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The *KAT6B*-related disorders Genitopatellar syndrome and Ohdo/SBBYS syndrome have distinct clinical features reflecting distinct molecular mechanisms

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Abstract

Genitopatellar syndrome (GPS) and Say-Barber-Biesecker-Young-Simpson syndrome (SBBYSS or Ohdo syndrome) have both recently been shown to be caused by distinct mutations in the histone acetyltransferase *KAT6B* (a.k.a. *MYST4/MORF*). All variants are *de novo* dominant mutations that lead to protein truncation. Mutations leading to GPS occur in the proximal portion of the last exon and lead to the expression of a protein without an activation domain. Mutations leading to SBBYSS occur either throughout the gene, leading to nonsense-mediated decay, or more distally in the last exon. Features present only in GPS are contractures, anomalies of the spine, ribs and pelvis, renal cysts, hydronephrosis and agenesis of the corpus callosum. Features present only in SBBYSS include long thumbs and long great toes and lacrimal duct abnormalities. Several features occur in both, such as intellectual disability, congenital heart defects, genital and patellar anomalies. We propose that haploinsufficiency or loss of a function mediated by the C-terminal domain causes the common features, whereas gain-of-function activities would explain the features unique to GPS. Further molecular studies and the compilation of mutations in a database for genotype-phenotype correlations (www.LOVD.nl/KAT6B) might help tease out answers to these questions and understand the developmental programs dysregulated by the different truncations.

Keywords

KAT6B; MYST4; mutation database; Genitopatellar syndrome; Ohdo Syndrome

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There are no competing interests.

INTRODUCTION

Whole exome sequencing recently facilitated the identification of mutations leading to the truncation of KAT6B (OMIM 605880), a histone acetyltransferase, in Genitopatellar syndrome (GPS) and SBBYSS (Campeau, et al., 2012; Clayton-Smith, et al., 2011; Simpson, et al., 2012). Genitopatellar syndrome (GPS) was first described in 1988 (Goldblatt, et al., 1988), and then delineated in 2000 (Cormier-Daire, et al., 2000). Characteristic findings are hypoplastic or absent patellae, flexion deformities, genital anomalies, microcephaly with agenesis of the corpus callosum and intellectual disability.

In 1986, Ohdo described two sibs and their cousin with blepharophimosis, ptosis, congenital heart defects, intellectual disability and hypoplastic teeth (Ohdo, et al., 1986). The Say-Barber-Biesecker-Young-Simpson (SBBYS) variant of Ohdo syndrome was later described by different physicians (Biesecker, 1991; Say and Barber, 1987; Young and Simpson, 1987) and is characterized by blepharophimosis, ptosis, an immobile mask-like face, a bulbous nasal tip, hypotonia, feeding problems, long thumbs and great toes, and dislocated or hypoplastic patellae. Congenital heart defects, cryptorchidism, dental anomalies and thyroid anomalies are often noted. The subjects in the original family described by Ohdo, in contrast to the later defined variant, had different facial features, proteinuria, no skeletal anomalies and a different mode of inheritance, and it is thus likely that they had a different condition from the SBBYS variant of Ohdo syndrome. An excellent classification and overview of blepharophimosis syndromes has been compiled (Verloes, et al., 2006) as well as a detailed analysis of the clinical features of the SBBYS variant of Ohdo syndrome (Day, et al., 2008).

KAT6B (a.k.a *MYST4* and *MORF*, *MOZ* related factor) was first cloned by searching collections of human expressed sequence tags for genes encoding MYST domain-containing proteins (Champagne, et al., 1999). *MOZ* (monocytic leukemia zinc-finger protein, a.k.a. MYST3 or more recently KAT6A, OMIM 601408) was itself first identified as a fusion protein with CBP deriving from translocations in acute myeloid leukemia (AML) (Borrow, et al., 1996), simultaneously to the identification of similar proteins with silencing roles in yeast (Reifsnyder, et al., 1996). *MOZ* has a highly conserved acetyltransferase domain shared with the yeast *YBF2*, *SAS2* and the human *TIP60* (KAT5, OMIM 601409), thus the term MYST-domain. *KAT6B* has the same highly conserved acetyltransferase domain and has been identified to also fuse with CBP (encoded by *CREBBP*, OMIM 600140) following translocations in acute myeloid leukemia and myelodysplastic syndrome, as reviewed in (Yang and Ullah, 2007). It is also disrupted by chromosomal translocations in multiple cases of uterine leiomyomata (Kojima, et al., 2003; Moore, et al., 2004; Murati, et al., 2004). *KAT6B* has been shown to interact with *RUNX2* (OMIM 600211) and *BRPF1* (OMIM 602410) in a tetrameric complex with *ING5* (OMIM 608525) and *MEAF6* (OMIM 611001) (Ullah, et al., 2008; Yang and Ullah, 2007). *KAT6B* was also co-immunoprecipitated with a PPAR-alpha interacting cofactor complex (Surapureddi, et al., 2002), and a yeast two-hybrid screen identified Atrophin-1 as a binding partner (Lim, et al., 2006). Mice hypomorphic for *Myst4* have a short stature, an absence of fusion of the tibia and fibula, microcephaly with neurogenesis defects, short palpebral fissures, low set ears and malocclusion (Kraft, et al., 2011; Merson, et al., 2006; Thomas and Voss, 2004; Thomas, et al., 2000). Despite these findings, the precise roles of *KAT6B* in regulating gene transcription during development have still to be defined. A better understanding of the phenotype resulting from *KAT6B* mutations may lead to insights into the molecular roles of *KAT6B*.

