Mutation identification and prediction for severe cardiomyopathy in Alström syndrome, and review of the literature for cardiomyopathy

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Research Article

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Abstract

Objective: Alström syndrome (ALMS1)(OMIM# 203800) is a rare autosomal recessive genetic disorder. Dilated cardiomyopathy (DCM) is one of the well-recognized feature of the syndrome ranging from sudden-onset infantile DCM, to adult onset cardiomyopathy, sometimes of the restrictive hypertrophic form with a poor prognosis. We aimed to evaluate severe cardiomyopathy in Alström syndrome in infancy and display susceptible specific mutations of the disease, which may be linked to severe DCM. Secondarily we reviewed published mutations of ALMS1 with cardiomyopathies in the literature.

Method: In this patient cohort, we represent new mutagenic alleles related with severe cardiomyopathy and cardiac outcome. We evaluated echocardiographic studies of nine Turkish patients diagnosed with Alström syndrome (between 2014 and 2020, at age two weeks to twenty years). Thus, we made a detailed examination of the cardiac manifestations of a single-center prospective series of nine children with specific ALMS1 mutations and multisystem involvement. All patients underwent genetic testing, biochemical testing, electrocardiogram, and echocardiographic imaging with speckle tracking to evaluate systolic strain.

Results: Four of the patients died with cardiomyopathy. Three patients (including three of the four fatalities) with the same novel mutation (c.7911dupC [p. Asn2638Glnfs*24]) had cardiomyopathy with intra-familial variability in severity of cardiomyopathy. Global longitudinal strain, a measure of systolic contractile function, was abnormal in all of patients that can be measured.

Conclusion: Cardiac function in ALMS1 patients with infantile cardiomyopathy appears to have different clinical spectrums depending on the mutagenic allele. The c.7911dupC (p. Asn2638Glnfs*24) mutation can be related to severe cardiomyopathy. Parents can be informed and consulted about the progression of serious cardiomyopathy in child carrying this mutagenic allele.

Introduction

Alström syndrome (ALMS1)(OMIM# 203800) is a rare autosomal recessive genetic disorder [1]. About 800 individuals diagnosed with Alström syndrome have been identified worldwide.

It is caused by mutations in the ALMS1 gene (chr 2q13), which encodes a 461.2 kDa protein. The functions of this protein include microtubule organization, particularly the formation and maintenance of cilia [2]. The metabolic abnormalities of Alström syndrome include severe insulin resistance, type 2 diabetes (T2D), hypertriglyceridemia, thyroid and hepatic dysfunction.

Dilated cardiomyopathy occurs in over 60% of patients with ALMS1 at different periods in their lives. The onset and progression of the cardiomyopathy shows intra-familial variability. More than 40% of infants with ALMS1 present severe dilated cardiomyopathy, although this is reported as improving after infancy [3, 4]. In about 20% of Alström syndrome cases, restrictive cardiomyopathy with fibrosis and pulmonary hypertension develops during adolescence or adulthood. Diffuse interstitial myocardial fibrosis in ALMS1 has been shown to be associated with left ventricular (LV) systolic function [5, 6].

Hence, ALMS1 is complex multisystem disorder particular mutations may explain variability of clinical presentations. The mutations related with severity of cardiomyopathy have not defined yet. Here, we represent a family with multiple affected members with ALMS1 with a highly deleterious mutation related with severe infantile cardiomyopathy and cardiac outcome in Alström syndrome patients. We aimed to evaluate severe cardiomyopathy in Alström syndrome in infancy and to display susceptible specific mutations of the disease, which may be linked to severe DCM. Secondarily we reviewed published mutations of ALMS1 with cardiomyopathies in the literature.

Materials And Methods

Between March 2014 and November 2020, the echocardiographic studies of nine Turkish patients diagnosed with ALMS1 were evaluated (Table 1). All the patients had mutations in the ALMS1 gene (Figure 1. Pedigree X and Y).

For all the patients, kidney and liver function tests, hemoglobin A1c (HbA1c), and lipid panel were measured and standard 12-lead transthoracic electrocardiograms (ECGs) were performed. Cardiac measurements performed according to American Society of Echocardiography (ASE) guidelines [7] (Table 2).

LV ejection and shortness fractions (LVEF and LVSF, respectively) were calculated using the Teichholz formula [7]. Right ventricular (RV) functions were analyzed with RV fractional area chance (FAC) and Tricuspid annular plane systolic excursion (TAPSE).

The recommended method for the assessment of ventricular diastolic dysfunction are Doppler and Tissue-Doppler scan recordings [7].

Further analysis of global myocardial function was performed with Speckle tracking echocardiography (GLS). Cardiac magnetic resonance imaging cardiac magnetic resonance (CMR) imaging studies were performed on two patients (Patients A and C) to assess cardiac anatomy.

Following the clinical diagnosis, the ALMS1 gene was sequenced for each patient, including all exons and exon-intron boundaries, using next-generation sequencing on the Illumina Miseq platform. Lipid panel, blood glucose, insulin, and thyroid function tests were enrolled. Eye findings were verified by ECG. Tympanometry and distortion product otoacoustic emissions (DPOE) testing were employed to evaluate the hearing situation (Table 2).

