

# Dominant Mutations in *KAT6A* Cause Intellectual Disability with Recognizable Syndromic Features

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Through a multi-center collaboration study, we here report six individuals from five unrelated families, with mutations in *KAT6A/MOZ* detected by whole-exome sequencing. All five different de novo heterozygous truncating mutations were located in the C-terminal transactivation domain of *KAT6A*: NM\_001099412.1: c.3116\_3117 delCT, p.(Ser1039\*); c.3830\_3831insTT, p.(Arg1278Serfs\*17); c.3879 dupA, p.(Glu1294Argfs\*19); c.4108G>T p.(Glu1370\*) and c.4292 dupT, p.(Leu1431Phefs\*8). An additional subject with a 0.23 MB microdeletion including the entire *KAT6A* reading frame was identified with genome-wide array comparative genomic hybridization. Finally, by detailed clinical characterization we provide evidence that heterozygous mutations in *KAT6A* cause a distinct intellectual disability syndrome. The common phenotype includes hypotonia, intellectual disability, early feeding and oromotor difficulties, microcephaly and/or craniosynostosis, and cardiac defects in combination with subtle facial features such as bitemporal narrowing, broad nasal tip, thin upper lip, posteriorly rotated or low-set ears, and microretrognathia. The identification of human subjects complements previous work from mice and zebrafish where knockouts of *Kat6a/kat6a* lead to developmental defects.

Intellectual disability (ID) or global developmental delay occurs in 1%–3% of all children. Copy-number variations and rare inherited (often X-linked or autosomal-recessive) conditions explain up to 25% of all cases. With massive parallel DNA sequencing, de novo heterozygous monogenic mutations have emerged as a major cause of different intellectual disability syndromes and are responsible for up to 40% of severe ID.<sup>1,2</sup> Mutations in several genes involved in the epigenetic regulation of gene expression have been linked to different ID-syndromes including K(lysine) acetyltransferases (e.g., *KAT6B* [MIM 605880]), histone deacetylases (e.g., *HDAC8* [MIM 300269]), or chromatin remodelers (such as *ATRX* [MIM 300032])<sup>3</sup>. Here we report the identification of mutations in histone K(lysine) acetyltransferase *KAT6A* [MIM 601408] by multi-center clinical diagnostic whole-exome sequencing of individuals with ID.

Five unrelated individuals with intellectual disability, hypotonia, feeding difficulties, cardiac defects, craniosynostosis, and distinct facial features were subjected to clinical WES in an attempt to identify the genetic cause of their intellectual disability syndrome (Figure 1, Table 1). All five were investigated and sequencing was ordered by four different hospitals: the Karolinska University Hospital, Children's Hospital of Philadelphia, Children's National Medical Center, and Medical City Hospital.

DNA was isolated from peripheral blood by standard procedures. WES was performed as trios in families 1, 2, 4, and

5 and subject 4 (II-2 in family 3, Figure 2C) from family 3 was sequenced as a single individual. For each subject, the parents provided written informed consent for WES. Individual 1 (II-1 in family 1, Figure 2A) was sequenced as part of a combined clinical/research project that was approved by the Ethics Committee of Karolinska Institutet/Karolinska University Hospital (Dnr 2012/2106-31/4). Coding sequences were prepared and captured with the Agilent SureSelect All Exon kit -v4 for subjects 1, 4, 5 (II-1 in family 4, Figure 2D) and 6 (II-1 in family 5, Figure 2E) and v5 for subject 3 (II-2 in family 2, Figure 2B) and sequenced on an Illumina HiSeq 2500 instrument in high output mode (2 × 100 bp) at either Oxford Gene Technology (OGT; Begbroke Science Park; subject 1), Children's Hospital of Philadelphia (subject 3) or GeneDx (subjects 4, 5, and 6). WES sequence data was mapped to the published human genome build UCSC hg19 reference genome using Burrows-Wheeler Aligner. Sequence variants were filtered for frequency and location using OGT software (subject 1); Cartagenia Bench Lab NGS software (subject 3) and GeneDx's XomeAnalyzer (subject 4–6). The average depth of coverage of the sequenced individuals and the average percentage of the exome that displayed at least 10× coverage was as follows: subject 1, 70×/98.5%; subject 3, 110×/98.7%; subject 4, 78×/96.6%; subject 5, 104×/96.5%; and subject 6, 186×/98.8%. Detected variants were selected for further analysis based on de novo and autosomal-recessive (homozygous

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<http://dx.doi.org/10.1016/j.ajhg.2015.01.016>. ©2015 by The American Society of Human Genetics. All rights reserved.



