NAA10 Variants in the NAA15 Interaction Domain present with more severe Cardiac Manifestations of Ogden Syndrome

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Introduction

- The NatA complex, comprised of a catalytic subunit N-acetyltransferase 10 (NAA10) and an accessory protein NAA15, plays a crucial role in N-alpha acetylation of post-translational proteins.
- The transcript of NAA10 is 235 AAs long with AA1-58 comprising the NAA15-interaction domain.
- Ogden syndrome (OS) is a pathogenic syndrome associated with NAA10 variants located on the X-chromosome.
- Several NAA10 and NAA15 variants have been discovered, exhibiting a range of clinical features, including congenital heart abnormalities,
- A significant proportion of individuals with NAA10 mutations, and to a lesser extent NAA15 mutations, exhibit cardiac abnormalities, including prolonged QT interval, congenital valvular defects, and cardiac arrest.

Objective

Assess the relationship between NAA10 variant location and cardiac pathology severity in Ogden Syndrome to further guide patient care and management.

Methods

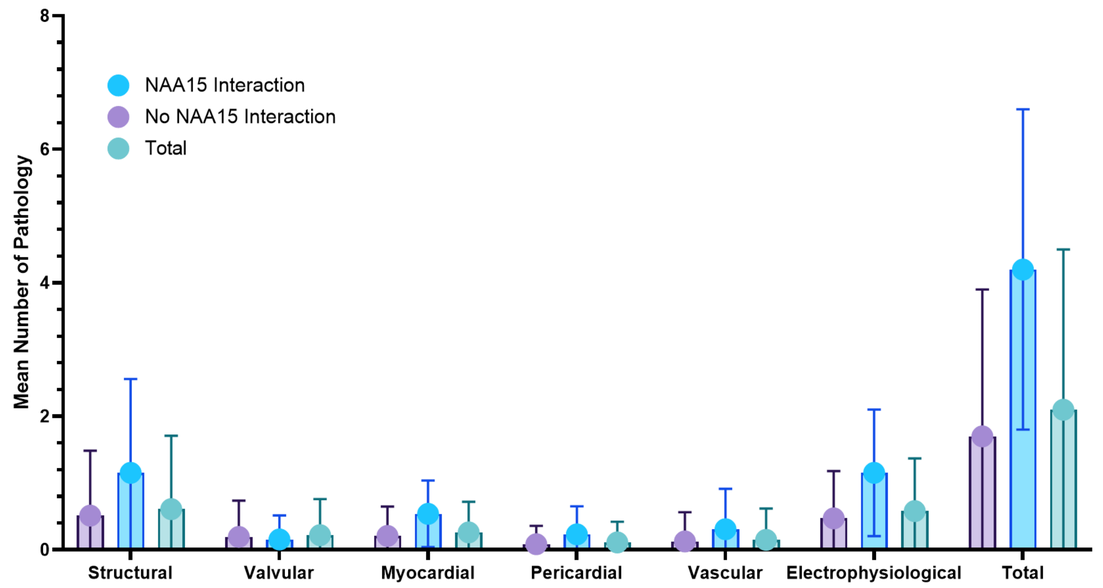
- N = 85 probands with OS
  - 13 with NAA15-interaction domain variants
  - 72 without variants within the domain
- Pathology categories
  - **Structural**: PFO, ASD, VSD, PDA, bicuspid aortic valve, aortic root dilatation, ascending aorta dilatation, overriding aorta, Tetralogy of Fallot
  - **Valvular**: TR, MR, PR, aortic stenosis, mitral stenosis
  - **Myocardial**: HOCM, nondescript ventricular hypertrophy, cardiomegaly
  - **Pericardial**: pericardial effusion, pericarditis, apical cyst
  - **Vascular**: persistent left superior vena cava, pHTN, pulmonary vessel stenosis, arterial stenosis, coronary fistula
  - **Electrophysiologic**: bradycardia, shortened PR, prolonged QT, SVT, AVNRT, AFib, VFib, Vtach
  - **Miscellaneous**: syncope, dextrocardia, cardiac arrest, MI, heart failure
- Two-sample t-tests and single tailed chi squared tests were calculated to compare groups with $\alpha = 0.05$

