Journal of Genetics and Genomics xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Genetics and Genomics

Journal homepage: www.journals.elsevier.com/journal-of-genetics-and-genomics/

Letter to the editor

Expanding the genetic landscape of Rett syndrome to include lysine acetyltransferase 6A (*KAT6A*)

Pathogenic variants in methyl-CpG protein 2 (*MECP2*; OMIM 300005) result in an X-linked, severe, and progressive epigenetic disorder, Rett syndrome (RTT, OMIM: 312750), that predominantly affects females (Rett, 1966). Using Neul's revised diagnostic criteria, affected individuals can be clinically classified as classic or atypical RTT (Neul et al., 2010). After 6–18 months of apparently normal development, girls with the classic form of RTT gradually start losing their previously acquired skills including spoken language and other communication, coordination, and social interaction. Along with acquired microcephaly, affected girls lose purposeful use of their hands and develop midline stereotypic hand movements, breathing irregularities, seizures, scoliosis, and disturbed sleeping patterns. The partial/complete loss of spoken language is one of the core diagnostic criteria which is essential to be present for an affected individual to be classified as an individual with classic RTT. However, it is not necessarily a required criterion when classifying individuals with atypical RTT (Neul et al., 2010; Schonewolf-Greulich et al., 2019). As per the definitions adopted in the article by Neul et al. (2010) "… an individual who had learned to babble but then loses this ability is considered to have a loss of acquired language …" Owing to the broad variability of the phenotype in individuals with RTT, a proportion of them satisfy some, but not all, of the necessary revised diagnostic criteria and are classified as atypical RTT. Furthermore, individuals may be classified as RTT-like, exhibiting some clinical features associated with RTT, but not enough to be classified as either classic or atypical RTT (Ip et al., 2018). Approximately 97% of individuals with classic RTT and 86% of individuals with atypical RTT have pathogenic variants in *MECP2* (Neul et al., 2014). A small proportion of individuals with clinical features overlapping with RTT have been reported with pathogenic variants in cyclin-dependent kinase-like 5 (*CDKL5*, OMIM: 300203) and forkhead box G1 (*FOXG1*, OMIM: 164874); however, a significant proportion of individuals clinically classified as RTT remain without a definite genetic diagnosis (Armani et al., 2012).

Functionally, MeCP2 binds to the methylated CpG dinucleotides and regulates epigenetic modifications via transcriptional repression and activation, chromatin remodeling, and RNA splicing, processes which are critical for brain development and function (Sanfeliu et al., 2019). The epigenetic modifiers histone deacetylases remove the acetyl group from histone tails, condensing the chromatin and preventing transcription, whereas histone acetyltransferases (HATs) acetylate the conserved lysine residue of histones, resulting in chromatin unfolding and transcriptional activation (Portela and Esteller, 2010). Based on their homology, all 20 known HATs belong to one of the four families, including the MYST family (MOZ, Ybf2/Sas3, Sas2, and Tip60), whereby lysine (K) acetyltransferase 6A (KAT6A/MOZ/MYST3) is involved in chromatin regulation by acetylating histone H3 at K-9 and K-14 (Yang, 2015). Various animal and cellular model-based studies have provided evidence that defects in the epigenetic coregulator KAT6A result in impaired neurogenesis and craniofacial abnormalities, which may be relevant to developmental disorders in humans (Kong et al., 2014).

De novo heterozygous variants in *KAT6A* (OMIM: 6162680) have previously been associated with *KAT6A*-related intellectual disability syndrome, a rare neurodevelopmental disorder with variable clinical features depending on the location of the pathogenic variant (Arboleda et al., 2015; Tham et al., 2015). Although more than 50 protein-truncating, 6 missense, and 4 splicing variants feature across the whole *KAT6A* gene, the severity of clinical symptoms, including intellectual disability, speech delay, microcephaly, cardiac anomalies, and gastrointestinal complications, has been observed to be more severe when the protein-truncating pathogenic variants affect the last two exons of the gene (exon 16 and 17) (Kennedy et al., 2019). Thus, the global regulatory role of MeCP2 supports the notion that pathogenic variants in other genes associated with transcriptional regulation may underlie the complex regulatory neurodevelopmental disorder, RTT (Gold and Christodoulou, 2015; Kaur et al., 2019; Sanfeliu et al., 2019).

