HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Am J Med Genet A. 2021 January ; 185(1): 228–233. doi:10.1002/ajmg.a.61928.

Variants in *NAA15* cause pediatric hypertrophic cardiomyopathy

Alyssa Ritter[1,2], **Justin H. Berger**[2], **Matthew Deardorff**[3], **Kosuke Izumi**[1,4], **Kimberly Y. Lin**[2], **Livija Medne**[1], **Rebecca C. Ahrens-Nicklas**[1,4]

[1]Division of Human Genetics, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[2]Divison of Cardiology, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[3]Department of Pathology and Laboratory Medicine and Pediatrics, Children's Hospital Los Angeles, Keck School of Medicine of the University of Southern California, Los Angeles, California

[4]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

The NatA N-acetyltransferase complex is important for cotranslational protein modification and regulation of multiple cellular processes. The NatA complex includes the core components of *NAA10,* the catalytic subunit, and *NAA15,* the auxiliary component. Both *NAA10* and *NAA15* have been associated with neurodevelopmental disorders with overlapping clinical features, including variable intellectual disability, dysmorphic facial features, and, less commonly, congenital anomalies such as cleft lip or palate. Cardiac arrhythmias, including long QT syndrome, ventricular tachycardia, and ventricular fibrillation were among the first reported cardiac manifestations in patients with NAA10-related syndrome. Recently, three individuals with NAA10-related syndrome have been reported to also have hypertrophic cardiomyopathy (HCM). The general and cardiac phenotypes of NAA15-related syndrome are not as well described as NAA10-related syndrome. Congenital heart disease, including ventricular septal defects, and arrhythmias, such as ectopic atrial tachycardia, have been reported in a small proportion of patients with NAA15-related syndrome. Given the relationship between *NAA10* and *NAA15*, we propose that HCM is also likely to occur in NAA15-related disorder. We present two patients with

CorrespondenceRebecca C. Ahrens-Nicklas, Children's Hospital of Philadelphia, 3615 Civic Center Blvd, Abramson 1016H, Philadelphia, PA 19104, USA. ahrensnicklasr@email.chop.edu.

AUTHOR CONTRIBUTIONS

Alyssa Ritter contributed to the concept, design, data collection, and manuscript writing. Justin H. Berger provided clinical data, including echocardiogram images, and contributed to manuscript writing. Matthew Deardorff, Kosuke Izumi, Kimberly Y. Lin, and Livija Medne provided clinical data for this manuscript. Rebecca C. Ahrens-Nicklas contributed to concept, design, general data collection, elaboration of text, and manuscript writing. All authors contributed to the critical review and editing of the manuscript and approved the final manuscript as written.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared due to privacy or ethical restrictions.

pediatric HCM found to have NAA15-related disorder via exome sequencing, providing the first evidence that variants in *NAA15* can cause HCM.

Keywords

exome sequencing; hypertrophic cardiomyopathy; *NAA10*; *NAA15*; neurodevelopmental disorder

1 | INTRODUCTION

The N-acetyltransferase (NatA) complex regulates multiple cellular functions, including cell survival and cell cycle control, through cotranslational protein modification (Arnesen et al., 2006; Deng et al., 2019; Dörfel & Lyon, 2015; Lee et al., 2018; Linster et al., 2015; Lyon, 2019; Mullen et al., 1989; Myklebust et al., 2015). The NatA complex is a trimer or tetramer composed of: NAA15-NAA10-HYPK, NAA15-NAA10-NAA50, or NAA15-NAA10-HYPK-NAA50; *NAA10* and *NAA15* are the core components for the NatA activity (Arnesen et al., 2010; Deng et al., 2020). *NAA10* is the catalytic subunit while *NAA15* is an obligatory auxiliary subunit providing ancohoring to the ribosome and proper substrate specificity of *NAA10* (Arnesen et al., 2005; Deng et al., 2019; Dörfel & Lyon, 2015; Gautschi et al., 2003; Lee et al., 2018; Liszczak et al., 2013; Lyon, 2019; Mullen et al., 1989; Myklebust et al., 2015; Van Damme et al., 2011). Both *NAA10* and *NAA15* have been associated with neurodevelopmental syndromes with overlapping clinical features, including variable intellectual disability, dysmorphic facial features, and, less commonly, congenital anomalies such as cleft lip or palate (Cheng et al., 2018, 2020).

