**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. 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].

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Publication</th>
<th>Clinical Features</th>
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<tbody>
<tr>
<td>p.Gln470*</td>
<td>de Ligt et al 2012; Willemsen et al 2013</td>
<td>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</td>
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<tr>
<td>p.Asn195Lysfs*30</td>
<td>de Ligt et al 2012; Willemsen et al 2013</td>
<td>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</td>
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<td>deletion</td>
<td>Willemsen et al 2013</td>
<td>childhood hypotonia, psychomotor delay, limited speech, hypermetropia,</td>
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| 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:


**Support Groups and Information:**
*Helping Hands For GAND*