

Paroxysmal Movement Disorder and Epilepsy caused by a *de-novo* truncating mutation in  
*KAT6A*

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**Abstract**

Mutations in *KAT6A* encoding a histone acetyltransferase (HAT) involved in chromatin remodelling and in other genes involved in histone acetylation and/or deacetylation have been implicated in broad phenotypes of congenital and developmental abnormalities. However, limited genotype-phenotype correlations are available for some of the most rare or recently reported genetic disorders related to chromatin dysregulation. We hereby report a *de-novo* truncating mutation in *KAT6A* (c.3338C>G; p.S1113X) in a young male Patient with intellectual disability associated to impaired speech and autistic features, who also presented with infantile seizures and a complex movement disorder phenotype with paroxysmal episodes of abnormal startle responses.

**Key words:** *KAT6A*, *startle reflex syndrome*, *global developmental delay*

A 21 year old man, born to unrelated healthy parents of French and Scottish descent (Fig. 1A), presented since birth with hypotonia, feeding difficulties and a small head circumference (31.75 cm; <3<sup>rd</sup> centile). Pregnancy and delivery were uncomplicated and there was no history of neurological disorders in the family, except for a maternal uncle who had epilepsy during his childhood. During the first months of life a delay of developmental milestones was evident and he also had a history of focal and generalized infantile seizures, not associated to any recognizable trigger event, which spontaneously improved since the age of 3 years. Abnormal motor coordination and walking difficulties became evident in early infancy and progressed over time. At the current age of 21 years, the Patient has no yet autonomous gait, and requires a walker or sometimes a wheelchair. Speech was absent in his childhood and he still has a non-verbal communication. As part of his neurological phenotype, he has exaggerated startle responses, especially triggered by unexpected noises (Video 1). These episodes usually last a few seconds with the patient experiencing generalized jerky movements that sometimes lead to sudden falls. The patient's paroxysmal episodes were not accompanied by any EEG ictal patterns, suggesting abnormal startle response rather than myoclonic seizures. Additionally, some distinctive facial features are also evident with a coarse face, dysplastic ears, prominent nasal bridge, prominent lower jaw, highly arched palate and mild bitemporal narrowing. (Fig. 1A).

Repeated electroencephalography and brain magnetic resonance imaging (MRI) studies performed during the follow-up were negative. Because of his complex clinical and neurological phenotype he underwent several metabolic and genetic (including array comparative genome hybridization and panel sequencing of 55 genes causing intellectual disability) investigations that

were all reported as normal. Thus, a trio-based whole exome sequencing (WES) was performed in the family (Fig. 1A: I-1, I-2, II-1) as described elsewhere (1). We identified a *de-novo* heterozygous mutation in the *KAT6A* gene (c.3338C>G; p.S1113X, NM\_006766) (Fig. 1C).

We hereby describe a 21-years old man with a complex clinical phenotype consisting in congenital microcephaly, hypotonia, global developmental delay, intellectual disability, seizures as an infant, absent speech, and a paroxysmal movement disorder consisting in exaggerated startle responses to sudden/unexpected noises. It is not clear if these are part of the underlying neurological disease or whether they represent functional (psychogenic) jerky movements, since we had not the opportunity to perform a neurophysiological evaluation to assess response and latency times (2). To investigate the genetic cause of the disease in the Proband, we performed WES and as part of our filtering strategy, only exonic and donor/acceptor splicing variants were considered. In accordance with the pedigree and phenotype, priority was given to rare variants [ $<0.01\%$  in public databases, including 1000 Genomes project, NHLBI Exome Variant Server, Complete Genomics 69, and Exome Aggregation Consortium (ExAC v0.2)] that were fitting a recessive (homozygous or compound heterozygous) or a *de-novo* model and/or variants in genes previously linked to intellectual disability and neurological disorders. There were neither homozygous variants nor plausible compound heterozygous variants segregating with the disease in the family. We also excluded other genes' variants that could be related to familiar benign epilepsy and paroxysmal movement disorders (for example *PRRT2*). We identified a *de-novo* non-sense variant in *KAT6A* (c.3338C>G; p.S1113X) as the most likely explanation for the disease pathogenesis. This is supported by a severe impact of the truncating mutation (Fig. 1D) and existing reports of patients (N=18) linking *de-novo* non-sense mutations in this gene to a similar phenotype (MIM# 616268) with global developmental delay, intellectual disability,

abnormal growth, and impaired (or absent) speech. In addition, 3 out of 18 had feeding difficulties, 6 had distinctive facial features and 4 had congenital cardiac defects (i.e. 3 an atrial septal defect, 1 a ventricular septal defect) (3-7). One of these cases had epilepsy that we observed in our patient, but none had the exaggerated startle responses (5).