NAA10 has been associated with a variant of phenotypes including an X-linked disorder with developmental delay, dysmorphic features and lethal cardiac arrhythmias, Lenz microphthalmia syndrome, Ogden syndrome, and neurodevelopmental disorders (Casey et al., 2015; Esmailpour et al., 2014; Johnston et al., 2019; Myklebust et al., 2015; Popp et al., 2015; Ree et al., 2019; Rope et al., 2011; Sauiner et al., 2016; Sidhu et al., 2017). The largest report of patients with NAA10-reated syndrome, as published by Cheng et al. in 2020, included 23 individuals from 23 families. Characteristic features included developmental delay, intellectual disability (ID), autism spectrum disorder, muscular hypotonia, dysmorphic facial features, and less commonly cardiac disease, including hypertrophic cardiomyopathy in a small number of patients (Cheng et al., 2020; Støve et al., 2018).

NAA15 was implicated in human disease after several studies identified de novo, loss-of-function *NAA15* variants in large cohorts of patients with autism spectrum disorder and/or ID (Stessman et al., 2017; Zhao et al., 2018). In a large cohort of 38 patients with *NAA15* variants from 33 families, common features included variable developmental delay, autism spectrum disorder or behavior abnormalities, muscular hypotonia, congenital cardiac defects, and skeletal or connective tissue abnormalities (Cheng et al., 2018, 2020). Notably, NAA10- and NAA15-related disorders have much phenotypic overlap, including variable ID, motor impairment, behavior abnormalities, and skeletal anomalies. Patients with missense variants have also been reported. These variants have been shown to affect either

stability or activity of the NatA complex (Cheng et al., 2018). However, the clinical spectrum of NAA15-related syndrome is less well-delineated than that of NAA10-related syndrome and less is known about the cardiac phenotype. Herein, we present the first two patients with NAA15-related disorder who presented with pediatric HCM, providing evidence that variants in *NAA15* are associated with pediatric HCM.

2 | METHODS

Clinical trio exome sequencing for Patient 1 was performed at the Division of GenomicDiagnostics at Children's Hospital of Philadelphia via methods previously described (Gibson et al., 2018). Clinical trio exome sequencing for Patient 2 was performed at GeneDx. Informed consent for publication of this information was obtainedfrom both families. Literature review using terms *"NAA10"*and *"NAA15"* was performed and three articles describingclinical information or clinical reports of patients with NAA15-related disorder were identified.

3 | RESULTS

Three publications were identified which reported clinical information for 38 individuals with NAA15-related disorder. Phenotypic findings are summarized in Table 1. The most commonly reported features include: intellectual disability, speech and motor delays, behavior issues, and mild dysmorphic features.

4 | CASE REPORTS

4.1 | Patient 1

Patient 1 initially presented to medical attention at 2 months of age with tachypnea and tachycardia. He was the product of a naturally conceived, uncomplicated pregnancy to a 38 year-old G4P3-P4 mother. He was born at 37 weeks gestation weighing 2.55 kg ($z = -1.78$) and measuring 47.5 cm ($z = -2.21$) in length. He had no major complications in the neonatal period. Echocardiographic evaluation (Figure 1) demonstrated HCM, with features including hyperdynamic left ventricle (LV) systolic function, quasi-obliteration of the LV cavity in systole, asymmetric septal hypertrophy (9 mm, Z-score + 8) and mild to moderate obstructive HCM with peak gradient of 52 mmHg (mean 22 mmHg). There was mild mitral regurgitation and mild diastolic dysfunction (by mitral inflow E/e', an echocardiographic measure of diastolic dysfunction focusing on mitral inflow to estimate LV compliance). His electrocardiogram (ECG) showed sinus rhythm with a normal QTc and met voltage criteria for LV hypertrophy. A comprehensive evaluation for inborn errors of metabolism and storage diseases was unremarkable. No family history of cardiomyopathy, arrhythmias, or neurodevelopmental disorders was reported. Chromosomal SNP microarray was normal. Expedited trio exome sequencing was recommended due to his new diagnosis of infantile cardiomyopathy. Clinical trio exome sequencing with confirmed parentality identified a de novo, pathogenic variant in *NAA15* [NM_057175.3]: c.1009_1012delGAAA, p.Glu337Arg*5. No other reportable or clinically significant variants were identified.

