NAA10*

Patient Description:

The presenting case at Montefiore was a 7-year-old girl with history of global developmental delay, abnormal eye movements, and seizures. She was the 8-pound product of a full-term pregnancy born via C section to a G32 mother. She was hospitalized in the NICU for 8 days for hyperbilirubinemia and neonatal jaundice. She was noted to have global developmental issues within the first year of life and had delayed acquisition of milestones. She sat alone at 16 months, walked after 18 months, and began saying “mama” and “papa” at 21 months of age, although not specifically or appropriately. At 4 years, she developed episodes where she would raise her head and have rapid eye blinking. EEG showed a single electroclinical event, which was a generalized spike followed by a paroxysmal fast for 4 seconds, associated with a head turn and unresponsiveness for the same period of time. Interictally, there were bilateral independent paroxysmal events. MRI of the brain at age 4 was normal. Physical exam was notable for a non-verbal 7-year-old child with microcephaly in the absence of dysmorphia. She had an abnormal wide-based gait, and diffuse hypotonia. The remainder of the physical exam was non-contributory. The family is nonconsanguineous with no similarly affected individuals. The child was given an extensive diagnostic evaluation which eventually resulted in whole exome sequencing with mitochondrial DNA sequencing. This revealed a de novo pathogenic variant C.346C>T in the NAA10 gene, associated with NAA10-related disorder, sometimes referred to as Ogden syndrome.

Additional descriptions of other children with variants in this gene can be found online https://www.ogdencares.org/meet-our-kids/millie

NAA10 Deficiency Features:

In 2011, five affected males from a single family and three males from an unrelated family were identified as having a mutation in the NAA10 gene (p.Ser37Pro).[1] The syndrome was named Ogden Syndrome after the city where the original family resided. The patients presented with an aged appearance, craniofacial anomalies, hypotonia, global developmental delays, cryptorchidism, and cardiac arrhythmias. They also had prominent eyes, large ears, and flared nostrils. In addition they had growth failure (weight and height) and very low levels of subcutaneous fat.[1] Shortly afterwards the NAA10 gene was linked to Lenz microphthalmia syndrome (eye malformations, developmental delay, and defects in the skeletal and genitourinary systems) and other forms of severe non-syndromic intellectual disability.[2; 3] Since the initial findings, numerous mutations in the NAA10 gene (see **Figure 1.** and **Table 1.**) have been reported. Patients present with a variety of phenotypes and heterogeneous levels of severity depending on the specific mutation present. Together these syndromes are referred to as NAA10-related N-terminal acetylation deficiency or NAA10 deficiency for short.[4]

*We thank Sarah Goebel for preparing this description of NAA10 deficiency.

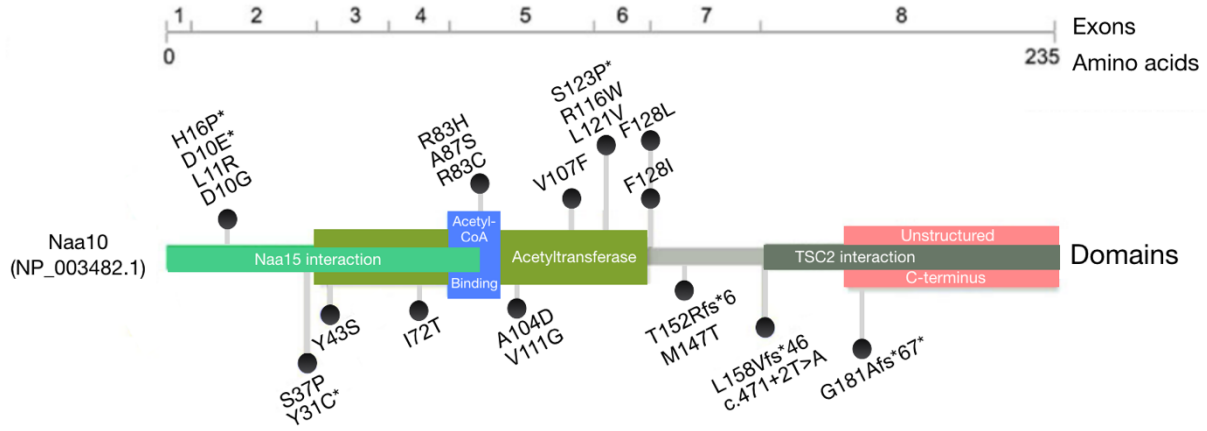

Figure 1. Location of known NAA10 mutations (Adapted from Saunier et al.,2016).[4]
* = mutations mentioned in an online presentation by Dr. Lyon not included in Table 1.