In this work, we describe the establishment of a mutation database, review genotype-phenotype associations, and explore the effect of mutations on protein function for *KAT6B*-related conditions.

MUTATION DATABASE AND GENOTYPE-PHENOTYPE CORRELATIONS

LOVD mutation database

Using the Leiden Open source Variation Database (LOVD) package hosted on the Leiden server, we have created a database for *KAT6B* (RefSeq NM_012330.2) which catalogs all known disease causing mutations (Fokkema, et al., 2011). The database can be publicly accessed at www.LOVD.nl/KAT6B. We have also added a column to the standard mutation database format to allow for detailed phenotype information to be entered (see Figure 1). Along with subjects with GPS and Ohdo (SBBYS) syndrome, we have also included a subject with a “Noonan-like” phenotype resulting from a translocation interrupting *KAT6B* in an early intron (Kraft, et al., 2011). Data on clinical features and mutations was drawn from recently published articles (Campeau, et al., 2012; Clayton-Smith, et al., 2011; Simpson, et al., 2012). A snapshot from this database can be seen in Figure 1.

Distribution of mutations

The distribution of the mutations for both conditions is shown in Table 1 and illustrated in Figure 2. Mutations causing GPS are seen in a cluster of residues encoded in exon 18 (the last exon); none of the GPS mutations have been shown to undergo-nonsense mediated decay and consequently truncated proteins are produced from these alleles. In contrast, mutations leading to SBBYSS occur seemingly randomly throughout the gene, leading to nonsense-mediated decay, or occur more distally in the last exon than the GPS-associated cluster.

Mechanism of mutations

The c.3769_3772delTCTA mutation recurring in 4 subjects with GPS occurs in a direct TCTA repeat, with the deletion of one TCTA repeat (see Figure 3 for diagrams). In SBBYSS, the recurring c.5201_5210dup mutation occurs in a palindromic repeat (TCGACGTCGT precedes the palindrome ACGACGTCGT which is duplicated by the mutation). Template-primer slippage would be the most likely mechanisms for these repeat mutations (Kunkel and Bebenek, 2000). Another unusual mutation is the c.4360_4368delinsAAAAACCAAAA mutation in GPS. Given the homology of the resulting DNA sequence to a region in an intron of *RALGAP2* (AAGAAGTACTGAAAAACCAAAAGA), it is possible that this mutation arises through a gene conversion event between *KAT6B*, located on chromosome 10, and *RALGAP2*, located on chromosome 20. The homology domain is however relatively short compared to most gene conversion events (Chen, et al., 2007).

Genotype-Phenotype correlation

With the use of the LOVD database, we have performed a detailed comparison of the clinical features, organized by syndrome, resulting from the various mutations in *KAT6B* (see table 2).

Skeletal features—Subjects with GPS have flexion contractures at the hips and knees and can also have club feet. A minority have radiological anomalies in the pelvis, spine and ribs. However, subjects with the same mutation do not consistently have these findings. In contrast, subjects with SBBYSS do not have skeletal anomalies but most have long thumbs and great toes, which are not seen in GPS. Interestingly, these features are only seen with distal truncations in *KAT6B*. Patellar anomalies are seen in both conditions, albeit more frequently in GPS.

Neurological features—Subjects with either syndrome have severe developmental delay and intellectual disability. Some have hypotonia at birth. Most subjects with GPS have microcephaly, whereas in SBBYSS many subjects have a smaller than average head circumference but not frank microcephaly. A thin or absent corpus callosum is seen in all subjects with GPS whereas this anomaly has not been observed in SBBYSS.

