R.C.P.U. NEWSLETTER

R.C. Philips Research and Education Unit

Editor: Heather J. Stalker, M.Sc. Director: Roberto T. Zori, M.D Vol. XXXII No. 2

A statewide commitment to the problems of intellectual disability June 2021

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KAT6A-Related Disorder

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Introduction

KAT6A-Related disorder is a rare and newly described genetic condition associated with intellectual disability. It was first described in 2015 by Arboleta et al. and Tham et al. with cohorts of 4 unrelated individuals and 6 individuals from 5 unrelated families, respectively. All of these individuals had *de novo* mutations in *KAT6A* with similar patterns of features including intellectual disability, microcephaly, heart defects, hypotonia, and distinct facial features. Since then, a larger study which analyzed a cohort of 76 patients with truncating mutations in *KAT6A* reported that all patients had intellectual disability and speech delay, establishing a clear phenotype for this condition. As of June 2021, the KAT6A Foundation reports 315 individuals known to have KAT6A-related disorder. It is thought that the true prevalence of KAT6A-related disorder is under-ascertained, and some researchers have predicted it may provide a genetic diagnosis for up to 1% of individuals with unexplained syndromic developmental delay.

Figure 1

Image from: https://doi.org/10.1016/j.ajhg.2015.01

Clinical Features:

- Intellectual disability
- Profound speech delay
- Feeding difficulties
- Cardiac malformations
- Microcephaly
- Autism/autistic feature
- Sleep disturbance
- Frequent infections
- Facial features
  - broad nasal tip, thin upper lip, ptosis, bitemporal narrowing, prominent nasal bridge, short flat philtrum, epicanthal folds, low set & posteriorly rotated ears.
- Eye features
  - Strabismus
  - Refractive errors
  - Cortical impairment
  - Astigmatism

Molecular Etiology:

KAT6A is located on chromosome 8p11.2 and codes for lysine acetyltransferase 6A, which belongs to the highly conserved group of MYST histone acetyltransferases. Histone acetylation

controls transcription via epigenetic changes. Proteins in this group are responsible for a variety of cellular functions including gene regulation, chromatin remodeling, translation, metabolism and cellular reproduction. *KAT6A* has critical roles in gene-specific histone 3 acetylation and in P53 acetylation and downstream pathway signaling. The p53 pathway is well-studied for its important role in tumor suppression; it has also proven to be an important pathway for regulating embryonic development. *In vivo* analysis found that when truncation occurs at the C terminus of KAT6A, 30 of 92 genes in the P53 pathway genes showed notable changes in expression. Thus, truncation of the KAT6A protein exhibits a damaging gain-of-function effect on organ development.