The *KAT6A* gene (MIM# 601408; also known as *MOZ* or *MYST3*) is abundantly expressed in the brain, with the highest levels during fetal development, and encodes a histone acetyltransferase (HAT) component of a multi-protein complex involved in several cellular processes (e.g. differentiation, metabolism, apoptosis) (5, 8). The gene contains 18 exons and encodes a large 2004 amino acid protein, which includes a nuclear localization domain, a double C2H2 zinc finger domain that binds to acetylated histone tails, and a histone acetyl-transferase (HAT) domain (Fig. 1D). Of interest, *KAT6A* knock-out mouse models have been reported with severe abnormalities affecting the brain, gastrointestinal tract and skeleton (9). Zebrafish genetic studies have also shown a crucial role of the chromatin remodeler gene *BRPF1* in regulating brain development through *KAT6A*- and *KAT6B*-mediated H3K23 acetylation (8). Yan *et al.* (10) showed that non-sense mutations either in *KAT6A* or *KAT6B* cause deficiency of histone H3K23 acetylation, indicating a new emerging group of (clinically) overlapping developmental disorders due to abnormal histone H3 acetylation.

In conclusion, we confirmed epilepsy as a possible early infantile presentation within the *KAT6A*-associated neurological phenotype and also added paroxysmal startle response as a potential novel feature associated to the neurological spectrum spectrum of this syndrome. The future description of other patients carrying *de-novo* *KAT6A* mutations will further expand the genotype-phenotype correlations in this rare and recently characterized genetic disorder.

## **CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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## **Ethical publication 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.

## **Author contributions**

Stephanie Efthymiou: study design and experimental data acquisition, analysis and interpretation of data

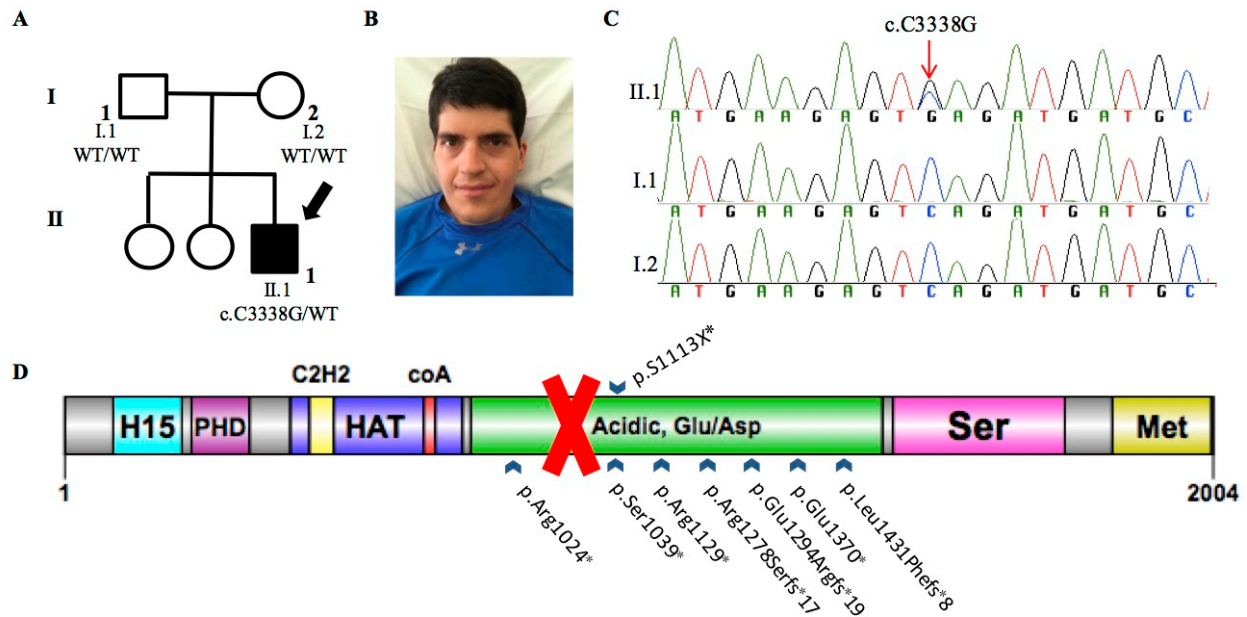
Dr. Vincenzo Salpietro: study concept and clinical data contribution to the manuscript, analysis and interpretation of data

Dr. Conceicao Bettencourt: critical revision of the manuscript document

Prof. Henry Houlden: study supervision

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**Figure 1.** (A) The pedigree diagram of the family. (B) The 21 year-old proband affected by exaggerated violent startle reflex syndrome due to *de-novo* *KAT6A* mutation. Note the distinctive facial features of prominent lower jaw and highly arched palate. (C) Individual results of Sanger sequencing showing the proband (II.1) carrying the *de-novo* *KAT6A* truncating mutation (c.C3338G; p.S1113\*) which is absent in both the parents (I.1, I.2). (D) A schematic illustration of the main functional domains of *KAT6A* protein: the nuclear localization domain (H15), a double-plant homeodomain finger (PHD), a histone-acetyl-transferase domain (HAT) containing a C2H2 zinc-finger domain (yellow), and an Acetyl-coenzyme-A-binding domain (red); an acidic glutamate/aspartate-rich domain and a transactivation domain with both a serine-rich (pink) and a methionine-rich (yellow) region. All previously reported *KAT6A* mutations indicated with arrows below while our mutated *de-novo* truncated version of *KAT6A* protein highlighted with the red cross and indicated with an arrow on the top.

**Video legend:** The proband experiences repeated episodes of exaggerated startle response



specifically in response to sudden or unexpected noise.