversed with perampanel therapy. (D) T2-signal intensity was increased in ATAD1+/− mice throughout the brain. Perampanel therapy normalized signal intensity in the striatum and thalamus. For all panels, n = 6. *p = 0.01–0.05, **p = 0.001–0.009, and ***p < 0.001.
showed no difference in rearing activity or average speed as compared to wild-type littermates (figure e-3). Extensive daily observations revealed that $ATAD1^{2/2}$ mice would have seizures on the day that they died. Video recording revealed that 5 of 5 vehicle-treated, as compared to zero of 5 perampanel-treated, $ATAD1^{2/2}$ mice demonstrated seizures (video 2). Finally, perampanel significantly prolonged average survival in $ATAD1^{2/2}$ mice by 115% (mean of 20 vs 43 days), while phenobarbital did not significantly increase survival (figure 3K). These results demonstrate the efficacy of targeted AMPAR blockade by perampanel in mice with impaired AMPAR endocytosis due to mutations in $ATAD1$.

**Perampanel response in humans.** Given the efficacy of perampanel in mice, we next considered a therapeutic trial in patients with $ATAD1$ mutations. Perampanel was recently approved by the FDA for the treatment of seizures and demonstrated minimal off-target toxicity in human studies\(^1\); we obtained permission for off-label compassionate use for treatment of affected individuals. Patient IV-6 was started on perampanel at 16 months of age; at this time, he had severe brain atrophy on MRI (figure 4A), hypertonia, absent cranial nerve reflexes, no spontaneous respiratory drive, and hypsarrhythmia on EEG. Within 8 days of starting perampanel, his tone improved and he developed a pupillary response to light. He continued to show dose-dependent neurologic improvement until his neurologic status plateaued at a dose of approximately 0.5 mg/kg/d (figures 4C, e-4, e-5). He also had resolution of hypsarrhythmia on EEG (figure 4, D-G). He was weaned off all nonperampanel antiepileptics, which included phenobarbital (dose at start of trial 6 mg/kg/d), topiramate (dose at start of trial 6 mg/kg/d), and valium (dose at start of trial 0.9 mg/kg/d). Despite therapy, he continued to have severe neurologic
deficits and worsening hydrocephalus requiring endoscopic third ventriculostomy.

In light of the clinical improvement seen in the proband, patient IV-3 was started on perampanel at 2.5 months of age. Given his young age, his neurologic function was more intact as compared to his cousin’s at the start of therapy. While he was profoundly hypertonic, he had normal cranial nerve reflexes and respiratory drive. After starting perampanel, he had rapid improvement in tone and normalization of his EEG (video 1). Like his cousin, he was weaned from his other seizure medications including phenobarbital (dose at start of trial of 2.5 mg/kg/d). Repeat brain MRI at 9 months of age showed no parenchymal volume loss while on perampanel (figure 4B), a finding that is dramatically different from what was seen in the proband at age 9 months (figure 4A, middle MRIs). Despite these
markers of improvement, he developed respiratory failure requiring intubation. However, his limited function was better as compared to his cousin who was untreated at the same age: he maintained all brain stem reflexes, sleep/wake cycles, the ability to withdraw and vocalize to pain, and spontaneous movements of all extremities (figure 4C, and supplemental information).

Functional improvement was also measured using the functional status score, a validated pediatric outcome measurement. This outcome assesses 6 functional domains (mental status, sensory, communication, motor, feeding, and respiratory function), each on a scale from 1 (normal) to 5 (severely impaired), and a composite score is calculated. Fully functioning children receive a score of 6, while maximal impairment is assigned a score of 30. Over the course of therapy, patient IV-6 had a score improvement from 29 to 24 (figure e-4, A and B). Patient IV-4 began the trial with a functional status score of 19 and showed an initial improvement to a low score of 17. However, his overall functional score worsened despite therapy at 3–4 months of age due to his respiratory failure (figure e-4, C and D). At the end of the therapeutic trial, his functional status score plateaued at 23, as compared to his untreated cousin’s score of 29 at the same age. This suggests that perampanel may improve functional outcomes but cannot completely prevent progression of disease.

