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CASE REPORT

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A rare case of pediatric cardiomyopathy: Alström syndrome identified by gene panel analysis

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Abstract

Genetic investigation of early-onset Dilatative cardiomyopathy phenotype, including molecular autopsy, is the key to appropriate recognition and management of rare etiologies and atypical presentations and to offer genetic counseling to the family.

KEYWORDS

Alström syndrome, dilated cardiomyopathy, next generation sequencing

1 | INTRODUCTION

A 1-month-old patient was referred for genetic testing of cardiomyopathies genes after a cardiac arrest and an apparently isolated Dilatative cardiomyopathy phenotype. Next generation sequencing analysis allowed a prompt diagnosis of Alström syndrome, guiding for the appropriate clinical management and enabling cascade testing and a genetic counseling to the family.

Alström syndrome (AS; MIM#203800) is a rare and monogenic recessively inherited disorder affecting numerous organ systems.[1,2,3] With approximately 950 reported cases and an incidence of 1-9 per million individuals, AS is caused by mutations in ALMS1, a 23-exons gene located on chromosome 2p13. Most reported variants are nonsense or frameshift and almost half of them are in exon 8,[4] although exons 10 and 16 are also involved. Clinical manifestations are heterogeneous and usually occur during the first decade of life (often in the first year). Among a wide spectrum of clinical manifestations, patients can develop dilated cardiomyopathy (DCM), often arising abruptly during the first months of life due to aberrant differentiation of cardiomyocytes.[5,6] ALMS1 localizes to centrosomes and basal bodies of ciliated cells where it has been shown to contribute to cell migration and extracellular matrix production.[7,8,9] Even if several roles of the protein in cell cycle regulation and intraciliary transport,[10,11,12,13], have been suggested, the molecular mechanisms underlying multiple organ pathologies have not been fully elucidated.[6] DCM, characterized by left ventricular dilation and systolic dysfunction, is a progressive degenerative disorder of cardiac muscle leading to heart failure and premature death. In children, it is the final common phenotype of several different genetic and nongenetic conditions.[6] Because of its rarity and variable clinical presentation, delayed diagnosis and misdiagnosis of AS are common, making estimates of its incidence difficult.[14] We present the case of an Italian 1-month-old infant with diagnosis of apparently isolated DCM in which genetic testing was essential to establish the molecular diagnosis of AS, allowing appropriate clinical management and counseling of the family.

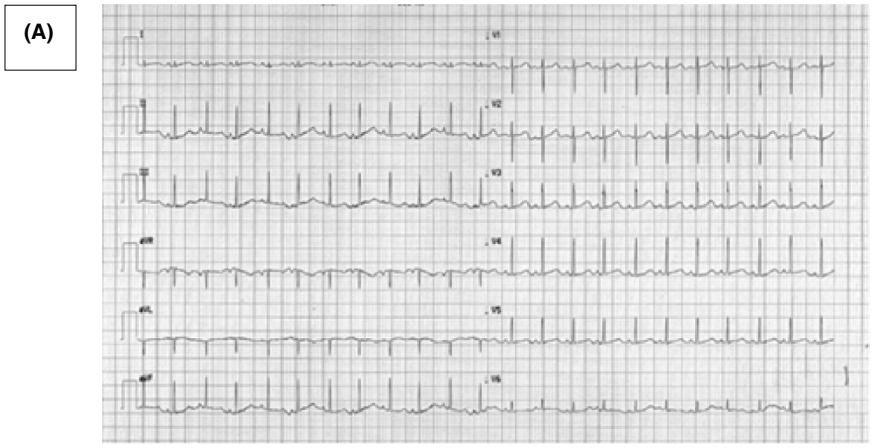

FIGURE 1 Proband's instrumental evaluation (EGG and echocardiogram). A, ECG shows low voltages and T wave inversion in the precordial leads. B, C, Instrumental evaluation shows a DCM (LVEF 50%) with undulating phenotype varying from mild (panel B) to severe systolic dysfunction (panel C)

