GATAD2B

Patient Description:
ALP is a 4-year-old who presented with developmental delay with absence of speech, hypotonia, macrocephaly and ankyloglossia. She has slightly dysmorphic facial features and growth delay. In 2016, she was diagnosed with metastatic Wilms tumor. Her affected kidney was surgically removed and she underwent radiation and chemotherapy. She is now in remission. Work-up, including karyotype and microarray comparative genomic hybridization was completed. Whole exome sequencing revealed a de novo pathogenic variant in *GATAD2B*.

Disease/Syndrome Features:
A study assessing the efficacy of diagnostic exome sequencing in individuals with intellectual disability identified two patients with severely disruptive mutations in *GATAD2B*. The patients shared similar facies and both had limited speech and severe cognitive and motor delays [de Ligt 2012]. This group identified an additional two patients with intellectual disability caused by *GATAD2B* loss-of-function mutations, and from this cohort described a recognizable syndrome [Willemsen 2013]. In addition to severe intellectual disability, features of *GATAD2B* haploinsufficiency may include limited speech, childhood hypotonia, thin hair, and facial features including a tubular shaped nose with broad tip, deeply set eyes, short philtrum, a grimacing expression, and strabismus [Willemsen 2013]. *GATAD2B* frameshift mutations were subsequently found to cause intellectual disability in two unrelated Chinese patients. These patients had shared facial features including a small palpebral fissure, ocular hypertelorism, and flat nasal bridge. Both patients showed severely limited speech. One individual showed motor delay while the other exhibited hyperactivity and autism-like features [Luo 2017]. In a study comparing individuals with *GATAD2B*-related syndrome (GS) to individuals with other rare genetic disorders, GS patients experienced relatively low rates of autism spectrum disorders but were noted to experience sleep problems, anxiety disorders, mood disorders, and regression [Vermeulen 2016].

Mutation	Publication	Clinical Features
p.Gln470*	de Ligt et al 2012; Willemsen et al 2013	severe cognitive delay, severe motor delay, limited speech, abnormal facies, childhood hypotonia, strabismus, thin hair, small palpebral fissure, tubular nose, short philtrum, grimace, long fingers
p.Asn195Lys*fs**30	de Ligt et al 2012; Willemsen et al 2013	severe cognitive delay, severe motor delay, limited speech, abnormal facies, tics, thin hair, deep set eyes, small palpebral fissure, strabismus, tubular nose, short philtrum, grimace, long fingers
deletion	Willemsen et al 2013	childhood hypotonia, psychomotor delay, limited speech, hypermetropia,

		strabismus, absence epilepsy, hypertelorism, broad forehead, flat nasal bridge, thin hair
p.GLn190Ala*fs**34	Willemsen et al 2013	childhood hypotonia, psychomotor delay, limited speech, hyperactivity, strabismus, constipation, broad nasal bridge, short philtrum, long palpebral fissures, thin hair, long figers
p.Leu28Met*fs**18	Luo et al 2017	small palpebral fissure, ocular hypertelorism, flat nasal bridge, motor delay, limited speech
p.Lys184Asn*fs**2	Luo et al 2017	small palpebral fissure, ocular hypertelorism, flat nasal bridge, dental misalignment, absent speech, hyperactivity

Protein/Pathway:

GATA zinc finger domain containing 2B (*GATAD2B*) encodes p66β, a subunit of the MeCP1-Mi-2/nucleosome remodeling and deacetylase (NuRD) complex. DNA methylation of CpG sequences mediates repression of genetic elements in order to silence for example transposons, imprinted genes, inactivated X chromosomes, and tissue-specific genes in tissues where they are not expressed. The MeCP1-Mi-2/NuRD complex features proteins with methyl-CpG-binding domains (MBD) that target and interact with methylated CpG sequences. At these sites, the activity of histone deacetylases within the complex generates chromatin conformations that are unfavorable for transcription and ultimately repress gene expression. Within this schema, p66β (and the related p66α) binds both MBD2 and deacetylated histones, and perturbation of p66 inhibits MBD2-mediated repression [Brackertz 2006].

Drosophila possess a single ortholog of *GATAD2B* and its closely related paralog *GATAD2A* (p66α). This *Drosophila* gene has been termed simjang (*simj*) and, like *GATAD2B*, it associates with the MeCP1-Mi-2/NuRD complex. As *simj* null mutations are lethal, a *Drosophila* model of GS was generated through the use of UAS-Gal4 and an inducible RNAi system to selectively repress *simj* expression in *Drosophila* neurons. *simj*-RNAi flies showed decreased habituation, a form of non-associative learning, when compared to wild-type controls. Additionally, these flies were found to have aberrant neuromuscular junctions with decreased synaptic area, decreased number of branches, and decreased number of active zones. Together, these experiments suggest a role for the *GATAD2B* ortholog in habituation as well as in the formation of normal synaptic architecture [Willemsen 2013].

Publications:

Brackertz, M., Gong, Z., Leers, J., & Renkawitz, R. (2006). p66 and p66 of the Mi-2/NuRD complex mediate MBD2 and histone interaction. Nucleic Acids Research, 34(2), 397–406. https://doi.org/10.1093/nar/gkj437

de Ligt, J., Willemsen, M. H., van Bon, B. W., Kleefstra, T., Yntema, H. G., Kroes, T., … ELM Vissers, L. (2012). Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability. *N Engl J Med*, *20367*(15), 1921–1929. https://doi.org/10.1056/NEJMoa1206524

Luo, X., Zou, Y., Tan, B., Zhang, Y., Guo, J., Zeng, L., … Wu, L. (2017). Novel GATAD2B loss-of-function mutations cause intellectual disability in two unrelated cases. *Journal of Human Genetics*, *62*(10), 513–516. https://doi.org/10.1038/jhg.2016.164

Vermeulen, K., de Boer, A., Janzing, J. G. E., Koolen, D. A., Ockeloen, C. W., Willemsen, M. H., … Kleefstra, T. (2017). Adaptive and maladaptive functioning in Kleefstra syndrome compared to other rare genetic disorders with intellectual disabilities. *American Journal of Medical Genetics Part A*, *173*(7), 1821–1830. https://doi.org/10.1002/ajmg.a.38280

Willemsen, M. H., Nijhof, B., Fenckova, M., Nillesen, W. M., H F Bongers, E. M., Castells-Nobau, A., … Kleefstra, T. (2013). GATAD2B loss-of-function mutations cause a recognisable syndrome with intellectual disability and are associated with learning deficits and synaptic undergrowth in Drosophila. *J Med Genet*, *50*, 507–514. https://doi.org/10.1136/jmedgenet-2012-101490

Support Groups and Information:

Helping Hands For GAND

Facebook groups:

GATAD2B Parent Group – private group, >200 members

GATAD2B community – private group, for family members of individuals with GATAD2B mutations and professionals with an interest in GATAD2B.

Last updated: 5/13/2020, MKR