**DISCUSSION** We describe a disorder of AMPAR recycling caused by mutations in *ATAD1*, a gene not previously known to cause human disease. Affected patients demonstrate hypertonicity, seizures, and early death. Targeted therapy with perampanel alters the pathogenic mechanism and provides benefit in both mouse models and patients.

This case series demonstrates the power of combining genomic testing and variant analysis using animal models. In addition, we confirm that combining detection of variants in novel genes and an understanding of disease mechanisms can inform care of an individual. This effort has achieved a clinical diagnosis, improved understanding of AMPAR function, and suggested therapeutic options.

As the first report of *ATAD1*-induced human disease, this work builds on previous observations that mutations that interrupt normal synaptic transmission can cause seizures. Postsynaptic receptor recycling is a known pathogenic mechanism in epilepsy; for example, mutations in *KIF5A* reduce postsynaptic expression of inhibitory GABA<sub>A</sub> receptors, reducing total inhibition and leading to seizures and encephalopathy. Unlike *KIF5A* mutations that decrease total inhibition, *ATAD1* mutations increase the population of excitatory postsynaptic receptors. Ultimately, either mechanism can disrupt the delicate balance between inhibitory and excitatory signaling and induce seizures.

While this study highlights the promise of personalized medicine, there are limitations to this work. *ATAD1* mutations have been identified in only one family. Typically, a gene is not considered as disease causing until it has been observed in 2 families. In this case, we have accumulated multiple lines of evidence supporting the pathogenicity of *ATAD*. First, the variant tracked within the family and LOD scores calculated both by a multipoint analysis method and the *ATAD1* variant itself showed statistically significant linkage. Second, we functionally showed loss of *ATAD1* protein in patient lymphocytes. Third, it is a stop-gain mutation and is absent from multiple control populations, and multiple computation programs predict its pathogenicity. Lastly, the *ATAD1* p.E276X variant is classified as pathogenic when applying the recently published ACMG variant analysis guidelines criteria for classification.

As this is a new, ultra-rare disorder, there is limited understanding of its natural history. This makes evaluation of perampanel efficacy difficult. For example, patient IV-3 required tracheostomy despite treatment with perampanel. It is possible that therapy was initiated too late in the natural progression of the disease or at too low of a dose to prevent this outcome. Nonetheless, he had better preservation of neurologic function than the few known untreated family members at the same age. The superior functional status scores in our patient initiated at a younger age could be related to drug effect or due to interindividual variation. Furthermore, we used an open-label therapeutic intervention strategy. This raises the possibility that treating physicians could be biased as to effect. To offset this, we used independent evaluation by multiple physicians. Clearly, more work is needed to fully determine the efficacy of perampanel in this syndrome and to elucidate the exact treatment paradigm to maximize outcomes.

Recently, a second function of *ATAD1* was reported; it acts as part of a quality control system for the mitochondrial membrane. It is unclear how this function may relate to the patients’ phenotype; perampanel would not be expected to reverse deficits in this pathway.

Despite the clear benefits of this individualized medicine approach, there is likely an intrinsic limitation to the maximal benefit of perampanel therapy in patients with *ATAD1* mutations. The high doses required in this disorder also inhibit the more subtle modulation of AMPA receptor activity that is crucial.
patients with receptor blocker, perampanel. These first studies to targeted therapy with an FDA-approved AMPA-receptor blocker, perampanel. These first studies establish the promise of this approach, but further studies are needed to elucidate both the natural history and the therapeutic potential of perampanel in patients with ATAD1 mutations.

AUTHOR CONTRIBUTIONS
Designing research studies: R.C.A.-N., G.K.E.U., N.S., M.A.D., T.M.D., V.I.D., and E.D.M. Statistical analysis: R.C.A.-N. and G.K.E.U. Conducting experiments: R.C.A.-N., G.K.E.U., N.S., M.A.D., A.B.W., L.K.C., A.B.S., A.N., J.J., E.M., and E.D.M. Analyzing data: R.C.A.-N., G.K.E.U., N.S., M.A.D., A.B.W., L.K.C., A.B.S., A.N., J.J., E.M., T.M.D., V.I.D., and E.D.M. Writing the manuscript: R.C.A.-N. and G.K.E.U. Editing the manuscript: R.C.A.-N., G.K.E.U., N.S., M.A.D., L.K.C., J.J., T.M.D., V.I.D., and E.D.M.

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