**Figure 1. Facial Characteristics of the Individuals with *KAT6A* Mutations**

Individuals with *KAT6A* mutations show distinct facial features. Subject 2 at 22 months (A) and 9 years (B); subject 3 at 22 months (C) and 9 years (D); subject 4 at 4 months (E) and 12 months of age (F); subject 5 at 10 months (G) and 4 years 4 months of age (H); subject 6 at 5 months (I) and 3.5 years (J); and subject 7 at 17 years (K and L). There are common features in all affected individuals, e.g., bitemporal narrowing, broad nasal tip, low-set ears, thin upper lip, and/or tented mouth, although other features such as ptosis, downturned corners of the mouth, micrognathia, and smooth philtrum can only be seen in a subset of the subjects. See [Table S1](#) for more details.

and compound heterozygous) inheritance. Targeted analysis did not identify a causal mutation in any gene present in the OMIM database and was therefore followed by a complete analysis of all coding regions.

The combined results showed de novo truncating mutations in *KAT6A* in all five affected individuals analyzed by WES ([Figure 2](#)). Four of the five detected *KAT6A* mutations were frameshift mutations caused by small insertions/deletions (indels): NM\_001099412.1: c.3116\_3117 delCT (p.Ser1039\*) in individual 3 (II-2 in family 2, [Figure 2B](#)); c.3830\_3831insTT (p.Arg1278Serfs\*17) in individual 6 (II-1 in family 5, [Figure 2E](#)); c.3879 dupA (p.Glu1294Argfs\*19) in individual 1 (II-1 in family 1, [Figure 2A](#)) and c.4292 dupT (p.Leu1431Phefs\*8) in individual 4 (II-2 in family 3, [Figure 2C](#)). The fifth subject (II-1 in family 4, [Figure 2D](#)) also had a truncating mutation in *KAT6A* that was caused by a nonsense change: c.4108G>T (p.Glu1370\*). All detected variants in *KAT6A* were verified by Sanger sequencing. Individual 2 (II-1 in family 2, [Figure 2B](#)) had the same c.3116\_3117 delCT *KAT6A* mutation found in her twin as shown by targeted Sanger sequencing. In summary, all six affected individuals harbored heterozygous de novo, truncating mutations in *KAT6A* that are unlikely to be benign variants ([Table 1](#)).

Next we browsed the DECIPHER database and identified an additional individual with a 0.23 MB deletion on chromosome 8, arr8p11.21(41786230–42022328)×1, NCBI build 37 (individual 7, II-1 in family 6, [Figure 2F](#); DECIPHER ID 271144; data not shown). The deletion had been identified by array comparative genomic hybridization (array CGH) at the Sheffield Diagnostic Genetic Services Laboratory (Sheffield Children's NHS Foundation Trust) using a genome-wide design from BlueGnome (BlueGnome 60k v2). The finding was confirmed by fluorescent in situ hybridization (FISH) using the BlueGnome RP11-

564G13 probe. Blood samples from both parents were also analyzed by FISH with the same probe and showed a normal signal pattern indicating that the deletion had occurred de novo in individual 7 ([Figure 2](#)). Two genes were affected by the heterozygous de novo deletion including the entire reading frame of *KAT6A* and two thirds of *AP3M2* (MIM 610469). Mutations in the latter gene have not been associated with a clinical phenotype.

To further delineate the phenotype of the *KAT6A* mutations, we focused our attention on the clinical findings in affected individuals. None had any family history of a similar phenotype (apart from the monozygotic twins in family 2; [Figure 2B](#)). Briefly, the subjects share several characteristics including hypotonia, developmental delay, early feeding and oromotor problems, microcephaly and/or craniosynostosis, and cardiac defects including patent ductus arteriosus (PDA) and atrial septal defect (ASD) ([Table 1](#)). Furthermore, they have subtle facial manifestations with resemblances including bitemporal narrowing, broad nasal tip, thin upper lip, posteriorly rotated or low-set ears, and microretrognathia ([Figure 1](#)). The detailed clinical information of all individuals with *KAT6A* mutations is provided in [Table 1](#) and [Table S1](#).