2 | CASE REPORT

A 1-month-old female, the fourth offspring of Italian nonconsanguineous parents, was brought to our laboratory for clinical genetic evaluation following the detection of an isolated DCM phenotype. The fetal period had been unremarkable. At 3 weeks of age, the baby was referred to the Pediatric Intensive Care Unit (PICU) of our hospital after a cardiac arrest. The ECG documented diffuse low voltages and T wave abnormalities (Figure 1, panel A),chest radiography evidenced cardiac enlargement and congestive heart failure (CHF); transthoracic

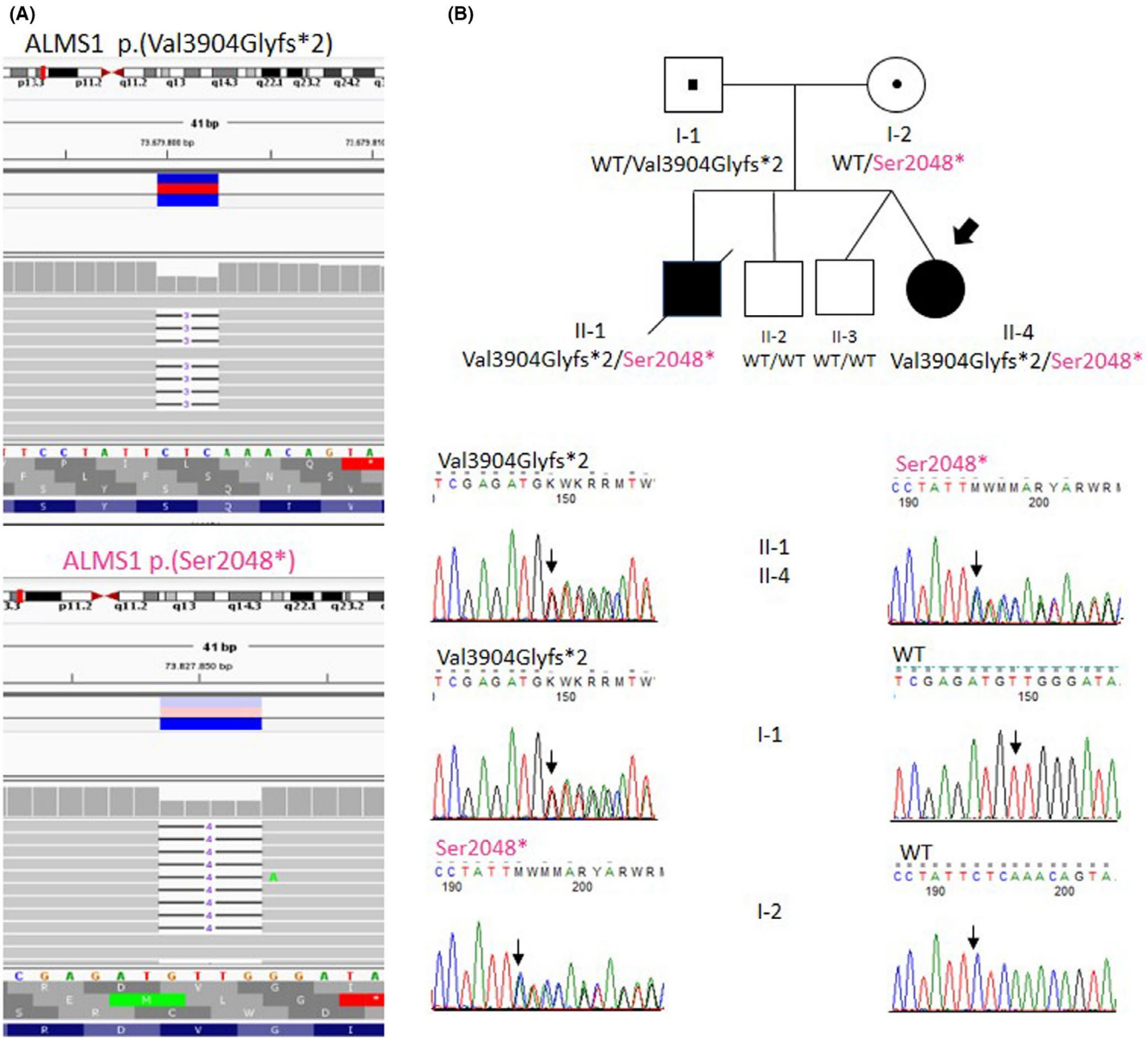

FIGURE 2 Pedigree and mutation analysis of the family. A, Visualization by IGV softwares of NGS data (through alignment of enhriched sequences to Hg 19) shows a 3 –base pair deletion (black) and a delins (pink) in ALMS1 gene. B, The proband II-4 (arrow) carried compound heterozygous mutations: p.(Val3904Glyfs*2) inherited from her father (I-1) and p.(Ser2048*) inherited from her mother (I-2), both identified in her deceased brother (II-1). The variants were not found in two unaffected brothers (II-2, II-3). The two variants detected in the proband by NGS had been confirmed by Sanger sequencing

echocardiogram (TTE) showed severe left ventricular (LV) dilatation and dysfunction, in the context of normal cardiac anatomy. After an appropriate inotropic and anticongestive HF treatment, LV recovered an ejection fraction up to 45%, reaching a mild dilated telediastolic diameter (LVTD z score 2,4) (Figure 1, panel B). Associated external malformations, facial dysmorphisms, and signs of systemic involvement were excluded. Neurological examination was normal, although the young age of the infant did not permit a definitive assessment of potential hearing or visual deficits. A comprehensive metabolic screening resulted negative. The first offspring of the couple, a male child, had died 9 years previously at 11 days of age following an episode of acute HF,autopsy demonstrated DCM with endomyocardial fibroelastosis. Cardiologic examination of the parents excluded cardiomyopathies and family history was