Variant	Females	Males	Total
p.Asp10Gly	1	1	2
p.His16Pro	1	0	1
p.Cys17Gly	0	1	1
p.Tyr31Cys	1	0	1
p.His34Tyr	0	1	1
p.Ser37Pro	0	4	4
p.Tyr43Ser	1	2	3
p.Ile72Thr	1	4	5
p.Arg83Cys	32	1	33
p.Ala87Ser	3	0	3
p.Gln88Pro	1	0	1
p.Glu100Lys	1	1	2
p.Ala104Asp	1	0	1
p.Arg116Gln	2	1	3
p.Arg116Trp	3	0	3
p.His120Pro	2	0	2
p.Leu121Val	1	0	1
p.Ser123Pro	1	0	1
p.Leu126Arg	1	0	1
p.Phe128Leu	7	0	7
p.Phe128Ser	1	0	1
p.Met147Thr	4	0	4
p.Arg149Trp	0	1	1
p.Thr152Arg*6	0	2	2
p.Glu181Ala*67	0	1	1
Total	65	20	85

Fig 1. Demographics
Variants above the dotted line refer to probands with variants within the NAA15 interaction domain (AA 1-58)

Results

- No statistically significant difference in the sex distribution of variant types
- NAA15-interacting variants had 4.2 cardiac abnormalities (SD=2.4),while non-interacting variants had 1.7 (SD 2.2). This was statistically significant (p = 0.005).
- Cohort had a mean of 2.1 abnormalities.
- NAA15-interacting variants had significantly more myocardial abnormalities than non-interacting variants (0.54 versus 0.21, respectively) (p = 0.047).
- NAA15-interacting variants had 1.15 electrophysiologic abnormalities, compared to 0.47 in non-interacting variants (p = 0.032).
- There was no significant difference in the number of structural, valvular, pericardial, or vascular abnormalities between these two groups.
- Mean QTc was not significantly different between the 2 groups, despite the significant difference in the prevalence of electrophysiologic abnormalities between groups.



Mean (SD)	Structural	Valvular	Myocardial	Pericardial	Vascular	Electrophysiologic	Total
Total	0.61 (1.1)	0.22 (0.54)	0.26 (0.46)	0.11 (0.31)	0.15 (0.47)	0.58 (0.79)	2.1 (2.4)
NAA15 Interaction (n = 13)	1.2 (1.4)	0.15 (0.36)	0.54 (0.5)	0.23 (0.42)	0.31 (0.61)	1.2 (0.95)	4.2 (2.4)
No NAA15 Interaction (n = 72)	0.51 (0.97)	0.24 (0.57)	0.21 (0.44)	0.08 (0.28)	0.13 (0.44)	0.47 (0.71)	1.7 (2.2)
p-value	0.08	0.4	0.02*	0.1	0.2	0.02*	0.002*

Figure 2. Mean Number of Cardiac Pathology per NAA15 and Non-NAA15 Interaction Domain Groups. Blue corresponds to the NAA15 interaction group. Purple refers to the Non-NAA15 interaction domain group. Green refers to the cohort as a whole. The information is repeated in tabular format below. Significant differences exist between groups for the myocardial, electrophysiologic, and total pathology groups.