Protein/Pathway:

The gene for N-alpha-acetyltransferase 10, (NAA10) is located on the X chromosome and encodes the catalytic subunit of the NatA complex, an N-acetyltransferase.[13; 14] In addition to NAA10, the NatA complex includes an auxiliary subunit (NAA15) and a regulatory subunit (HYPK).[15; 16] Nat complexes are responsible for the most commonly found protein modification, N-alpha-acetylation, which occurs in 80-90% of human proteins.[17] N-acetylation is the process by which an acetyl group from Acetyl-CoA is transferred to the N-terminal of nascent peptides and is important for protein stability, protein-protein interaction, and ER transport. NatA specifically targets proteins with a Ser, Ala, Gly, or Thr at their termini, which is estimated to be around 40% of the proteins in humans.[18; 19] NatA associates with ribosomal subunits and can N-acetylate proteins co- and post-translationally.[15] It was originally hypothesized that disease severity was related to the catalytic activity of NatA because patients with less catalytic activity generally presented with a more severe clinical phenotype.[3] However, as more NAA10 mutations were discovered this distinction became less clear.[5] The spatiotemporal expression of NAA10 is dependent on the tissue observed. In general it is broadly expressed and is present both during development and in the adult.[20] Complete loss of function of NAA10 is embryonic lethal in *D. melanogaster*, *T. brucei*, and *C. elegans*[21-23]. In humans, this is predicted to also be true, but has yet to be tested.[1]

There are limited studies examining NAA10 function in the brain, however NatA acetylation may be involved in proper neuronal development. NatA colocalizes with microtubules in hippocampal neurons and can regulate dendrite arborization through its N-acetyltransferase activity.[24] In addition areas of cell division and migration initially have high expression levels of NAA10 and NAA15 that decrease throughout development expanding the possible roles of NAA10 to include neuronal differentiation.[25] However, additional research is needed to verify the functional role of NAA10 in brain development.

NAA10 not only acts through the NatA complex to acetylate proteins, but also has the ability to acetylate lysine residues following auto-acetylation.[26] Through this mode of action, NAA10 can control osteoblast development and bone formation, providing a possible link between NAA10 and the skeletal impairments seen in patients.[27] Interestingly, RNA expression of NAA10 is highest in skeletal tissue (Human Protein Atlas) again suggesting the skeletal deficits seen in patients could be related to NAA10 function.

NAA10 may also have acetylation-independent functions. A recent study using NAA10-null mice suggests that NAA10 can bind to imprinting control regions of DNA and recruit DNA methyltransferases.[28] Genomic imprinting occurs due to epigenetic silencing and suppression of one copy of a gene (either the maternal or paternal copy). Genomic imprinting is important for fetal growth and postnatal development.[29] This paper further demonstrated that several patient derived NAA10 mutations resulted in decreased binding of NAA10 and the DNA methyltransferase Dnmt1 to the imprinting control region.[28] While this demonstrates a role of NAA10 in genomic imprinting, others argue that this data does not rule out the possibility that NAA10 acetylation may occur prior to DNA binding. Therefore this may not necessarily be an acetylation independent role of NAA10.[20]

Table 1. Functional and clinical phenotypes of known NAA10 mutations (Adapted from Geithus 2018).[12] ID = intellectual disability, PPI = protein-protein interactions, FS = Frameshift, NAA10 deficiency = developmental delay, growth deficiency, post-natal growth failure, cardiac and skeletal anomalies.[4; 12]

Mutations	Function	Phenotype
c.109T>C p.(Ser37Pro)[1]	Reduced catalytic activity (20-80%), impaired complex formation, impaired substrate binding	Severe NAA10 deficiency, truncal hypotonia, scoliosis, prominent eyes, aged appearance, lethal cardiac arrythmia and cardiomyopathy
c.471+2T>A[2]	C-terminal truncation, impaired PPI, dysregulation of pathways	NAA10 deficiency, anophthalmia or microphthalmia, scoliosis, hypotonia, renal abnormalities
c.128A>C p.(Tyr43Ser)[5]	Reduced catalytic activity (85%), reduced protein stability, form aggregates	Mild NAA10 deficiency, hypotonia, scoliosis, prolonged QT
c.247C>T p.(Arg83Cys)[4; 6]	Reduced (60%) NAA10 activity, increased NatA catalytic activity, impaired Ac-CoA binding	Severe/moderate NAA10 deficiency, hypotonia, limited speech and mobility, facial dysmorphism, microcephaly
c.346C>T p.(Arg116Trp)[3; 7]	Reduced catalytic activity (15%), Impaired Ac-CoA binding	NAA10 deficiency, hypotonia, minor facial features, behavioral anomalies

