HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Am J Med Genet A. 2015 April ; 0(4): 886–890. doi:10.1002/ajmg.a.36994.

Exome Sequencing Establishes Diagnosis of Alström Syndrome in an Infant Presenting with Non-Syndromic Dilated Cardiomyopathy

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Abstract

Idiopathic dilated cardiomyopathy is a heritable, genetically heterogeneous disorder characterized by progressive heart failure. Dilated cardiomyopathy typically exhibits autosomal dominant inheritance, yet frequently remains clinically silent until adulthood. We sought to discover the molecular basis of idiopathic, non-syndromic dilated cardiomyopathy in a one-month-old male presenting with severe heart failure. Previous comprehensive testing of blood, urine, and skin biopsy specimen was negative for metabolic, mitochondrial, storage, and infectious etiologies. Ophthalmologic examination was normal. Chromosomal microarray and commercial dilated cardiomyopathy gene panel testing failed to identify a causative mutation. Parental screening echocardiograms revealed no evidence of clinically silent dilated cardiomyopathy. Whole exome sequencing was carried out on the family trio on a research basis, filtering for rare, deleterious, recessive and *de novo* genetic variants. Pathogenic compound heterozygous truncating mutations were identified in *ALMS1*, diagnostic of Alström syndrome and prompting disclosure of genetic findings. Alström syndrome is a known cause for dilated cardiomyopathy in children yet delayed and mis-diagnosis are common owing to its rarity and age-dependent emergence of multisystem clinical manifestations. At six months of age the patient ultimately developed bilateral nystagmus and hyperopia, features characteristic of the syndrome. Early diagnosis is guiding clinical monitoring of other organ systems and allowing for presymptomatic intervention. Furthermore, recognition of recessive inheritance as the mechanism for sporadic disease has informed family planning. This case highlights a limitation of standard gene testing panels for pediatric dilated

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The remaining authors have no conflicts of interest relevant to this article to disclose.

cardiomyopathy and exemplifies the potential for whole exome sequencing to solve a diagnostic dilemma and enable personalized care.

Keywords

Alström syndrome; dilated cardiomyopathy; heart failure; massively-parallel sequencing; pediatrics; individualized medicine

INTRODUCTION

Dilated cardiomyopathy (DCM), characterized by left ventricular dilation and systolic dysfunction, is a progressive degenerative disorder of cardiac muscle that leads to heart failure and premature death. Coronary artery disease and myocarditis are the most common identifiable causes in adults and children, respectively, yet DCM is an idiopathic condition in 50% of adults and 66% of children [Felker et al., 2000; Towbin et al., 2006] and the most common indication for cardiac transplantation in both age groups [Lund et al., 2013; Dipchand et al., 2013]. Recognition of idiopathic DCM as a familial disorder in 20% to 48% of cases has provided a rationale for routine screening echocardiography in at-risk relatives to detect pre-symptomatic disease [Michels et al., 1992; Grünig et al., 1998; Baig et al., 1998]. Moreover, it has been the impetus for ongoing human genetic investigations to uncover the molecular bases of DCM using locus mapping and/or candidate gene approaches, culminating in discovery of over 40 DCM genes [Hershberger et al., 2011; Olson et al., 2013]. Heart failure in familial DCM is often insidious and clinically silent in childhood, with delayed diagnosis of advanced cardiomyopathy at a mean age of 45 years [Michels et al., 1992]. However, a subset of patients develops sporadic, idiopathic DCM with symptomatic heart failure in childhood, suggesting unique pathogenic mechanisms within the pediatric age group. Among 591 children presenting with DCM at <1 year of age, 78% were classified as having idiopathic DCM while only 4.4% were found to have familial DCM, 4.7% had an inborn error of metabolism, and 1.7% had a syndromic form of DCM [Towbin et al., 2006]. The transformative technological breakthrough of whole exome sequencing (WES), enabling comprehensive, hypothesis-free survey of ~20,000 genes, is poised to accelerate familial DCM gene discovery [Theis et al., 2011; Theis et al., 2014]. Moreover, WES for the first time provides a genomic strategy to uncover the molecular genetic bases of sporadic pediatric DCM [Boycott et al., 2013]. Here, we report application of WES to establish a molecular diagnosis in an enigmatic case of idiopathic DCM and severe heart failure in an infant.