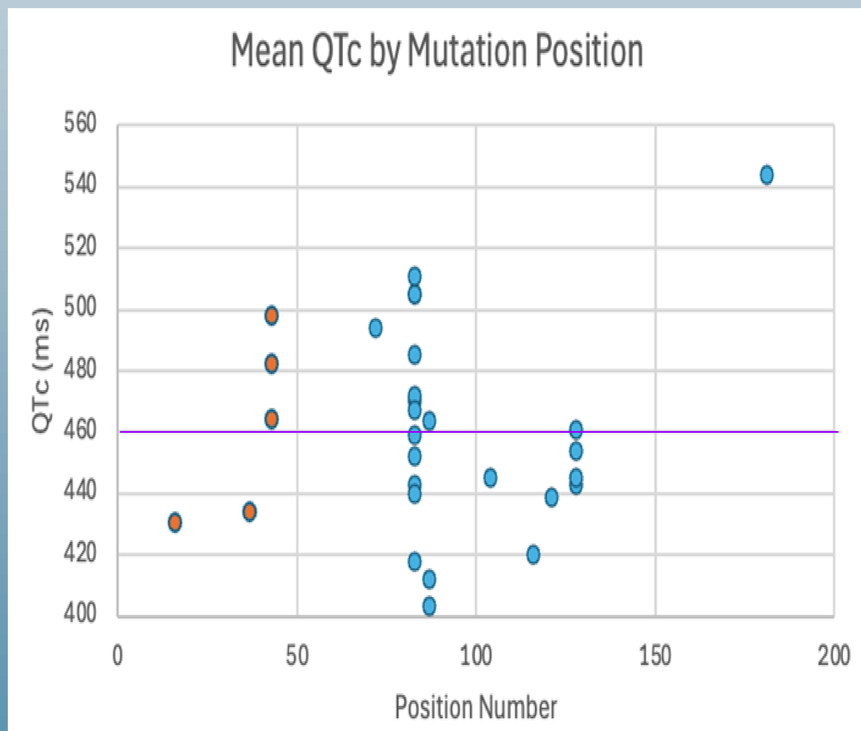


Figure 3. Mean QTc by AA Mutation Position Number. NAA15-interacting mutations are orange (AA < 58) (n=5) and NAA15 Non-Interacting mutations are blue (AA > 59) (n=24). QTc prolongation is defined as QTc > 460 ms, as demarcated by the purple line.

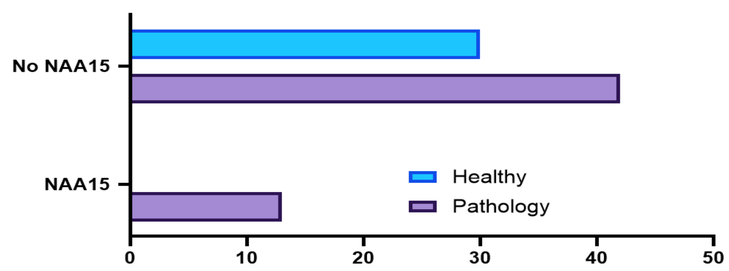


Figure 4. Graphical and Tabular Comparison of the Presence of Normal Cardiac Anatomy and Physiology between OS Variant Types. There was a significant difference in the presence of normal cardiac pathology between the two groups (p = 0.002). None of the included cohort with variants within the NAA15-interaction domain had normal cardiac anatomy or physiology

	Pathology	Healthy
Variant within AA 1-58	13	0
Variant in AA > 58	42	30

Conclusions

- Probands with variants within the NAA15 interaction domain tended to have more severe cardiac manifestations of disease as evidenced by the greater prevalence of total, myocardial, and electrophysiologic abnormalities
- NAA15-related neurodevelopmental disease has also been associated with hypertrophic obstructive cardiomyopathy (HOCM) suggesting NAA15 has a role in NatA's function in cardiac homeostasis.
- Characterization of cardiac ion channels of iPSC's modeling OS variants p.S37P and p.Y43S both exhibited a long QT (LQT) phenotype and the increased prevalence of electrophysiologic abnormalities in this group further supports this assertion.

Future Directions and Clinical Recommendations

- Further study is required to assess the impact of NAA10, NAA15, and the NatA complex on cardiac function and homeostasis.
- Our findings suggest that providers should lower their threshold for referral to cardiology for patients with OS with NAA15-interacting variants.
- Pediatric cardiology follow-up is strongly recommended in any patient diagnosed with Ogden Syndrome or NAA15-related neurodevelopmental syndrome due to the strong correlation between these conditions and cardiac abnormalities.
- Medications that prolong the QT interval (i.e. certain antiarrhythmics, antidepressants, antipsychotics, antibiotics, etc.) should be used with caution or with supervision from cardiology in patients with mutations in the NatA complex due to these patients' predilections for prolonged QT interval at baseline.

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