In this study, we present seven unrelated individuals between the ages of 3 years 8 months and 21 years 6 months identified as RTT or RTT-like, all of whom have different *de novo* heterozygous, late truncating variants in *KAT6A*. Based on Neul's revised diagnostic criteria (Neul et al., 2010), we have classified individuals 1 and 5 as potentially being compatible with a clinical diagnosis of atypical RTT. Five other individuals (individuals 2, 3, 4, 6, and 7) had a diagnosis of *KAT6A*-related intellectual disability, who on further review were found to have many RTT-like clinical features (Table S1). Among these five individuals classified as RTT-like, two individuals, individuals 6 and 7, were identified through the systematic reanalysis of previously published 76 individuals with *KAT6A*-related intellectual disability (Kennedy et al., 2019). All seven individuals had clinical features that are typical of *KAT6A*-related intellectual disability (Tham et al., 2015; Kennedy et al., 2019) (Table S2). Our findings highlight the importance of considering *KAT6A* as an alternative genetic etiology in individuals who might appear to have RTT syndrome or a RTT-like phenotype but who are negative on *MECP2* testing.

The cost of next-generation sequencing (NGS) potentially restricts access to the technology in individuals; however, several recent studies have highlighted the diagnostic impact of NGS

https://doi.org/10.1016/j.jgg.2020.09.003

techniques at a comparatively reasonable rate when used at an early stage in the diagnostic journey for individuals with severe intellectual disability (Stark et al., 2016). Thus, using NGS and reinterrogation of reported individuals with *KAT6A*-related intellectual disability, seven different variants in *KAT6A* were identified in this cohort (Table 1). Four individuals had nonsense variants: NM_006766.5:c.3385C>T; NP_006757.2:p.(Arg1129*) in individual 1, NM_006766.5:c.3820G>T; NP_006757.2: p.(Glu1274*) in individual 2, NM_006766.5:c.3631_3632del; NP_006757.2:p.(Val1211*) in individual 5, and NM_006766.5: c.3661G>T; NP_006757.2:p.(Glu 1221*) in individual 7. The other three individuals had frameshift variants that result in early truncation of protein translation: NM_006766.5:c.3399_3400dup; NP_006757.2:p.(Lys1134Argfs*14) in individual 3, NM_006766.5:c.3377del; NP_006757.2:p.(Ser1126 Phefs*8) in individual 4, and NM_006766.5:c.4254_4257del; NP_006757.2:p.(Glu1419Trpfs*12) in individual 6 (Fig. S1).

All *KAT6A* variants were *de novo*, monoallelic, and clustered in the last exon (exon 17) of *KAT6A*. Of the seven different variants, four were novel (individuals 2 to 5), whereas the variant in individuals 1, 6, and 7 had been previously reported in individuals with significant developmental delay, cardiac defects, and facial dysmorphism (Fig. S1 and 2; Table 1) (Arboleda et al., 2015; Kennedy et al., 2019), the latter of which distinguishes the *KAT6A*-related intellectual disability from RTT. Six of the variants (individuals 1 to 5 and individual 7) were predicted to result in partial loss of the well-conserved glutamate/aspartate-rich acidic domain and complete loss of serine/methionine-rich (Ser/Met) domain of KAT6A, whereas the variant in individual 6 resulted in complete loss of only the Ser/Met domain (Fig. S2 and 3). All seven *KAT6A* variants reported here are absent in the gnomAD population database. Moreover, the pLI score 1.0 in gnomAD highlights that *KAT6A* is extremely intolerant of loss-of-function variants. As per MutationTaster, these variants are likely to be disease causing (Table 1). In addition, using the American College of Medical Genetics (ACMG) guidelines, all the variants were rated as class 5 (pathogenic) (Table S3).