CLINICAL REPORT

A 5-week-old male, born at term following a normal pregnancy and uncomplicated delivery, presented with a one week history of diaphoresis and tachypnea during feedings and was hospitalized for further evaluation and management. Medical history was otherwise unremarkable and family history was negative for heart failure, sudden death, and consanguinity. On physical examination, he was non-dysmorphic and had normal muscle tone. Temperature, blood pressure, and heart rate were normal but he was moderately tachypneic with subcostal retractions. A gallop was noted on cardiac auscultation and mild

hepatomegaly was present. Electrocardiography showed sinus rhythm with right ventricular hypertrophy and non-specific T wave abnormalities. Chest radiography demonstrated moderate to marked cardiac enlargement and mild pulmonary venous congestion. Echocardiography revealed diagnostic features of DCM with severe left ventricular dilation (Z-score for diastolic dimension 4.8) and systolic dysfunction (ejection fraction 25%, normal ≥55%) associated with moderate mitral valve regurgitation. Marked elevation of left ventricular end-diastolic pressure (21 mmHg, normal <12 mmHg) at cardiac catheterization reflected concomitant severe diastolic dysfunction. Anomalous origin of the left coronary artery was excluded by angiography. Routine laboratory studies were unremarkable except for a significantly elevated NT-Pro BNP level (21,171 pg/mL, normal ≤51 pg/mL). Comprehensive standard and metabolic testing was normal, including electrolytes, creatinine, venous pH, liver function tests, thyroid function tests, urinalysis, lactate, ammonia, glucose, creatine kinase; plasma carnitine, acylcarnitine, amino acids, beta-hydroxybutyrate, and lysosomal enzymes; urine mucopolysaccharides, oligosaccharides, and organic acids. Viral antigen and serologic testing ruled out infection caused by adenovirus, enterovirus, influenza A/B, parvovirus B19, CMV, EBV, HHV-6, and RSV. Skin biopsy revealed no diagnostic ultrastructural features of storage disease. Mitochondria were normal in number and configuration and did not demonstrate abnormalities of cristae or crystalloid inclusions. Ophthalmologic examination, including fundoscopy, was normal. Subsequent screening echocardiograms revealed no signs of clinically silent DCM in the patient's parents (father, 39 years; mother, 32 years), findings consistent with a *de novo* mutation or recessive mode of inheritance. Clinical genetic testing was then pursued. Chromosomal microarray detected a maternally inherited 1.5 megabase interstitial duplication at 18q23 deemed most likely a familial variant without phenotypic significance (Chr18: 74,673,394-76,127,279; genes within duplicated region: *ZNF236*, *MBP*, *GALR1*). Targeted DNA sequencing with a commercially available 38-gene DCM panel (GeneDx, Gaithersburg, MD) identified a missense variant of unknown significance in *ANKRD1*, also maternally inherited and identified in 9 control samples in a publicly available database. Collectively, negative screening test results excluded known causes for heart failure, leading to a diagnosis of idiopathic DCM. The patient was hospitalized for 14 days on a continuous intravenous milrinone infusion and ultimately transitioned to an oral heart failure regimen of digoxin, carvedilol, enalapril, spironolactone, and aspirin. He was scheduled for close outpatient pediatric cardiology follow-up to monitor his DCM.