Patient 1 is now 17 months old with a history of severe infantile eczema, chronic constipation, lower eyelid entropion, and muscular hypotonia (Table 1). His cardiac function and degree of hypertrophy have remained stable on propanolol monotherapy. He has global developmental delays, first achieving sitting at 9 months and walking at 17 months. He has significant expressive speech delay. Growth paramters at last evaluation were notable for height at 77.5 cm ($z = -1.45$), weight at 10.4 kg ($z = -0.30$), and head circumference at 47.5 cm ($z = 0.22$). Physical examination was notable for epicanthal folds, cupped and prominent ears, muscular hypotonia, and dry skin with erythema and excoriation.

4.2 | Patient 2

Patient 2 is an 8-year-old male who presented at 6-years-old to cardiology for evaluation of a heart murmur identified at a routine pediatrics visit. Echocardiogram was notable for normal LV systolic function, trivial LV outflow obstruction (peak 11 mmHg, mean 6 mmHg) secondary to a localized septal thickening (10 mm, Z-score + 5) and systolic anterior motion of the mitral valve (Figure 1). His ECG showed normal QTc and lateral q waves, suggestive of septal hypertrophy. Subsequent evaluations noted persistent focal septal hypertrophy (maximally 14 mm, Z-score + 10), consistent with a diagnosis of mild-moderate HCM without obstruction. He does not currently require any cardiac medications.

He was the product of an uncomplicated pregnancy to a 31-year-old G1P0-P1 mother. He was born at 38 weeks 6 days gestation weighing 2.77 8 kg ($z = -1.28$) and measuring 46.4 cm ($z = -1.36$) in length. He had no major complications in the neonatal period. His medical history is notable for muscular hypotonia, amblyopia, recurrent otitis media, unilateral mild-to-moderate conductive hearing loss, and lateral penile chordee (Table 1). He had global developmental delays, with sitting at 7 months, walking at 19 months, and first word at 18 months. Neuropsychological testing was notable for full scale intellectual quotient (FSIQ) of 94. He is currently receiving special education services for specific learning disabilities, including attention difficulties, deficits in working memory, and fine motor delay. No family history of cardiomyopathy, arrhythmia, neurodevelopmental disorders, or congenital anomalies was reported. Physical examination at 7 years old was notable for epicanthal folds, upslanting palpebral fissures, prominent forehead, depressed nasal bridge with broad nasal tip, and bilateral fifth finger clinodactyly of both fingers and toes. Growth was notable for height at 122.7 cm ($z = -1.29$), weight at 24.6 kg ($z = -0.56$), and head circumference at 50.5 cm ($z = -1.42$).

A multi-gene cardiomyopathy panel identified a variant of uncertain significance (VUS) in FLNC (NM_001458.5, c. 8019C>G, p. His2673Gln) and a single intronic VUS in GAA (NM_000152.5, c. 858 + 4C>G). Chromosomal microarray was normal. Clinical trio exome sequencing with confirmed parentality identified a de novo, likely pathogenic variant in *NAA15* [NM_057175.3]: c.79A>G, p.R27G. No additional reportable or clinically relevant variants were identified.

4.3 | Variant interpretation

The de novo variant identified in Patient 1, *NAA15* c.1009_1012delGAAA, results in a frameshift in the transcript followed by a premature stop codon five amino acids

downstream. The variant has been previously reported in two unrelated individuals with NAA15-related syndrome who have heterotaxy, congenital heart disease, developmental delay, and muscular hypotonia (Cheng et al., 2018; Zaidi et al., 2013). Functional analysis has shown almost complete absence of mutant *NAA15* mRNA, supporting that this variant results in nonsense-medicated delay resulting in loss of function allele (Cheng et al., 2018). This variant meets criteria to be classified as pathogenic using American College of Medical Genetics criteria PVS1 and PS2 (Richards et al., 2015).