otherwise unremarkable. Four weeks after hospital discharge, the baby was readmitted due to overt HF. The echocardiogram showed a progressive LV dysfunction with moderate mitral insufficiency and pulmonary hypertension; moreover, the right ventricle was involved with dilatation and dysfunction (Figure 1, panel C). Despite

optimized pharmacologic treatment, the patient died at the age of 2-months, due to refractory HF. Next generation sequencing (NGS) was performed at initial clinical presentation over a panel of 174 genes using the TruSight™ Cardio Sequencing Kit (Illumina Inc). The analysis identified two novel frameshift variants in ALMS1 (Ensembl transcript id ENST00000264448.6,Genebank transcript id NM_015120.4): c.11711_11714del p.(Val3904Glyfs*2) and c.6143_6148delinsGAG p.(Ser2048*) Figure 2, panel A). The c.11711_11714del p.(Val3904Glyfs*2) variant, localized in exon 18, has not previously described in patients and is reported in the general population with an allele frequency of 0.0003997% (https://gnomad.broadinstitute.org/). The c.6143_6148delinsGAG p.(Ser2048*) variant, localized in exon 8, is also novel and does not have a gnomAD frequency. Sanger sequencing used to confirm the detected variants showed that c.11711_11714del was paternally inherited and c.6143_6148delinsGAG was maternally inherited, consistent with a recessive model of inheritance. Both variants were identified also in the deceased brother, by analyzing DNA extracted from the routine post-birth screening blood spot (Figure 2, panel B). Notably, the sample had been insufficient for a complete *postmortem* genetic test. The two surviving brothers tested negative for both variants (Figure 2, panel B). From the functional standpoint, both variants are predicted to determine a truncated protein and the c.6143_6148delinsGAG is localized in a hot spot exon (exon 8) of ALMS1. According to the ACMG guidelines,[15] both variants can be classified as likely pathogenic. The compound heterozygous genotype observed in our infant, associated with the clinical context, was consistent with Alström syndrome (MIM#203800).