The patient and his unaffected parents (Fig 1a) were enrolled in a DCM research study approved by the Mayo Clinic Institutional Review Board, following informed written consent. Genomic DNA was extracted from peripheral blood white cells collected from the family trio and subject to WES by the Mayo Clinic Medical Genome Facility, utilizing the Agilent SureSelect Human All Exon v4+UTRs capture kit (Agilent, Santa Clara, CA) and Illumina HiSeq 2000 platform (Illumina, Inc., San Diego, CA). Each sample yielded more than 105 million 101 base pair, paired-end reads. Raw sequence alignment and variant calling were carried out by the Mayo Clinic Bioinformatics Core. The reads were aligned to the hg19 reference genome with Novoalign (http://novocraft.com) followed by the sorting and marking of duplicate reads using Picard (http://picard.sourceforge.net). Local realignment of insertions/deletions (INDELs) and base quality score recalibration were then

performed using the Genome Analysis Toolkit (GATK) [McKenna et al., 2010]. Single nucleotide variants (SNVs) and INDELs were called across all three samples simultaneously using GATK's UnifiedGenotyper with variant quality score recalibration [DePristo et al., 2011]. Over 98% of the reads mapped to the genome and over 93% of the 71 megabase capture region had ≥20× coverage. Approximately 72,000 SNVs and 9,000 INDELs were identified in the coding region of each sample. To identify a pathogenic mutation(s) among the vast number of SNVs and INDELs identified by WES, variant call format files were loaded into QIAGEN's Ingenuity® Variant Analysis™ software (www.qiagen.com/ingenuityfromQIAGENRedwoodCity) and an iterative filtering process was employed (Fig 1b). Variants that mapped to the coding region and passed quality score recalibration were filtered to exclude variants that were located in the top 0.5% of the most exonically-variable genes and present in three or more in-house, non-DCM controls (n = 115). Variants were then filtered to select for rare variants with a minor allele frequency <1.0% in 3 publicly available databases comprised of 7,664 individuals [Exome Variant Server, NHLBI GO Exome Sequencing Project; 1000 genomes project consortium et al., 2012; Drmanac et al., 2010]. Next, variants were restricted to those most likely to be functionally significant, including missense, truncation, and canonical splice-site variants. Finally, filtered data were analyzed for all potential modes of inheritance for sporadic DCM including homozygous recessive, compound heterozygous, X-linked recessive, uniparental disomy, and *de novo*. This comprehensive filtering process resulted in a short list of 9 candidate variants in seven genes on distinct chromosomes (*BRAT1, ALMS1, ANXA11, TXLNG, CT47B1, UTP14A*, and *FAM58A*), each confirmed by Sanger sequencing. Compound heterozygous mutations in the Alström syndrome 1 gene (*ALMS1*) were identified, diagnostic of the syndrome for which the gene was named [Alström et al., 1959; Marshall et al., 2007]. Both mutations, classified as the only pathogenic mutations by Ingenuity® Variant Analysis™ (QIAGEN, Redwood City, CA), resulted in premature truncation of the ALMS1 protein product. A 1-basepair insertion mutation c.4156insA, p.Thr1386fs*15 was paternally inherited, while a nonsense mutation c.6436C>T, p.Arg2146* was maternally inherited (GenBank NM_015120.4; Fig 1a). Our findings were disclosed to the family for genetic counseling and confirmed by targeted sequencing of *ALMS1* in a specialized CLIA-approved clinical laboratory (University of Chicago, Chicago, IL). Six weeks earlier, the patient had been diagnosed with benign asymmetric pendular bilateral nystagmus and hyperopia, following a negative workup for brain tumor and neuroblastoma. In retrospect, these were early non-cardiac features of Alström syndrome. At 15 months of age, the patient's DCM had significantly improved on intensive medical therapy for congestive heart failure (Z-score for left ventricular diastolic dimension 3.6; ejection fraction 50%).

DISCUSSION

Despite discovery of over 40 DCM genes, there remains incomplete knowledge of the full spectrum of molecular defects that underlie DCM, thereby limiting the clinical utility of standard panel testing with a diagnostic yield of only 37% [Pugh et al., 2014]. To this end, WES has proved to be a valuable research tool for familial DCM gene discovery [Theis et al., 2011; Theis et al., 2014]. As exemplified in this clinical report, it also provides a new platform to identify rare or novel genes for sporadic DCM. Indeed, WES is rapidly making