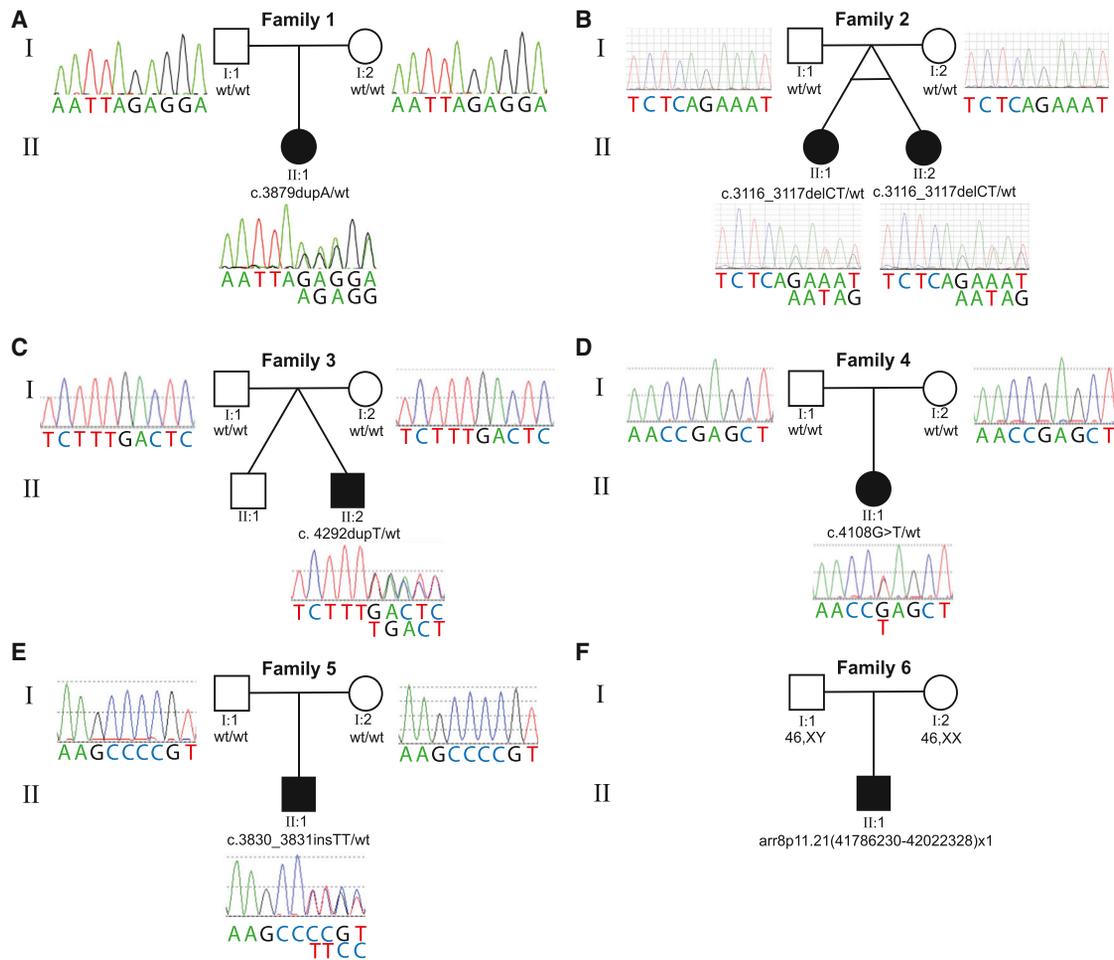
Six individuals were delivered by emergency cesarean section, and four showed severe life-threatening neonatal problems including respiratory distress and/or low Apgar scores. Five out of seven subjects had congenital heart defects (CHD), four of which needed surgical reparation. The most common CHDs were atrial septal defects (four), persistent ductus arteriosus (five), while ventricle septal defect and persistent foramen ovale was found in one subject each.