3 | DISCUSSION

Alström syndrome, described for the first time in 1959,[1] is characterized by multiple clinical manifestations with a recessive inheritance model due to ALMS1 gene mutations. The diagnosis of AS is based on clinical findings but may be difficult to establish because of the variable phenotype, even within the same family, with multiorgan involvement.[6]. Cardinal clinical features of AS are obesity, cone-rod dystrophy, progressive sensorineural hearing impairment, dilated or restrictive cardiomyopathy, insulin resistance and multiple organ failures emerge throughout infancy, childhood or young adulthood.[5] DCM may present early after birth, prior to the appearance of other clinical features of Alström syndrome and can lead to early cardiac death due to refractory HF, such as in the brother of our index case [7,16,17]. More often, clinical outcome of infantile DCM widely varies, even within families.[18,19] Notably, more than 40% of AS infants have a transient but severe infant onset DCM, between age 3 weeks and 4 months of age.[14]. However, after an initial and apparent recovery of cardiac function following medical treatment, about 10%-15% show a spontaneous recurrence of clinical symptoms and signs of HF, with rapid progressive left and right ventricle dysfunction and a poor clinical prognosis. On the other side, about 20% of individuals with AS develop an adult-onset restrictive cardiomyopathy phenotype, identified between the teens to the late 30s. Molecular genetic testing of ALMS1, the only gene known to cause AS, is estimated to detect pathogenic variants in 70%-80% of individuals of northern European descent, and approximately 40% worldwide. In 2015, Marshall et al identified 109 novel ALMS1 mutations and defined exons 8, 10, and 16 as mutational hotspots for this gene. Recently, similar mutation profiles were described by Rethanavelu K et al, in a chinese cohort, where the authors identified 57% mutations in exon 8, 12% in exon 10 and 18% in exon 16. In this cohort, most of the reported mutations were nonsense and frameshift (insertions or deletions), with 18 novel variants and 4 recurrent mutations. In particular, the c.2084C >A, p. (Ser695*) presented in the study was suggestive to be a founder mutation in people of Chinese ancestry.[20] The compound heterozygous genotype found in our index patient, consistent with the recessive inheritance model of AS, presents both a nonsense and a frameshift variant according to previously referred for ALMS1 gene.[21] Moreover, our study contributed to emphasize the AS mutations spectrum heterogeneity between ethnies, as newly mentioned for the East and South East Asian people,[20] describing a novel genetic profile of AS in an infant originating from Italy. In an infant presenting with DCM, a timely diagnosis of AS is essential for an appropriate clinical management, but also for the clinical monitoring of known comorbidities involving other organ systems. In our case of isolated infant onset DCM phenotype, genetic testing gave a key contribution to diagnosis, helping to identify the underlying etiology. Indeed, in light of this genetic result, our patient was not listed for heart transplantation, due to the several possible associated comorbidities that are expected to shorten life expectancy, independently from the transplant. Furthermore, identification of the exact disease-causing mutations in the index child is key in identifying the pattern of inheritance and providing appropriate counseling to the family regarding risk of recurrence in future offspring.[6] As a case in point, the lack of a molecular autopsy in the first son prevented the immediate search for ALMS1 mutations in the other living family members, delaying the diagnosis of AS in the female twin or, potentially, prenatal diagnosis. In conclusion, genetic testing allowed a prompt diagnosis of AS in an infant with an apparently isolated DCM phenotype, guiding for the appropriate clinical management and enabling cascade testing in the family. Genetic investigation of early-onset DCM by wide-gene panel or whole exome sequencing, including molecular autopsy, is the key to appropriate recognition and appropriate management of rare etiologies and atypical presentations.

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

FG: designed the study, made substantial contributions to the analysis and interpretation of data, and critically revised the manuscript for important intellectual content analyzed. VS: drafted the manuscript, made contributions to the analysis and interpretation of data. SF, IO, CM, and MI: reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed in this study.

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