The variant identified in Patient 2, *NAA15* c.79A>G, is a de novo missense variant in exon 2 of 20. It is not present in large population cohorts (Karczewski et al., 2020). In silico analyses support a deleterious effect (Choi & Chan, 2015; Ng & Henikoff, 2003; Schwartz et al., 2014). Missense variants occur significantly less often than expected per investigation of population databses (Karczewski et al., 2020). Other missense variants have been reported in *NAA15* with variable features ranging from isolated neurodevelopmental disability to congenital heart disease (Cheng et al., 2020). This variant meets criteria to be classified as likely pathogenic using ACMG criteria PS2-moderate, PM2, PP2, and PP3 (Richards et al., 2015).

5 | DISCUSSION

Both patients reported here presented for genetics evaluation due to hypertrophic cardiomyopathy and were subsequently identified to have likely pathogenic or pathogenic de novo variants in *NAA15*. They also other common features of the disorder, including muscular hypotonia, developmental delays, mild dysmorphic features, and ophthalmologic findings. Similar to several patients with missense variants in *NAA15,* Patient 2 has a history of mild developmental delay and specific learning disabilities, but relatively preserved intellectual functioning on neuropsychological testing (Cheng et al., 2018). A review of previously reported patients with NAA15-related disorder, as summarized in Table 1, noted one patient with a history of cardiac arrhythmias and no other patients with HCM (Cheng et al., 2018, 2020). Other rare findings in our patients include lower eyelid ectropion, refractive errors, and conductive hearing loss. Reassuringly, both patients have had relatively stable cardiac function since diagnosis; however, it is too early to predict the clinical course of NAA15-related HCM.

Given the functional relationship between *NAA10* and *NAA15* and previous reports of HCM due to *NAA10* variants, it is logical that pathologic variants in *NAA15* could also lead to HCM. It is possible that *NAA10* and *NAA15* are more frequently responsible for genetic predisposition to HCM than was previously recognized, due in part to the variability of manifestations and to relatively mild intellectual impairments, which may not prompt a clinical genetics evaluation.

Further identification of patients with NAA15-related syndrome is needed in order to fully delineate the phenotypic spectrum of this diagnosis, including the proportion of patients with HCM. Early identification of HCM is key for management and treatment of the disease. Given the variable age of onset seen in our two patients, and the variable age of onset of HCM as a whole, it is critically important that clinicians are aware of the risk for HCM in

NAA15-related syndrome and provide appropriate cardiac surveillance over the lifespan. In conclusion, NAA15-related syndrome should be considered as a differential diagnosis for any pediatric patient presenting with HCM and developmental delay.

ACKNOWLEDGMENTS

The authors greatly appreciate the families for permission to publish this article. Dr. Berger receives support from the National Institutes of Health/National Heart Lung and Blood Institute (T32 HL1007915). Dr. Ahrens-Nicklas receives support from the National Institutes of Health (NINDS, K08NS105865).

Funding information

National Heart, Lung, and Blood Institute, Grant/Award Numbers: T32, HL1007915; National Institute of Neurological Disorders and Stroke, Grant/Award Number: K08NS105865

REFERENCES

Arnesen T, Anderson D, Baldersheim C, Lanotte M, Varhaug JE, & Lillehaug JR (2005). Identification and characterization of the human ARD1-NATH protein acetyltransferase complex. Biochemical Journal, 386(Pt 3), 433–443.