its way into the clinical setting as a diagnostic tool for a spectrum of idiopathic, odyssey cases [Boycott et al., 2013; Lee et al., 2014, Yang et al., 2013, Yang et al., 2014]. Ongoing challenges to clinical application of WES include <100% coverage of protein coding regions and discriminating pathogenic mutations from the large number of polymorphisms unrelated to the primary disease phenotype in each individual's exome. Establishing a genetic diagnosis in our patient was facilitated by *ALMS1* as a known, albeit rare, gene for pediatric DCM that is not currently included on standard DCM gene testing panels. While clinical whole exome sequencing would have led to a molecular diagnosis of Alström syndrome in this patient, many infantile cases of DCM are attributable to mutations in novel DCM genes (our unpublished data) and only about one-third of DCM in children <2 years of age is caused by mutations in genes comprising DCM genetic testing panels [Pugh et al., 2014]. Therefore, DCM panel testing in conjunction with whole exome sequencing on a research basis is optimal, enabling targeted, full-coverage screening for mutations in established DCM genes and potential identification of novel DCM genes when panel testing is inconclusive. In sporadic cases attributable to inherited or *de novo* mutations, a WES strategy that includes phenotypically normal parents and siblings is a critical element for variant filtering and ultimate diagnostic success. Even so, WES of the family trio uncovered nine rare, functionally significant variants in seven genes that passed a rigorous filtering process, illustrating the challenge of interpreting exome data and identifying disease-causing mutations.

Alström syndrome [OMIM 203800] is a recessively-inherited, multisystem disorder caused primarily by nonsense and frameshift mutations in the *ALMS1* gene, leading to premature protein truncation [Marshall et al., 2011]. It is characterized universally by age-dependent emergence of nystagmus, cone-rod dystrophy leading to blindness, insulin resistance and obesity [Marshall et al., 2011]. Additionally, variable degrees of sensorineural hearing loss; and pulmonary, hepatic and renal dysfunction can occur [Marshall et al., 2011]. DCM is diagnosed in approximately two thirds of patients, 60% of whom present with heart failure in infancy [Marshall et al., 2007]. Many recover low-normal cardiac function for many years while on medical therapy, yet DCM may suddenly recur with rapid progression and poor clinical outcome [Marshall et al., 2007, Marshall et al., 2011]. While recognition of Alström syndrome is usually delayed or possibly missed owing to its rarity and age-dependent expression of pleiotropic clinical features [Hoffman et al., 2005], the use of whole exome sequencing in our patient enabled a pre-emptive diagnosis of Alström syndrome and establishment of the etiology for heart failure. Moreover, a definitive diagnosis is guiding clinical monitoring for extra-cardiac manifestations of the disorder [Monitoring guidelines, Alström syndrome international website] and facilitating early intervention planning, such as enrollment in a specialty school for the blind for inevitable visual loss and dietary counseling to mitigate obesity [Lee et al., 2009]. Beyond optimization of the patient's care, recognition of recessive inheritance as the underlying mechanism for sporadic disease, conferring a 25% recurrence risk, has informed family planning. Insights into the pathobiology of mitogenic cardiomyopathy, a form of DCM in Alström syndrome characterized by myocyte nuclear hypertrophy and marked mitotic activity, are emerging [Chang et al., 2010, Shenje et al., 2014, Louw et al., 2014], but further research will be

required to develop individualized, mechanism-based therapy beyond traditional reverse cardiac remodeling drugs.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health [R01 HL071225 (T.M.O.)], Pre-Doctoral Training Program in Molecular Pharmacology [T32GM072474 (P.A.L.)], and an American Heart Association Pre-Doctoral Fellowship [14PRE18070007 (P.A.L.)].

Dr. Olson is a co-inventor on a patent for genetic testing of *ACTC1* in dilated cardiomyopathy and has received royalties.