Anal and Genital anomalies—Anal anomalies such as anal atresia or stenosis, rectal duplication and an anteriorly positioned anus are occasionally seen in GPS but not in SBBYSS. Most females with GPS have clitoromegaly and/or hypoplasia of the labia (minora or majora). Cryptorchidism is seen in both conditions but scrotal hypoplasia has only been reported in GPS.

Renal and Cardiac anomalies—Hydronephrosis is seen in a majority of subjects with GPS and multiple renal cysts are seen in a minority. In a subject with SBBYSS whose mutation status is unknown, vesicoureteric reflux was reported (Day, et al., 2008), but otherwise subjects with SBBYSS do not have renal anomalies. Congenital heart defects are noted in about 50% of subjects with either syndrome, the most frequent defects being atrial septal defects, ventricular septal defects, and a patent foramen ovale.

Facial features—See figure 4 for a correlation of facial features with the location of the mutations. Subjects with SBBYSS have a very distinctive facial appearance with a mask-like facies, blepharophimosis and ptosis. Several subjects with Ohdo also have lacrimal duct abnormalities. Interestingly, a subject with GPS with a more distal mutation of *KAT6B* that overlaps with the region associated with SBBYSS has some degree of blepharophimosis and ptosis. Subjects with either condition can have prominent cheeks, and a nose with either a bulbous end or a broad or prominent base. Several subjects with either condition have micro/retrognathia or prognathism. Bitemporal narrowing and prominent eyes is noted in the GPS subjects with the p.Lys1258Glyfs*13 mutation (BCM4, KCL2 and KCL3).

Other features—Feeding difficulties are seen in both conditions. Contributing factors may be hypotonia in both syndromes, laryngomalacia in a minority of GPS subjects and cleft palate in some individuals with SBBYSS. Respiratory difficulties were noted in several infants with GPS; again, the hypotonia and laryngomalacia might have been contributing factors. Dental anomalies, thyroid anomalies, and hearing loss are seen in both syndromes, but more frequently in SBBYSS. Rarer features present in GPS are discussed in (Campeau, et al., 2012) and (Penttinen, et al., 2009), whereas those present in SBBYSS are discussed in (Day, et al., 2008).

CONCLUDING REMARKS

Proposed criteria to conduct molecular investigations

To help decide when to investigate *KAT6B* in subjects who present with features of GPS syndrome, we propose the following criteria:

- Children with patellar agenesis/hypoplasia who do not meet the criteria for other syndromes, such as Nail patella syndrome (*LMX1B*, OMIM 602575), small patella syndrome (*TBX4*, OMIM 601719), RAPADILINO syndrome (*RECQL4*, OMIM 603780) and Meier–Gorlin syndrome (OMIM 224690, pre-replication complex genes). A discussion on syndromes with patellar anomalies has been written by Bongers et al. (Bongers, et al., 2005).
- Children with 2 major criteria or 1 major criterion and 2 minor criteria:

- Major criteria: patellar anomalies, genital anomalies, flexion contractures including club feet, agenesis of the corpus callosum with microcephaly, and hydronephrosis or multiple renal cysts.
- Minor criteria: congenital heart defect, dental anomalies, hearing loss, thyroid anomalies, anal anomalies, hypotonia, developmental delay/ intellectual disability

Criteria for the clinical diagnosis of Ohdo/SBBYSS syndrome were proposed by White et al. (White, et al., 2003). These criteria included a mandatory presentation of blepharophimosis, ptosis, and intellectual disability. Supporting features included depressed nasal bridge, hypoplastic teeth, deafness, undescended testes and hypotonia. While these criteria are useful for a clinical diagnosis, this strict rubric may result in false negatives if used for genetic testing, due to variability in presentation. We feel the criteria to prompt molecular testing for *KAT6B* should be broader. We propose criteria similar to GPS that employ two major criteria or one major criterion and two minor criteria.

- Major criteria: Long thumbs/great toes, immobile mask-like face, blepharophimosis/ptosis, lacrimal duct anomalies, patellar anomalies
- Minor criteria: congenital heart defect, dental anomalies, hearing loss, thyroid anomalies, cleft palate, genital anomalies, hypotonia, developmental delay/ intellectual disability.

Insight in the molecular consequences of the mutations

Mutations proximal to the last exon, leading to reductions in protein levels (haploinsufficiency) lead to an SBBYSS phenotype. Distal mutations in the last exon, which also give SBBYSS phenotype, may thus lead to a similar phenotype by a loss-of-function mechanism. Yet, some of the facial and digit features of SBBYSS are only seen in individuals with the most distal mutations.