Although variants in *KAT6A* have previously been associated with the *KAT6A*-related intellectual disability spectrum of disorders, the association with RTT appears to have been previously unrecognized. We report seven individuals with pathogenic variants in *KAT6A* who have overlapping clinical features with RTT. Individuals 1 and 2 were clinically diagnosed as atypical RTT and RTT-like, respectively. Individuals 3 to 7 have a diagnosis of *KAT6A*-related intellectual disability, of which individuals 6 and 7 have been previously published (Kennedy et al., 2019). We collected additional clinical information on these five individuals from their referring clinicians and based on the Neul criteria (Neul et al., 2010); were it not for their facial dysmorphism, these individuals could be classified as atypical RTT (individual 5) or RTT-like (individuals 3, 4, 6, and 7). Only individual 1 and 5 exhibited a period of regression, followed by recovery or stabilization, and they had at least 2 of the 4 main criteria (not including loss of acquired spoken language) and 5 of the 11 supportive criteria, thus satisfying the requirements for an atypical RTT classification (Neul et al., 2010). All variants (4 novel and 3 previously reported) were predicted to be pathogenic and to cause C-terminal protein truncation, resulting in loss of the transactivation domain (glutamate/aspartate-rich acidic domain and Ser/Met domain) of the KAT6A protein. The nonsense-mediated mRNA decay (NMD) pathway is an evolutionarily conserved surveillance system that examines mRNA transcripts for premature termination codon errors and eliminates them from the transcriptome to avoid accumulation of deleterious proteins in the cell. However, the efficiency of NMD largely depends on the position of the protein-truncating variant within the gene. Based on the exon junction complex model, if the premature termination codon is present at least 50 nucleotides upstream of the last exon-exon boundary, it is predicted to trigger NMD (Lindeboom et al., 2016). All the *KAT6A* variants discussed in this study are clustered in the last exon of the gene and so are predicted to escape NMD, resulting in the generation of a truncated protein. Such a truncated protein may cause its effect through a dominant negative or gain-of-function effect, potentially contributing to the phenotypic variability observed among individuals with *KAT6A* variants (Kennedy et al., 2019). This proposition is supported by a report that showed no significant decrease in the *KAT6A* mRNA levels in fibroblasts derived from two unrelated individuals with the p.(Arg1129*) variant compared with controls (Arboleda et al., 2015), indicating that NMD is not active in protein-truncating variants affecting the last exon of *KAT6A*.

The variant in individual 1 [p.(Arg1129*)] is located at a CpG base, which is the most recurrent variant in *KAT6A* and has been previously reported in eight affected individuals with the autosomal dominant form of cognitive disability (Arboleda et al., 2015). Consistent with eight previously published individuals with *KAT6A* syndrome and with p.(Arg1129*) variant, individual 1 in our cohort also exhibited intellectual disability, microcephaly, sleep disturbances, sleep apnea, severe speech delay, feeding difficulties, gastroesophageal reflux, constipation, mild facial dysmorphism, and dental abnormalities and also had congenital cardiac defects (atrial septal defects and a ventricular septal defect). However, unlike reported individuals, she did not exhibit recurrent infections or hypotonia and did not have a broad nasal tip. The proband also had infantile spasms with hypsarrhythmia, episodes of hyperventilation, and breath holding, which are not often reported in individuals with *KAT6A*-related intellectual disability, further highlighting the phenotypic variability among individuals with KAT6A variants. Arboleda et al., 2015 reported that this variant does not affect transcript stability; however, analysis of global histone acetylation patterns showed reduced H3K9 and enhanced H3K18 acetylation, suggesting dysregulated histone protein acetylation. Unfortunately, there was insufficient clinical information in those publications to allow us to apply the Neul criteria with confidence (Arboleda et al., 2015; Kennedy et al., 2019).

All the reported individuals exhibited global development delay, severe intellectual disability, absence of speech or severely delayed speech, abnormal muscle tone, and sleep problems. All individuals with *KAT6A* syndrome except individual 6 never acquired any speech, including single words, and thus, because no clear shift was noticed in their verbal development, they never lost an acquired verbal skill. Moreover, they did not have capability to sign or use assisted communication devices. With regard to individual 6, regression in speech can be ascribed to because she stopped verbalizing after learning to babble at 11.5 months of age, as described in supplementary information (Table S4). In addition, all the patients had feeding difficulties, gastroesophageal reflux, and constipation, which are common in individuals with late truncating pathogenic variants in *KAT6A* (Kennedy et al., 2019). Interestingly, individual 1 also had an intestinal malrotation associated with recurrent bowel obstruction. All the individuals in this report showed discrete but overlapping dysmorphic facial features seen in individuals with *KAT6A*-related intellectual disability. While only half of the individuals showed a broad nasal tip, bitemporal narrowing, high arched palate, and philtrum defects, almost all of the individuals had a thin upper lip, prominent nasal bridge, and dental abnormalities. Four individuals (individual 1, 5, 6, and 7) had congenital cardiac defects, notably atrial septal defect, ventricular septal defect, persistent ductus arteriosus, patent foramen ovale, leaky mitral valve, or pulmonary artery stenosis. Although individuals 1 and 4 were not reported to have recurrent infections, the other five reported individuals (individuals 2, 3, 5, 6, and 7)

Please cite this article as: S. Kaur, N.J. Van Bergen, B. Ben-Zeev *et al.*, Expanding the genetic landscape of Rett syndrome to include lysine acetyltransferase 6A (*KAT6A*), Journal of Genetics and Genomics, https://doi.org/10.1016/j.jgg.2020.09.003

Table 1
KAT6A variant analysis for individuals classified as RTT/RTT-like.