Arnesen T, Gromyko D, Pendino F, Ryningen A, Varhaug JE, & Lillehaug JR (2006). Induction of apoptosis in human cells by RNAi-mediated knockdown of hARD1 and NATH, components of the protein N-alpha-acetyltransferase complex. Oncogene, 25(31), 4350–4360. [PubMed: 16518407]

Arnesen T, Starheim KK, Van Damme P, Evjenth R, Dinh H, Betts MJ,… Anderson D (2010). The chaperone-like protein HYPK acts together with NatA in Cotranslational N-terminal acetylation and prevention of Huntingtin aggregation. Molecular and Cellular Biology, 30(8), 1898–1909. 10.1128/mcb.01199-09 [PubMed: 20154145]

Casey JP, Støve SI, McGorrian C, Galvin J, Blenski M, Dunne A,… Lynch SA (2015). NAA10 mutation causing a novel intellectual disability syndrome with long QT due to N-terminal acetyltransferase impairment. Scientific Reports, 5, 16022. [PubMed: 26522270]

Cheng H, Dharmadhikari AV, Varland S, Ma N, Domingo D, Kleyner R,… Lyon GJ (2018). Truncating variants in NAA15 are associated with variable levels of intellectual disability, autism Spectrum disorder, and congenital anomalies. American Journal of Human Genetics, 102(5), 985–994. [PubMed: 29656860]

Cheng H, Gottlieb L, Marchi E, Kleyner R, Bhardwaj P, Rope AF,… Lyon GJ (2020). Phenotypic and biochemical analysis of an international cohort of individuals with variants in NAA10 and NAA15. Human Molecular Genetics, 29, 877–878. 10.1093/hmg/ddz173 [PubMed: 32027362]

Choi Y, & Chan AP (2015). PROVEAN web server: A tool to predict the functional effect of amino acid substitutions and indels. Bioinformatics, 31(16), 2745–2747. [PubMed: 25851949]

Deng S, Magin RS, Wei X, Pan B, Petersson EJ, & Marmorstein R (2019). Structure and mechanism of acetylation by the N-terminal dual enzyme NatA/Naa50 complex. Structure, 27(7), 1057–1070.e4. [PubMed: 31155310]

Deng S, McTiernan N, Wei X, Arnesen T, & Marmorstein R (2020). Molecular basis for N-terminal acetylation by human NatE and its modulation by HYPK. Nature Communications, 11(1), 818.

Dörfel MJ, & Lyon GJ (2015). The biological functions of Naa10: From amino-terminal acetylation to human disease. Gene, 567(2), 103–131. [PubMed: 25987439]

Esmailpour T, Riazifar H, Liu L, Donkervoort S, Huang VH,Madaan S,… Huang T (2014). A splice donor mutation in NAA10 results in the dysregulation of the retinoic acid signalling pathway and causes Lenz microphthalmia syndrome. Journal of Medical Genetics, 51 (3), 185–196. [PubMed: 24431331]

Gautschi M, Just S, Mun A, Ross S, Rücknagel P, Dubaquié Y,… Rospert S (2003). The yeast N(alpha)-acetyltransferase NatA is quantitatively anchored to the ribosome and interacts with nascent polypeptides. Molecular and Cellular Biology, 23(20), 7403–7414. [PubMed: 14517307]

Gibson KM, Nesbitt A, Cao K, Yu Z, Denenberg E, DeChene E,… Santani A (2018). Novel findings with reassessment of exome data: Implications for validation testing and interpretation of genomic

data. Genetics in Medicine: Official Journal of the American College of Medical Genetics, 20(3), 329–336. [PubMed: 29389922]

Johnston JJ, Williamson KA, Chou CM, Sapp JC, Ansari M, Chapman HM,… Biesecker LG (2019). NAA10 polyadenylation signal variants cause syndromic microphthalmia. Journal of Medical Genetics, 56(7), 444–452. [PubMed: 30842225]

Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q,… MacArthur DG (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. Nature, 581(7809), 434–443. [PubMed: 32461654]

Lee M-N, Kweon HY, & Oh GT (2018). N-α-acetyltransferase 10 (NAA10) in development: The role of NAA10. Experimental & Molecular Medicine, 50(7), 1–11.

Linster E, Stephan I, Bienvenut WV, Maple-Grødem J, Myklebust LM, Huber M,… Wirtz M (2015). Downregulation of N-terminal acetylation triggers ABA-mediated drought responses in Arabidopsis. Nature Communications, 6, 7640.

Liszczak G, Goldberg JM, Foyn H, Petersson EJ, Arnesen T, & Marmorstein R (2013). Molecular basis for N-terminal acetylation by the heterodimeric NatA complex. Nature Structural & Molecular Biology, 20(9), 1098–1105.