c.319G>T p.(Val107Phe)[3; 4]	Reduced catalytic activity (95%), reduced protein stability	NAA10 deficiency, hypotonia, minor facial features, behavioral anomalies
c.382T>A p.(Phe128Ile)[4]	Reduced catalytic activity, reduced protein stability	NAA10 deficiency, microcephaly, hypotonia, limited speech and mobility, facial dysmorphism
c.384T>A p.(Phe128Leu)[4]	Reduced catalytic activity (>90%), reduced protein stability, form aggregates	NAA10 deficiency, hypotonia, limited speech and mobility, facial dysmorphism
c.332 T > G p.(Val111Gly)[8]	Reduced protein stability (85%), reduced NAA10 activity (no change in NatA activity)	Mild NAA10 deficiency, delayed motor- and language development
c.29A>G p.(Asp10Gly)[6; 9]	No change/decreased in NatA activity (depending on study), reduced NAA10 activity, impaired NatA complex formation	Developmental delay, brain malformations, cardiac abnormalities, hearing loss and dysmorphic features
c.32T>G p.(Leu11Arg)[6; 9]	Reduced NatA activity, normal NAA10 activity, impaired NatA complex formation	Developmental delay, brain malformations and strabismus
c.215T>C p.(Ile72Thr)[10]	Reduced protein stability, reduced NAA10 activity, predicted intact complex formation, normal/decreased NatA activity (depending on study)	Developmental delay, ID, and cardiac abnormalities
c.248G > A, p.(Arg83His)[11]	Reduced NAA10 catalytic activity, predicted impaired Ac-CoA binding	Developmental delay, ID, ADHD like behavior, limited speech, and cardiac abnormalities
c.259G>T p.(Ala87Ser)[6]	Not assessed biochemically	Global developmental delay, gross motor development delay, growth delay, severe ID, non-verbal, generalized hypotonia, spastic paraplegia, facial dysmorphism, seizures, hearing impairment, ADHD, autistic behavior
c.311C>A p.(Ala104Asp)[6]	Reduced NatA activity, impaired NatA complex formation	Global developmental delay, growth hormone deficiency, sensory processing disorder, ADHD (combined type), mixed receptive and expressive language disorder, hypotonia, fine motor delay, short stature, anxiety, astigmatism, anisometropia conjunctivae and sleep disorder

c.361C>G p.(Leu121Val)[6]	Not assessed biochemically	Global developmental delay, severe ID, motor delay and poor coordination, non-verbal
c.384T>G p.(Phe128Leu)[6]	Not assessed biochemically	Delayed motor development, Microcephaly, relatively short stature, poor eye contact, chorea; overriding toes; single crease hand line
c.440T>C p.(Met147Thr)[6]	Normal NatA activity	Developmental delay, coordination issues, sensory processing disorder and self-stimulatory behaviors, thinning corpus callosum, microcephaly, stigmatism, cortical visual impairment, acne, body odor, adrenarche and is a light sleeper
c.455_458del p.(Thr152Argfs*6)[6]	C-terminal truncation with the acetyltransferase domain intact	Share many phenotypes with c.471+2T>A patient; microphthalmia, severe ID, scoliosis and syndactyly

Support Groups/Additional Information:

An Ogden Syndrome Foundation has recently been established:
https://www.ogdencares.org/home

NAA10 Families Together Facebook Group and Website
https://www.facebook.com/NAA10FamiliesTogether/?ref=page_internal
https://www.naa10gene.com/

Ogden Syndrome Foundation US Facebook
https://www.facebook.com/people/Ogden-Syndrome-Foundation-US/100067718586138/

Link to a presentation on NAA10 from Dr. Gholson Lyon (Institute for Basic Research in Developmental Disabilities (IBR), Staten Island, NY)
https://www.naa10gene.com/research

Availability of NAA10 patient iPSCs
New York Stem Cell Foundation and Dr. Lyon have created iPSCs available for any researcher to use. Could not find a direct link to this, but worth reaching out to Dr. Lyon if any research team is interested.

Mouse Line Availability
There are also two mouse lines to use for NAA10 research.[30]

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