Category	Individual 1 (II:3) (family 1)	Individual 2 (II:1) (family 2)	Individual 3 (II:2) (family 3)	Individual 4 (II:2) (family 4)	Individual 5 (II:2) (family 5)	Individual 6 (II:1) (family 6)	Individual 7 (II:1) (family 7)
Classification	Atypical RTT	RTT-like	RTT-like	RTT-like	Atypical RTT	RTT-like	RTT-like
Genetic screening method	Singleton; WES	Trio; WES	Singleton; targeted sequencing	Singleton; WES	Singleton; WES	Singleton; WES	Singleton; WES
Variant	chr8:41792353G>A c.3385C>T; p.(Arg1129*)	chr8:41791918C>A c.3820G>T p.(Glu1274*)	chr8:41792338_41792339dup c.3399_3400dup p.(Lys1134Argfs*14)	chr8:41792361delC c.3377del p.(Ser1126Phefs*8)	chr8:41792106_41792107delGT c.3631_3632del p.(Val1211*)	chr8:41791481_41791484del c.4254_4257del p.(Glu1419Trpfs*12)	chr8:41792077C>A c.3661G>T p.(Glu1221*)
Zygosity	Het	Het	Het	Het	Het	Het	Het
Segregation	*De novo*	*De novo*	*De novo*	Not investigated[^]	Not investigated[^]	*De novo*[$]	*De novo*[$]
Loss of conserved domains	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Novel or reported	Reported, Arboleda et al. (2015)	Novel	Novel	Novel	Novel	Reported, Kennedy et al. (2019); (patient 13)	Reported, Kennedy et al. (2019); (patient 43)
Affected exon	Exon (17/17)	Exon (17/17)	Exon (17/17)	Exon (17/17)	Exon (17/17)	Exon (17/17)	Exon (17/17)
Location of the variant	Acidic domain and Ser/Met domain	Acidic domain and Ser/Met domain	Acidic domain and Ser/Met domain	Acidic domain and Ser/Met domain	Acidic domain and Ser/Met domain	Ser/Met domain only	Acidic domain and Ser/Met domain
In silico (MutationTaster)	Disease causing	Disease causing	Disease causing	Disease causing	Disease causing	Disease causing	Disease causing
gnomAD	Absent	Absent	Absent	Absent	Absent	Absent	Absent
ClinVar	Present	Absent	Absent	Absent	Absent	Present	Present
ACMG Rclassification	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic

RTT, Rett syndrome. WES, whole exome sequencing. GenBank transcript ID: NM_006766.5 (longest isoform), position: hg19:chr8:41,786,997-41,909,505, size: 122,509 bp, total exon count: 17; NCBI protein ID: NP_006757.2 (longest isoform), protein domains: N-term region of ENOK, MOZ, or MORF (NEMM domain; aa 1–206), plant homeodomain (PHD domain; 207–313), histone acetyltransferases (HAT domain; aa 314–787), glutamate/aspartate-rich acidic domain (788–1414), and serine- and methionine-rich transactivation domain (Ser/Met domain; aa 1414–2004).

[^] Testing was conducted in a NATA-accredited laboratory. The Integrated Genomic Viewer reads showed high-quality variants.

[$] Variants already reported to be *de novo* (Arboleda et al., 2015; Kennedy et al., 2019).

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had recurrent episodes of infections, which is a common feature observed in *KAT6A*-related intellectual disability. Some individuals showed abnormalities in magnetic resonance imaging of the brain: delayed myelination (individuals 2 and 5), craniosynostosis (individuals 3 and 7), and Arnold-Chiari type I malformation (individual 5). Most of the reported individuals also had ocular abnormalities: myopia (individuals 1 and 4), cortical visual impairment (individuals 3, 5, and 7), or strabismus, and three individuals had epicanthal folds (individuals 4, 5, and 6). Two males (individuals 3 and 5) also reported genitourinary problems including hydronephrosis and cryptorchidism.