Lyon GJ (2019). From molecular understanding to organismal biology of N-terminal acetyltransferases [*review of From Molecular Understanding to Organismal Biology of N-Terminal Acetyltransferases*]. Structure, 27(7), 1053–1055. [PubMed: 31269458]

Mullen JR, Kayne PS, Moerschell RP, Tsunasawa S, Gribskov M, Colavito-Shepanski M,… Sternglanz R (1989). Identification and characterization of genes and mutants for an N-terminal acetyltransferase from yeast. The EMBO Journal, 8(7), 2067–2075. [PubMed: 2551674]

Myklebust LM, Støve SI, & Arnesen T (2015). Naa10 in development and disease. Oncotarget, 6(33), 34041–34042. [PubMed: 26431279]

Ng PC, & Henikoff S (2003). SIFT: Predicting amino acid changes that affect protein function. Nucleic Acids Research, 31(13), 3812–3814. [PubMed: 12824425]

Popp B, Støve SI, Endele S, Myklebust LM, Hoyer J, Sticht H,… Reis A (2015). De novo missense mutations in the NAA10 gene cause severe non-syndromic developmental delay in males and females. European Journal of Human Genetics, 23(5), 602–609. [PubMed: 25099252]

Ree R, Geithus AS, Tørring PM, Sørensen KP, Damkjær M, DDD study,… Arnesen T (2019). A novel NAA10 p.(R83H) variant with impaired acetyltransferase activity identified in two boys with ID and microcephaly. BMC Medical Genetics, 20(1), 101. [PubMed: 31174490]

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J,… ACMG Laboratory Quality Assurance Committee. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine: Official Journal of the American College of Medical Genetics, 17(5), 405–424. [PubMed: 25741868]

Rope AF, Wang K, Evjenth R, Xing J, Johnston JJ, Swensen JJ,… Lyon GJ (2011). Using VAAST to identify an X-linked disorder resulting in lethality in male infants due to N-terminal acetyltransferase deficiency. American Journal of Human Genetics, 89(1), 28–43. [PubMed: 21700266]

Saunier C, Støve SI, Popp B, Gérard B, Blenski M, AhMew N,… Zweier C (2016). Expanding the phenotype associated with NAA10-related N-terminal acetylation deficiency. Human Mutation, 37 (8), 755–764. [PubMed: 27094817]

Schwarz JM, Cooper DN, Schuelke M, & Seelow D (2014). MutationTaster2: Mutation prediction for the deep-sequencing age. Nature Methods, 11(4), 361–362. [PubMed: 24681721]

Sidhu M, Brady L, Tarnopolsky M, & Ronen GM (2017). Clinical manifestations associated with the N-terminal-acetyltransferase NAA10 gene mutation in a girl: Ogden syndrome. Pediatric Neurology, 76, 82–85. [PubMed: 28967461]

Stessman HAF, Xiong B, Coe BP, Wang T, Hoekzema K, Fenckova M, … Eichler EE (2017). Targeted sequencing identifies 91 neurodevelopmental-disorder risk genes with autism and developmental-disability biases. Nature Genetics, 49(4), 515–526. [PubMed: 28191889]

Støve SI, Blenski M, Stray-Pedersen A, Wierenga KJ, Jhangiani SN, Akdemir ZC, … Arnesen T (2018). A novel NAA10 variant with impaired acetyltransferase activity causes developmental

delay, intellectual disability, and hypertrophic cardiomyopathy. European Journal of Human Genetics, 26(9), 1294–1305. [PubMed: 29748569]

Van Damme P, Evjenth R, Foyn H, Demeyer K, de Bock P-J, Lillehaug JR, . Gevaert K (2011). Proteome-derived peptide libraryies allow detailed analysis of the substrate specificities of N(alpha)-acetyltransferases and point to hNaa10p as the post-translational actin N(alpha)-acetyltransferase. Molecular & Cellular Proteomics, 10(5), M110.004580.