During the neonatal period, hypotonia was evident in six individuals (subjects 1–6) and three individuals (subjects 2, 3, and 5) were initially tested for Prader-Willi

**Table 1. Major Characteristics of Individuals with KAT6A Mutations**

Characteristic	Individual 1 (II-1), Family 1	Individual 2 (II-1) (Twin A), Family 2	Individual 3 (II-2) (Twin B), Family 2	Individual 4 (II-2), Family 3	Individual 5 (II-1), Family 4	Individual 6 (II-1), Family 5	Individual 7 (II-1), Family 6
KAT6A mutation/ exon	c.3879 dupA p.Glu1294Argfs*19 exon 18	c.3116_3117 delCT p.Ser1039* exon 17	c.3116_3117 delCT p.Ser1039* exon 17	c.4292 dupT p.Leu1431Phefs*8 exon 18	c.4108G>T p.Glu1370* exon 18	c.3830_3831insTT p.Arg1278Serfs*17 exon 18	arr 8p11.21 (41,786,230-42,022,328) exons 1–18
Sex/current age	F-2.3y	F-10y	F- sudden death, 10y	M-1.3y	F-6.5y	M-2.2y	M-17y
Birth weight and age of gestation	3.3 kg, 37 wks	2.2 kg, 32 wks	2.0 kg, 32 wks	2.18 kg, 36 wks	3.2 kg, 39 wks	2.4 kg, 38 wks	2.37 kg, 37 wks
<b>Neurological features</b>							
Global dev. delay	+	+	+	+	+	+	+
Speech delay	+	+(Sign language)	+(Sign language)	+	+	+	+
Neonatal hypotonia	+(Axial, stiff extremities)	+	+Infantile, then mild	+Significant	+	+(Axial, stiff extremities)	?
<b>Craniofacial features</b>							
Skull abnormality	Craniosynostosis, microcephaly	Craniosynostosis	Recurrent craniosynostosis	(Large AF)	–	Plagiocephaly, microcephaly	Microcephaly
Bitemporal narrowing	+	+	+	+	+	+	+
Broad nasal tip	+	+	+	+	+	+	+
Large/low set/posteriorly rotated ears	+/+/+	+/(+)	+/(+)	-/+/+	-/-/-	-/+/+	-/-/+
Thin upper lip	+	+(tent)	+(tent)	+(tent)	+(tent)	+	+
DT corners mouth	+	+	+	+	(+)	Triangular mouth	–
<b>Other features</b>							
Cardiac defect/ Method of closure	PDA, ASD/ Surgery	PDA, ASD/ Catheter	PDA, PFO/ Spontaneous closure	PDA, ASD, VSD/ Surgery	ASD sec, PDA/ Catheter	–	?
Feeding problems	+	+	+	+	–	+	–
Eye problems	–	Ptosis, strabismus	Ptosis, strabismus	Nasolacrimal stenosis	Strabismus, suspected CVI	Limited fixation, suspected CVI	Strabismus, hypermetropia
Other features	5 <sup>th</sup> clinodactyly 3 hemangiomas Widely spaced nipples	Pre-auricular pits		Hypospadias Pre-auricular pits Widely spaced nipples Peg-shaped teeth	Epicanthal folds, L single transverse palmar crease, Right Sydney crease 5 <sup>th</sup> clinodactyly	Bilateral single palmar creases	Broad eyebrows, Crowded, abnormally shaped teeth

+, present; –, absent or investigation not performed; ?, no information available; F, female; M, male; AF, anterior fontanelle; DT, down-turned; PDA, patent ductus arteriosus; ASD, atrial septal defect; PFO, patent foramen ovale; VSD, ventricle septum defect; CVI, cortical visual impairment; L, left; 5<sup>th</sup> clinodactyly, clinodactyly of the fifth finger bilaterally.



**Figure 2. Pedigrees of the Families with *KAT6A* Mutations with Individual Results of Sanger Sequencing**

Pedigrees and *KAT6A* Sanger sequencing traces (A–E; with reverse strand in B) or array-CGH findings (F) in all families with *KAT6A* mutations. Squares denote males and circles denote females. Blackened symbols represent the affected children. The generation numbers are shown to the left and individual identification numbers are shown underneath the symbols.