Figure 2

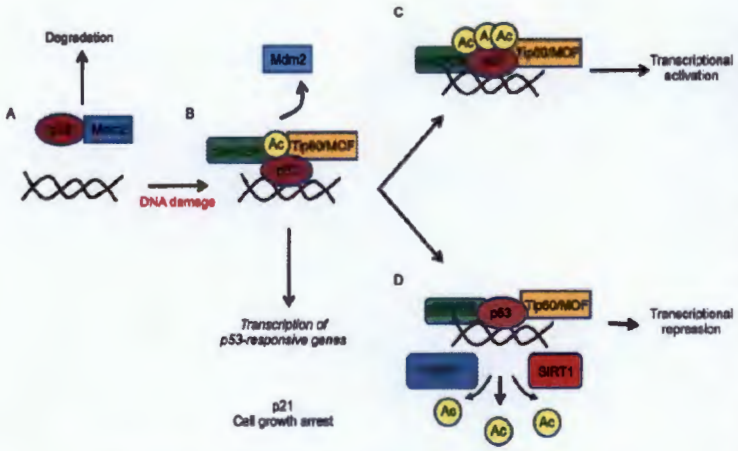

Image: https://doi-org.ezproxy.lib.usf.edu/10.1007/s13238-011-1063-9

Genotype-Phenotype Correlations:
Further supporting functional analysis predictions of damaging effects of the truncated KAT6A protein, Kennedy et al. recognized that individuals with late truncating mutations (in exons 16-17) have a more severe phenotype than those with missense variants or truncation in earlier exons. Individuals with late-truncating mutations were more likely to have more severe intellectual disability, microcephaly, neonatal hypotonia, feeding difficulty, reflux, constipation, and frequent infections. This suggests that the larger size of the truncated protein contributes to its ability to cause developmental harm. Further, an individual with a complete gene deletion of *KAT6A* exhibited mild intellectual disability than individuals with other types of KAT6A mutations.

Genetic Testing:
All cases of KAT6A-related disorder reported on in the literature have been identified by whole exome sequencing (WES). While the individuals with the condition exhibit significant concordance with one another, there is no unique feature to raise specific clinical suspicion. It is likely to continue to be identified on WES or expanded gene panels that are aimed at finding genetic etiology for intellectual disability.

Feeding Difficulty:
Some children with KAT6A-related disorder may present with failure to thrive in early life before developmental delay is noticeable. The feeding difficulties associated with this condition can be due to dysfunctional intestinal motility, oromotor dysfunction, or some combination of both. Lack of intestinal motility may cause reflux, persistent vomiting, or constipation. Oromotor dysfunction creates risk for aspiration and dysphagia and may cause difficulty establishing feeding from birth, requiring feeding interventions.

KAT6A-Related Disorder & Speech:
All patients with KAT6A-related disorder have some degree of speech delay. Although some individuals have been able to develop speech, many individuals never do. It is possible that the degree of intellectual disability in individuals with absent speech is overestimated on the basis that they are unable to communicate. These individuals typically have receptive language skills that are much stronger than expressive language. For non-verbal or significantly speech-delayed patients, it is important to work on alternative means of communication such as sign language or communication devices. Providing means to communicate can work to maximize their learning potential as well as decrease frustration, thereby reducing behavioral

concerns. When counseling families, it is important to remind them that providing their child with an alternative means of communication will not prevent the development of speech.

Management:

Management of individuals with KAT6A-related disorder is dependent on their specific features. Affected individuals are likely already followed by many of the recommended specialists before a genetic diagnosis is made. However, it is important to initiate baseline evaluations by specialists they have not yet seen at diagnosis to make sure all manifestations of the condition have been identified. Those recommendations are as follows:

- Cardiology
- Speech therapy
- Ophthalmology
- Formal developmental assessment
- Gastroenterology
- PCP to monitor growth and overall development.

Genetic Counseling:

KAT6A-related disorder is inherited in an autosomal dominant fashion. Thus far, all reported individuals have *de novo* mutations that are not inherited from an affected parent. Families with children identified to have *de novo* KAT6A-related disorder should be counseled that the recurrence risk for future children is below 1%. KAT6A-related disorder is a newly described condition; instances of children inheriting the condition from an affected parent have not been reported since the majority of patients are pediatric. It is important to counsel older children and families on the 50% recurrence risk to children of the affected individual.

Support Network:

Given the rarity of KAT6A-related disorder, there is an impressive presence of syndrome specific advocacy and support. The KAT6A Foundation is a 501(c)(3) nonprofit organization that was created to support individuals with KAT6A- and KAT6B- related disorders and their families. They also work to raise funds that further research into these conditions. Their aim is to inform, raise awareness, and identify more individuals with these conditions. They host a patient registry, a support group on Facebook with greater than 800 members, as well as an annual walk. Unique (rarechromo.org) has a comprehensive and patient friendly resource available for free online.

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About the RCPU:

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate disorders of intellectual disability through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

Acknowledgments:

The RCPU Newsletter is funded by the Raymond C. Philips Research and Education contract with the Department of Health, Children's Medical Services.