Zaidi S, Choi M, Wakimoto H, Ma L, Jiang J, Overton JD, … Lifton RP (2013). De novo mutations in histone-modifying genes in congenital heart disease. Nature, 498(7453), 220–223. [PubMed: 23665959]

Zhao JJ, Halvardson J, Zander CS, Zaghlool A, Georgii-Hemming P, Mansson E,… Feuk L (2018). Exome sequencing reveals NAA15 and PUF60 as candidate genes associated with intellectual disability. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics, 177(1), 10-20.

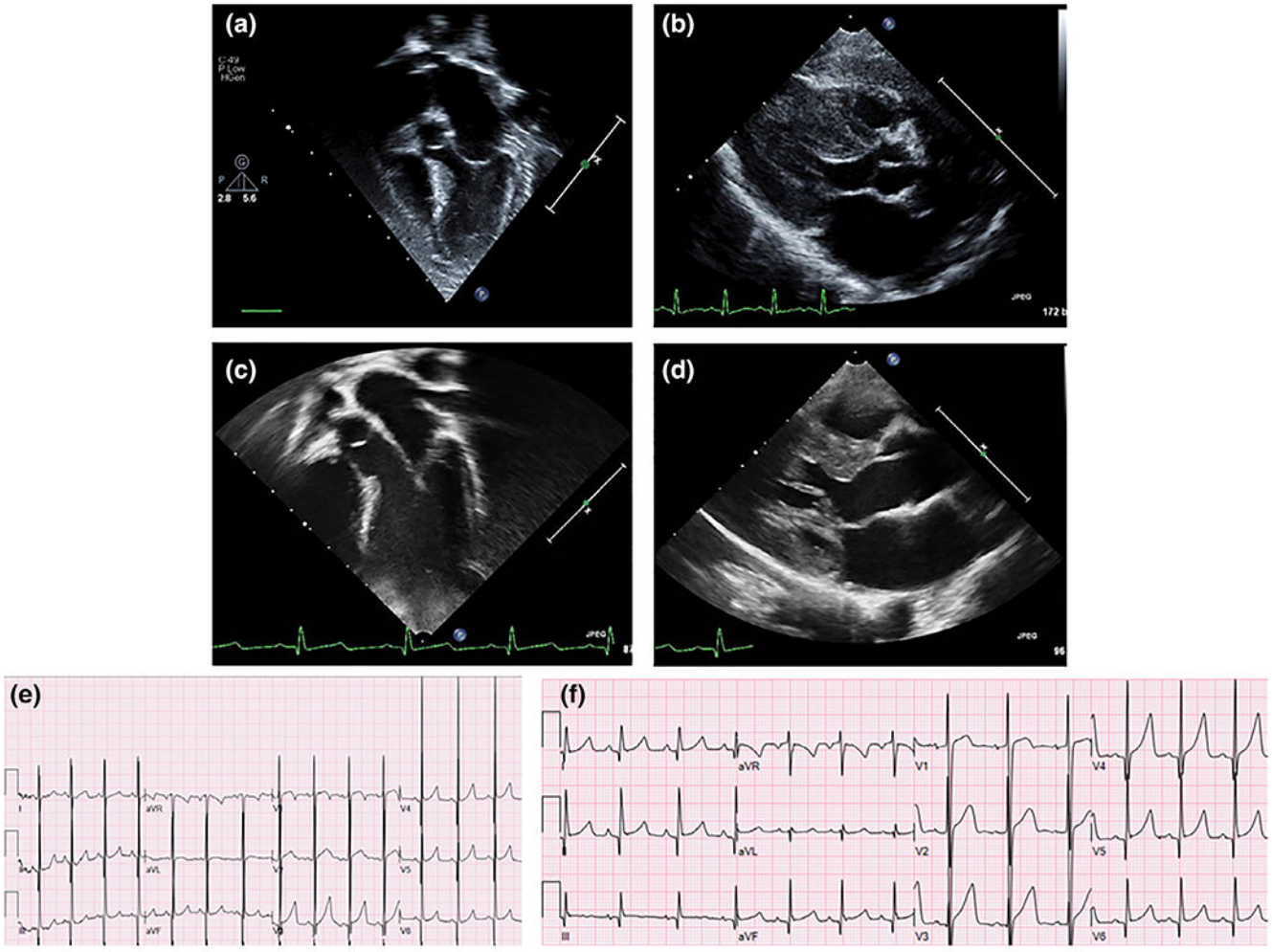

FIGURE 1.