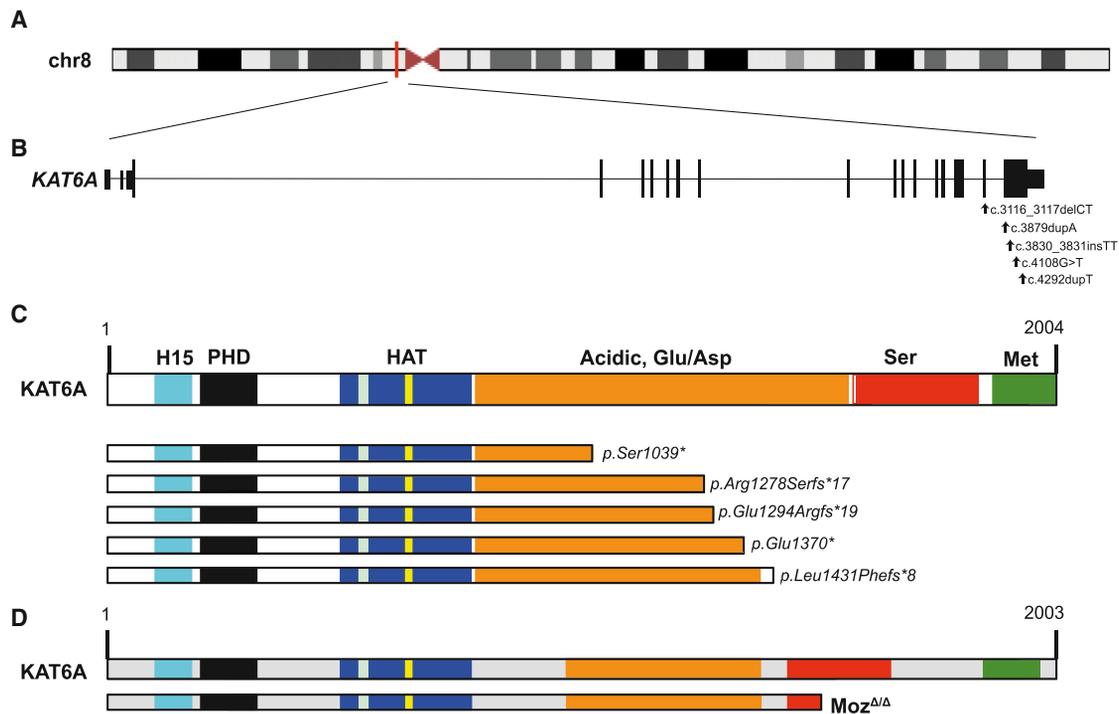
Syndrome (MIM 176270). In individual 1 and 6, the hypotonia was clearly axial with hypertonicity in the legs. In five individuals, a primary issue during infancy and childhood was feeding difficulties. Three required a gastrostomy tube (subjects 2, 3, and 6), one was fed by nasogastric tube (subject 4) and the last was flask fed with severe difficulties (subject 1). Individual 4 had a bilateral brain hemorrhage in subject 6. In addition, subject 4 had a large anterior fontanel.

Several individuals also had eye problems. Strabismus was evident in four children (subjects 2, 3, 5, and 7). Individual 3 was treated with patching and subject 5 with botox. Poor vision was found in three children with suspected cortical visual impairment in two (subject 5 and 6) and hypermetropia in one (subject 7). Ptosis requiring surgical correction was present in subject 2 and 3. Finally, Individual 4 had surgery due to nasolacrimal stenosis.

Global developmental delay was apparent in all individuals during the first year of life. The two youngest stood with support at 21 and 26 months of age, respectively, and four subjects walked independently starting at the ages of 17.5, 21, 36, and 36 months of age. An expressive

differed with only metopic suture closure not requiring surgical correction in subject 1, a squamous and slight inferior coronal craniosynostosis requiring two separate repair procedures in subject 2, a sagittal craniosynostosis requiring surgery and secondary metopic and sagittal recurrence requiring additional surgery in subject 3, and plagiocephaly in subject 6. In addition, subject 4 had a large anterior fontanel.

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**Figure 3. Genetic Location and Functional Consequences of Detected *KAT6A* Mutations**

(A) Schematic human chromosome 8. A vertical red line indicates the position of *KAT6A* at 8p11.21.

(B) A zoomed depiction of the *KAT6A* locus with a schematic illustration of exons (vertical black bars). The genetic position of all of the five *KAT6A* point mutations is marked by black arrows.