We thus hypothesize that features which overlap both GPS and SBBYSS such as developmental delay/ intellectual disability, patellar anomalies, heart defects, genital anomalies, and dental anomalies are likely to result of either haploinsufficiency or a the loss of a function normally mediated by the C-terminal region of the acidic domain (Fig 1). However, there are some unique features of GPS independent of SBBYSS. GPS mutations, which all lead to expression of a truncated protein (Campeau, et al., 2012; Simpson, et al., 2012), may account for the features of GPS that are distinct from those given by the haploinsufficiency mutations. These mutations may indicate that a truncated protein of a given length may gain a new function. We hypothesize that a gain-of-function may be caused by an altered binding affinity or dysregulated interactions with natural binding partners of *KAT6B*. In SBBYSS, the specific phenotypic consequences associated with longer but still truncated proteins imply that these proteins lack this new function.

Documentation of further genotypes and phenotypes into the LOVD database (discussed above) will likely provide a useful foundation from which to conduct future genotype-phenotype studies.

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Reference	Exon	DNA change	Protein	Patient ID	Disease	Clinical features
Simpson et al.	18	c.3773dup	p.Trp1259ValfsX12	KCL5	Genitopatellar syndrome	Female Clitoral hypertrophy Hypoplastic labia minora Absent patellae Flexion contractures of the hips Flexion contractures of the knees Aplasia of corpus callosum Severe intellectual disability Delayed motor milestones Microcephaly Coarse face Broad/bulbous nose Micrognathia Pelvic anomaly

Figure 1.

Partial snapshot of the *KAT6B* mutation database representing important information included in the database. The database includes the nucleotide and amino acid changes as well as a detailed list of clinical features presented by each subject.

Location of Genitopatellar syndrome mutations

Location of Ohdo/SBBYS syndrome mutations

Figure 2.

Diagram representing the location of the mutations associated with GPS and SBBYSS in MYST4 isoform 1 (RefSeq NP_036462.2). GPS-associated mutations are indicated above the gene, and SBBYSS mutations are shown below the gene. NEMM, N-terminal part of Enok, MOZ, or MORF; PHD, tandem plant homeodomain-linked zinc fingers; ED, glutamate/aspartate-rich region; SM, serine/methionine-rich region..

Genitopatellar syndrome

Ohdo/SBBYS syndrome

Figure 4.

Composite image of the location of the mutations in the last exon of *KAT6B* and the subjects carrying these mutations. Permissions to reproduce these images have been obtained from the publishers. Images are from the references in table 1, as well as references (Day, et al., 2008; Lammer and Abrams, 2002; Lifchez, et al., 2003; Reardon, 2002).

Table 1
Mutations identified in KAT6B-related conditions, in the order they are found in the gene.

Exon/Intron	DNA change	Protein	Subject ID ^a	Reference	Condition
Intron 3	t(10;13)(q22.3;q34)(c.621+26310_c.621+26311)	-	FAU1	(Kraft, et al., 2011)	Noonan syndrome-like phenotype
3	c.527dup	p.Tyr176*	CMFT11	(Clayton-Smith, et al., 2011)	Atypical SBBYSS
15	c.3018del	p.Glu1007Argfs* ₅	CMFT3	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.3680_3695del	p.Asp1227Glu fs* ₁₁	KCL1	(Simpson, et al., 2012)	Genitopatellar syndrome
18	c.3769_3772delTCTA	p.Lys1258Glyfs* ₁₃	BCM4	(Campeau, et al., 2012)	Genitopatellar syndrome
18	c.3769_3772delTCTA	p.Lys1258Glyfs* ₁₃	BCM6	(Campeau, et al., 2012)	Genitopatellar syndrome
18	c.3769_3772delTCTA	p.Lys1258Glyfs* ₁₃	KCL2	(Simpson, et al., 2012)	Genitopatellar syndrome
18	c.3769_3772delTCTA	p.Lys1258Glyfs* ₁₃	KCL3	(Simpson, et al., 2012)	Genitopatellar syndrome
18	c.3773dup	p.Trp1259Valfs* ₁₂	KCL5	(Simpson, et al., 2012)	Genitopatellar syndrome
18	c.3788_3789delIAA	p.Lys1263Argfs* ₇	BCM5	(Campeau, et al., 2012)	Genitopatellar syndrome
18	c.3802G>T	p.Gly1268*	BCM3	(Campeau, et al., 2012)	Genitopatellar syndrome
18	c.3877A>T	p.Lys1293*	KCL4		Genitopatellar syndrome
18	c.3892G>T	p.Gly1298*	BCM1	(Campeau, et al., 2012)	Genitopatellar syndrome
18	c.4069G>T	p.Glu1357*	CMFT4	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.4205_4206del	p.Ser1402Cysfs* ₅	CMFT5	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.4205_4206del	p.Ser1402Cysfs* ₅	CMFT10	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.4360_4368delinsAAAAACCAAAA	p.Glu1454Lysfs* ₈	BCM2	(Campeau, et al., 2012)	Genitopatellar syndrome
18	c.4405dup	p.Ser1469Phefs* ₁₈	CMFT1	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.4911_4921del	p.Val1638Alafs* ₇	CMFT12	(Clayton-Smith, et al., 2011)	SBBYSS