According to Neul's diagnostic criteria for RTT, individuals with classic RTT exhibit developmental regression followed by stabilization and must also have all four of the main criteria (partial or complete loss of acquired purposeful hand skills, partial or complete loss of acquired spoken language, gait abnormalities, and stereotypic hand movements). Individuals with atypical RTT on the other hand may have at least 2 of the main criteria and 5 of the 11 supportive criteria. The individuals reported in this study have been classified on the basis of their key main and supporting criteria, and the two individuals (individuals 1 and 5) classified as atypical RTT meet those criteria, as highlighted in Table S1. All our reported individuals are nonverbal, which is also a common clinical feature observed in individuals with *KAT6A*-related intellectual disability. RTT is certainly less commonly diagnosed in males owing to its X-linked inheritance pattern, and the incorrect assumption is that it would likely be embryonically lethal in males (Reichow et al., 2015). Moreover, males with previously identified pathogenic variants in *MECP2* usually present with an earlier onset and more severe phenotype than females, typical of X-linked disorders. Interestingly, males who are mosaic for a pathogenic *MECP2* mutation may manifest a phenotype more characteristic of females with classical RTT (Schonewolf-Greulich et al., 2019). Of the three males reported in this study, individual 5 has been classified as an individual with atypical RTT based on the Neul's diagnostic criteria. This highlights the importance of careful consideration of RTT features during clinical assessment in genetically undiagnosed individuals carrying pathogenic variants in *KAT6A*, be they male or female, and in considering *KAT6A* during the genetic assessment in individuals with RTT.

Overall, although the reported individuals classified as RTT/RTT-like had a number of overlapping *KAT6A*-associated features, they exhibited considerable variability in their phenotypic presentations. This may be partly explained by the histone acetylation function of KAT6A, which is regulated by additional epigenetic and environmental factors (Kennedy et al., 2019). Mice with a homozygous deletion of *Kat6a* die during embryogenesis or in the perinatal phase owing to gastrointestinal abnormalities, cardiac defects, and skeletal, hematological, and immunological abnormalities. Of note, only approximately half of the *Kat6a* heterozygous mice have developmental abnormalities of the palate, thymus, cardiovascular system, and facial structures (Voss et al., 2012). These authors suggested that Kat6a may regulate the T-box transcription factor (*Tbx1*) locus. Further investigation of potential genetic and environmental factors suggested that abnormalities were due to either retinoic acid exposure or *Tbx1* haploinsufficiency (Voss et al., 2012). It is possible that the broad and complex phenotype of *KAT6A*-related intellectual disability with overlapping RTT features may be a consequence of the pathogenic variants in *KAT6A* interacting with a combination of environmental and/or epigenetic factors.

In conclusion, we have identified pathogenic protein-truncating variants in *KAT6A* in seven individuals who, were it not for their facial dysmorphism, could be classified as RTT/RTT-like. We suggest that analysis of *KAT6A* should also be considered in the curation of genomic data of individuals with a clinical diagnosis of RTT, particularly when features overlapping with *KAT6A*-related intellectual disability are observed. Our work has highlighted the critical role of chromatin regulators in the pathogenesis of RTT, which could be considered as a potential for targeted drug therapies aiming at restoring a normal acetylation profile in individuals classified as RTT/RTT-like with *KAT6A* variants.

Acknowledgments

We thank all the family members for taking part in this study. The research conducted at the Murdoch Children's Research Institute was supported by the Victorian Government's Operational Infrastructure Support Program, and Research Training Program scholarship (to S.K.). The work conducted at the University of Padova was supported by Italian Ministry of Health Young Investigator (GR-2011-02347754, to E.L.), and Fondazione Istituto di Ricerca Pediatrica – Città della Speranza (18-04, to E.L.). We acknowledge the Victorian Clinical Genetics Services for performing whole exome sequencing (WES). We also thank Chris Ieng and Damien Zammit for running the next-generation sequencing data on Cpipe. We would also like to acknowledge Vanessa Atkinson and Dr. Karen Carpenter from Diagnostic Genomics Laboratory, PathWest, for performing sequencing on individual 3. Recruitment and data collection of individual 7 was supported by the Australian NHMRC Centre of Research Excellence in Speech and Language Neurobiology (CRE-SLANG) (1116976).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgg.2020.09.003.

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12 February 2020
Available online xxx

Please cite this article as: S. Kaur, N.J. Van Bergen, B. Ben-Zeev *et al.*, Expanding the genetic landscape of Rett syndrome to include lysine acetyltransferase 6A (*KAT6A*), Journal of Genetics and Genomics, https://doi.org/10.1016/j.jgg.2020.09.003