(C) A schematic illustration of the main functional units of human *KAT6A*: the nuclear localization domain (H15), a double-plant homeodomain finger (PHD), a histone-acetyl-transferase domain (HAT) containing a C2H2 zinc-finger domain (light blue), and an Acetyl-coenzyme-A-binding domain (yellow); an acidic glutamate/aspartate-rich domain and a transactivation domain with both a serine-rich (red) and a methionine-rich (green) region are also shown. The truncated *KAT6A* forms are shown below.

(D) The relative position of the truncated *KAT6A* in mutant mouse (*Moz*<sup>ΔΔ</sup>).<sup>11</sup>

language disorder was present in all, with a better non-verbal than verbal communication. The twin girls from family 2 communicated fully through sign language at age 10 years while individual 5 spoke 4- to 5-word sentences at age 6. The full extent of the cognitive disability in *KAT6A* mutation carriers will need to be further evaluated, as the affected individuals grow older. The limited data available today show that the two 10 year olds reached the approximate cognitive level of 5 years. However, the oldest individual (individual 7), with a heterozygous whole-gene deletion, showed only mild intellectual disability and was able to follow mainstream school with extra help.

Finally, discreet but overlapping facial features were evident. All had a broad nasal tip, bitemporal narrowing, a thin upper lip, and/or a tented mouth. Other common but variable features were low-set posteriorly rotated ears, smooth philtrum, down-turned corners of the mouth, and mild micrognathia (Figure 1; Table 1, Table S1).

*KAT6A*, also known as *MOZ* or *MYST3*, is located on chromosome 8p11 and was first identified as a fusion protein in individuals with acute myelogenous leukemia.<sup>4</sup> The full-length gene comprises 18 exons (16 coding) and has at least three major splice forms that differ in their 5' UTR, but all encode a protein 2004 amino acids in size. *KAT6A* contains several important functional domains: a nuclear

localization domain (including H15), a double-plant homeodomain finger that binds to acetylated histone H3 tails (PHD 1 and 2), a histone-acetyl-transferase domain (HAT), an acidic glutamate/aspartate-rich region, and a serine and methionine-rich region that comprises a transactivation domain<sup>4-7</sup> (Figure 3).

In humans, *KAT6A* is expressed in 49 out of 79 tissues analyzed in the human protein atlas including brain (high) and heart (low). The protein forms part of a histone acetyltransferase complex that acetylates lysine-9 residues in histone H3 (H3K9). Acetylated H3K9 is associated with transcriptionally active genes, whereas histone deacetylation is associated with transcriptional silencing. In this way, the *KAT6A* complex regulates a multitude of genes including the developmental Hox genes and is important for homeotic regulation.<sup>8</sup>

In zebrafish, *kat6a* is expressed in the head and is required for normal development of pharyngeal segments and for neural stem cell renewal.<sup>8-10</sup> In rodents, *Kat6a* is required for normal development of the thymus, the hematopoietic system, and the skeleton, and it is expressed in most tissues both in the embryo and in the adult mouse.<sup>8,11,12</sup> Further, mice heterozygous for a C-terminal deletion similar in size to that found in our families (Figure 3) displayed an intermediate phenotype compared

to the homozygous and wild-type pups as regards the number and function of hematopoietic progenitor cells, as well as the expression of Hox genes, showing that the *KAT6A* effect is dosage-dependent.<sup>8,11</sup>

A dosage-dependent mechanism is further supported by individual 7 in our study. He had a deletion of the entire *KAT6A* gene and displayed similar facial manifestations and symptoms to the subjects with truncating mutations, supporting the notion that haploinsufficiency of *KAT6A* is the cause of the phenotype in our subjects. All other detected mutations reported here cluster in exon 17 and 18, affecting the acidic glutamate/aspartate-rich region and truncating the protein at an amino-acid position somewhere between residue 1039 and 1439, resulting in loss of 29%–52% of the protein (Figure 3). Hence, the HAT domain is not directly affected by these *KAT6A* mutations. However, the human C-terminal region (amino acid 1039–2004) is highly conserved in multiple species with 55% overall identity to that of zebrafish; 85%–87% to chicken, mouse, and cow and 92% identity to dog (data not shown; Clustal Omega). Several important domains are located within this region including the transactivation domain of *KAT6A*. Unfortunately samples were not available from our subjects for mRNA or protein analysis, thus we could not determine whether or not the truncated mRNA was subject to nonsense mediated mRNA decay (NMD). Of note, the mice heterozygous for a C-terminal deletion of *Kat6a* comprising amino acid 1538–2003 (Figure 3) showed normal levels of mRNA but *KAT6A* was not detectable, suggesting a deficient translation or protein instability.<sup>11</sup>