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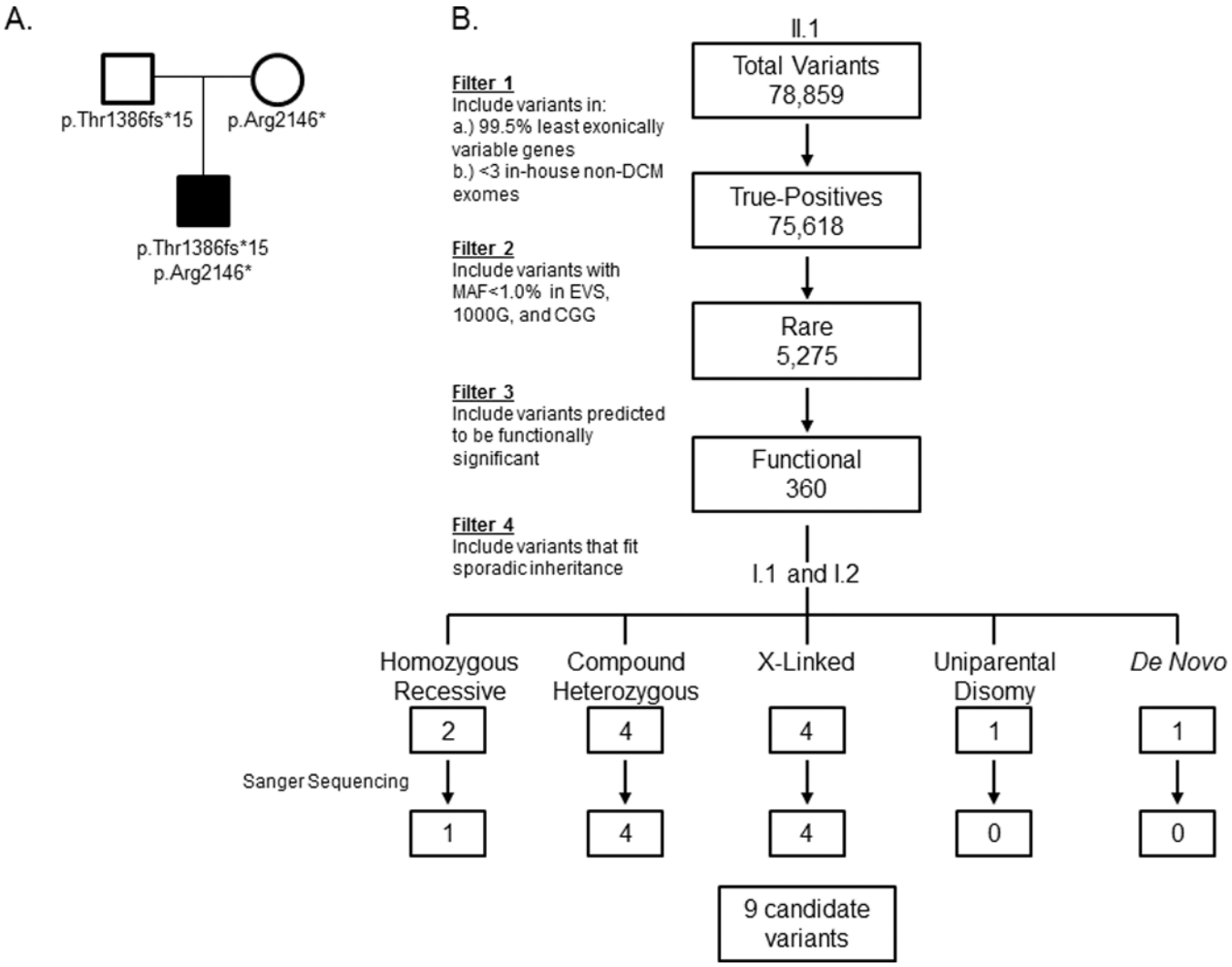

Figure 1.

Whole exome sequencing reveals compound heterozygous truncating *ALMS1* mutations in sporadic, pediatric dilated cardiomyopathy. A. Family pedigree. Square = male; circle = female; solid = affected; open = unaffected. Inheritance of *ALMS1* mutations is shown. B. Iterative filtering scheme for whole exome sequencing data. Number of variants identified in patient are shown. EVS = Exome Variant Server, 1000G = 1000 Genomes; CG = Complete Genomics