Exon/Intron	DNA change	Protein	Subject ID ^a	Reference	Condition
18	c.5030del	p.Thr1677Metfs* 38	CMFT7	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.5201_5210dup	p.Gln1737Hisfs* 41	CMFT8	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.5201_5210dup	p.Gln1737Hisfs* 41	CMFT9	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.5370_5373dup	p.Ile1792Glnfs*1 2	CMFT2	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.5389C>T	p.Arg1797*	CMFT13	(Clayton-Smith, et al., 2011)	SBBYSS
18	c.5734A>T	p.Arg1912*	CMFT6	(Clayton-Smith, et al., 2011)	SBBYSS

^aThe letters represent the institution of the authors describing the mutations.

Table 2

Clinical features of the subjects, in the order in which their mutations are found in the gene.

Subject/Feature	C M FT 11	C M FT 3	K C L 1	B C M 4	B C M 6	K C L 2	K C L 3	K C L 5	B C M 5	B C M 3	K C L 4	B C M 1	C M FT 4	C M FT 5	C M FT 10	B C M 2	C M FT 1	C M FT 12	C M FT 7	C M FT 8	C M FT 9	C M FT 2	C M FT 13	C M FT 6
Gender	M	F	F	M	M	F	M	F	F	F	M	F	M	M	F	M	M	F	F	M	F	F	F	F
Common mutations															Ser1402 Cysfs*5					Gln173 7Hisfs* 41				
Flexion contractures			+	+	+	+	+	+	+	+	+	+					+							
Club feet			+	+	+	+	+		+	+	+	+					+							
Pelvic anomalies				+		+		+			+	+												
Rib/spine anomalies				+					+	+		+												
Microcephaly			+	+		+	+	+	+	+		+					+							
Absent or thin corpus callosum			+	+	+	+	+	+	+	+	+	+					+							
Tracheo/laryngomalacia, Resp distress										+		+					+							
Anal atresia/stenosis or malposition				+						+		+												
Clitoromegaly/Hypospadias			+			+		+	+	+		+												
Hydronephrosis/multicystic kidneys			+	+	+	+	+		+	+	+	+					+							
Absent or hypoplastic patellae			+	+	+	+	+	+	+	+	+	+	+	+							+			
Scrotal hypoplasia/cryptorchidism/hypospadias	+			+	+		+				+		+	+			+		+					
Hypotonia, developmental delay or intellectual disability	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Congenital heart defect			+	+						+		+	+	+			+		+		+			+
Feeding difficulties	+	+		+					+	+			+	+	+	+	+	+	+	+	+	+	+	+

Subject/Feature	C M FT 11	C M FT 3	K C L 1	B C M 4	B C L 6	K C L 2	K C L 3	K C L 5	B C M 5	B C M 3	K C L 4	B C M 1	C M FT 4	C M FT 5	C M FT 10	B C M 2	C M FT 1	C M FT 12	C M FT 7	C M FT 8	C M FT 9	C M FT 2	C M FT 13	C M FT 6
Dental anomalies		+		+						+				+	+	+	+	+	+	+	+	+	+	+
Hearing loss		+										+	+	+			+		+	+	+	+		
Thyroid anomalies		+							+				+						+	+	+			+
Mask-like facies and/or blepharophimosis													+	+	+	+	+	+	+	+	+	+	+	+
Cleft palate													+						+	+	+			
Lacrimal duct anomalies		+											+	+					+	+	+	+		+
Long thumbs													+	+	+	+	+	+			+	+		+
Long great toes													+	+	+	+		+	+		+	+		+

Columns in light gray represent subjects with SBBYSS