Further highlighting the importance of the C-terminal region is a recent study that summarized 62 unrelated individuals with mutations in *KAT6B*, demonstrating that 89% of all mutations in *KAT6B* are truncating mutations located in the similar C-terminal region.<sup>13</sup> This *KAT6A* paralogue has a 60% overall amino-acid sequence identity to *KAT6A* and causes two different ID syndromes: genitopatellar syndrome (MIM 606170) or Ohdo syndrome/Say-Barber-Biesecker-Young-Simpson syndrome (MIM 603736).<sup>14–16</sup>

Our subjects display some differences in their phenotypic presentation. However, phenotypic variation is expected because *KAT6A* encodes a histone-acetylating component of a multi-protein complex that will be prone to genetic, epigenetic, and environmental modifiers. Interestingly, in the report by Voss et al., the murine phenotype was dependent on both genetic and environmental factors, the first shown by the additive effect of co-expression of *Tbx1* haploinsufficiency (MIM 602054) on the phenotype of *Kat6a* heterozygote mice, the second by fact that up to 42% of apparently healthy pups heterozygous for a C-terminal deletion of *Kat6a* developed severe cardiac anomalies, cleft palate, and thymic aplasia upon exposure to retinoic acid.<sup>17</sup>

In conclusion, after WES, array CGH, and careful clinical characterization, we propose that heterozygous truncating

mutations in *KAT6A*, as well as deletions of the same locus, cause a syndrome characterized by intellectual disability, craniosynostosis, cardiac defects, feeding difficulties, and distinct facial features. Additional subjects and functional studies will be needed to further delineate this rare disorder.

### Accession Numbers

The ClinVar accession numbers for the mutations in *KAT6A* reported in this paper are SCV000196161, SCV000196746, SCV000196511, SCV000196512, and SCV000196513.

### Supplemental Data

Supplemental data include one table and can be found with this article online at <http://dx.doi.org/10.1016/j.ajhg.2015.01.016>.

### Acknowledgments

We would like to thank all the individuals and their families for participating in this study and especially acknowledge the diligence and persistence of subject 4's mother whose relentless pursuit of a diagnosis for her son included a Facebook page that brought other children with *KAT6A* mutations to our attention. There is also a patient organization for individuals with *KAT6A* mutations: <http://www.chloekat6a.org>. This work was supported through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, by grants from Kronprinsessan Lovisa, Frimurare Barnhuset i Stockholm, Karolinska Institutet, The Cancer Research Foundations of Radiumhemmet, The Swedish Childhood Cancer Foundation, the Harald och Greta Jeansson's Foundation, the Nilsson-Ehle Foundation, the Erik Rönnerberg Foundation, the Swedish Research Council, The Swedish Brain Foundation (Hjärnfonden), and the Karolinska Institutet research funds.

Received: October 24, 2014

Accepted: January 20, 2015

Published: February 26, 2015

### Web Resources

The URLs for data presented herein are as follows:

1000 Genomes, <http://browser.1000genomes.org>  
ClinVar, <https://www.ncbi.nlm.nih.gov/clinvar/>  
Clustal Omega, <http://www.ebi.ac.uk/Tools/msa/clustalo/>  
DECIPHER, <http://decipher.sanger.ac.uk/>  
Ensembl Genome Browser, <http://www.ensembl.org/index.html>  
Mutalyzer, <https://mutalyzer.nl/index>  
NCBI, <http://www.ncbi.nlm.nih.gov/>  
OMIM, <http://www.omim.org/>  
RefSeq, <http://www.ncbi.nlm.nih.gov/RefSeq>  
The Human Protein Atlas, <http://www.proteinatlas.org/>  
UCSC Genome Browser, <http://genome.ucsc.edu>  
UniProt, <http://www.uniprot.org/>

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