Representative cardiac testing from *NAA15* patients. Echocardiographic images from Patient 1 (a-b) at diagnosis at 2 months and Patient 2 (c-d) at age 7 years. (a) Apical five-chamber image demonstrating asymmetrical septal hypertrophy measuring 9 mm in end-diastole (z score + 8). In supplemental video, there is hyperdynamic LV systolic function with near-complete cavitary obliteration in systole. With color Doppler (not shown), there is mild mitral regurgitation, no aortic insufficiency and flow acceleration beginning in the mid-LV cavity (peak 52/mean 22 mmHg). There is mild diastolic dysfunction by mitral inflow *E*/e' (echocardiographic measure of diastolic dysfunction focusing on mitral inflow to estimate LV compliance, data not shown). (b) Parasternal long axis image in end-diastole re-demonstrating moderate asymmetric septal hypertrophy. (c) Apical five-chamber demonstrating a focal area of septal hypertrophy measuring 10 mm (z score + 5). In supplemental videos, there is normal LV systolic shortening. With color Doppler, there is no mitral or aortic regurgitation, and minimal flow acceleration beginning at the area of septal hypertrophy (peak 11/mean 6 mmHg). (d) Parasternal long axis images in end-diastole with septal hypertrophy. There is systolic anterior motion of the mitral valve in the supplemental video. (e) Parasternal short axis demonstrates otherwise-normal appearing LV cavity. (f)

EKG from Patient 1 is normal sinus rhythm with left ventricular hypertrophy and reciprocal ST segment changes. (h), EKG from Patient 2 with normal sinus rhythm and mid-precordial q waves suggestive of septal hypertrophy [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Summary of clinical features of NAA15-related disorder

	Patient #1	Patient #2				
NAA15 variant	c.1009_1012delGAAA	c.79A > G				
Transcript	NM_057175.4	NM_057175.3				
AA change	p.Glu337fs	p.Arg27Gly				
Inheritance	de novo	de novo				
Classification	Pathogenic	Likely pathogenic				
Publication	Not previously published	Not previously published	Cheng et al. 2018	Cheng et al. 2020	Total	Percent
Brain structure/function						
Intellectual disability	Too young	Mild	23/23	4/6	28/30	93.3
ASD/ADHD/behavior issues	Too young	+	30/33	4/6	35/40	87.5
Abnormal brain MRI	Not done	Not done	2/11	1/3	3/14	21.4
Speech delay	+	+	32/33	3/5	37/40	92.5
Seizures	−	−	6/26	4/5	10/33	30.3
Motor impairment						
Motor delay	+	+	31/32	3/5	36/39	92.3
Muscular Hypotonia	+	+	7/18	0/4	9/24	37.5
Feeding difficulties	+	−	8/14	0/3	9/19	47.4
Cardiovascular						
Congenital cardiac defects	−	−	4/19	1/4	5/23	21.7
Major vessel anomalies	−	−	2/19	Unk	2/19	10.5
Arrhythmias	−	−	1/19	Unk	1/19	5.3
Hypertension	−	−	1/19	Unk	1/19	5.3
HCM	+	+	0/19	0/6	2/27	7.4
Other						
Mild dysmorphic features	+	+	18/28	4/5	24/35	68.6
Skeletal or connective tissue defects	+	+	8/20	1/4	11/26	42.3
Ophthalmologic	+, entropion with corneal irritation; hyperopia	+, amblyopia	2/28	3/6	7/36	19.4
ENT	Bilateral hearing loss	Mild to moderate conductive hearing loss; chronic OM	0/32	0/6	2/40	5.0

Abbreviations: +, positive/present; −, negative/absent; AA, amino acid; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; ENT, otolaryngology; HCM, hypertrophic cardiomyopathy; MRI, magnetic resonance imaging; OM, otitis media; unk, unknown.