Results

Demografic and clinical characteristics of the patients were displayed on Table 2. Eight of the patients (8/9,) had been diagnosed with cardiomyopathy. Six patients had infancy onset cardiomyopathy, while other 2 patients had been diagnosed after infancy/ adolesence or early adulthood. Two patients of the 6 infantile onset cardiomyopathy with the same mutation died before 2 years old, 14 months and 22 months respectively. Three patients with adolesence onset CMP responded partially to heart failure medications but their recent ejection fractions were still at the lower end of the normal range in two and detoriated in one patient. In 2 families with multiple affected children (Families X,Y), the siblings had similar spectrums for cardiomyopathy; in Family X the older patient had mild cardiomyopathy while his sister, who was monitored by echocardiograms biannually since birth, displayed severe infantile cardiomyopathy until age of 2 then improved with heart failure treatement to mild form of cardiomyopathy.

At the time of the evaluation, 5 patients were clinically stable, without symptoms or signs of heart failure. There was no significant resting tachycardia and normal blood pressure. All patients were receiving beta blockers, and angiotensin converting enzyme inhibitors, The ECG was normal in 3 patients and abnormal in 2 patients. Abnormalities included left ventricular hypertrophy (n = 1), left axis deviation (n = 3), non-specific T wave changes (n = 3), right axis deviation (n = 1), second-degree atrioventricular block (n = 1). and the ECG was otherwise normal.

Among all patients, we found left ventricular dilatation or systolic dysfunction in all patients (Table 1). Valvular involvement was also noted in two patients with thickened mitral valve leaflets and moderate mitral regurgitation. One patient had restrictive cardiomyopathy and 1 showed prominent LV trabeculations with deep intertrabecular recesses that filled with blood from the ventricular cavity. Hypertrabeculation with multiple crypts at the apical postero-lateral aspects of the left ventricle.

Strain parameters of the left ventricle, including GLS, were calculated in three patients, for whom available. GLS of the left ventricle was abnormal in 3 of children (Fig.2). CMR was performed in two children and had evidence of decreased left ventricular function.

Genetic testing

ALMS1 whole gene sequencing was performed for all the nine patients in this study (Table 3, Figure 2). A homozygous single nucleotide duplication was detected on exon 10 of the ALMS1 gene (LRG_741t1 c.7911dupC (p. Asn2638Glnfs*24) as previously reported by Marshall et al.[8]. This mutation is predicted to form a truncated protein, thus being highly deleterious and possibly responsible for the severe phenotype. The mutation was then confirmed by sanger sequencing.

Outcome of patients with novel c.7911dupC (p. Asn2638Glnfs*24) mutation

Patients in Pedigree X had similar onset, progression, and outcome of the disease processes of Alström syndrome (Fig 1). The dilated cardiomyopathy was reported in infancy, although in two cases it was evident soon after birth whom progressed to death, with severe dilated and worsening cardiomyopathy, despite the anti-congestive medication. The other four patients with the same mutation manifested dilated cardiomyopathy several months later but survived beyond infancy. The seven-year-old and five years old girls had systolic dysfunction on echocardiography, and one of them was determined to have had cardiomyopathy during infancy, since when he has systolic dysfunction (Figure 2).

Discussion

Here, we have represented severe infantile-onset cardiomyopathy in a family with a recently recognized mutation of ALMS1 [8]. Although genotype-phenotype correlation has not been demonstrated for specific clinical spectrum for the individual mutations in ALMS1 in all reported articles to cardiomyopathies, we think that the c.7911dupC (p. Asn2638Glnfs*24) novel mutation may be one of the major determinants of the severe cardiomyopathy.

The cohort of patients with ALMS1 has demonstrated two different major clinical spectrums in relation to cardiomyopathy: those with infantile onset (43%) and those with later onset (18%). Cardiomyopathy has not been diagnosed in the remaining patients (39%, ages 2–33 years). Patients with infantile onset of cardiomyopathy have had apparent recovery of cardiac function within three years [4]. Previous reports have suggested complete recovery of infantile onset cardiomyopathy in Alström syndrome patients [9].

Bond et al. observed seven families in which heart failure due to dilated cardiomyopathy had been presented as a symptom within the first three months. In that study, all patients responded to conventional supportive therapy, and the cardiomyopathy appeared to resolve spontaneously within six months. The authors suggested that dilated cardiomyopathy in ALMS1 presenting in the first year of life can regress completely [10].

Brofferio et al. suggested that cardiac involvement in ALMS1 is more common than previously reported. A third (13 of 38) of patients in their study had infantile cardiomyopathy, with EF results ranging from 40 to 66%. The authors proposed longitudinal follow-up studies to determine whether this mild cardiomyopathy progresses into more significant disease in all Alström syndrome patients [11].

Due to the reported outcomes of cardiomyopathy in ALMS1, most series report cardiac function with a history of infantile cardiomyopathy that improves within the first 2–3 years of life [12,13]. However, we suggest that recovery of cardiac function is not best characterized by time; rather, it is a matter of the type and characterization of the mutation. The severity of cardiomyopathy depends on the truncated protein accordingly the mutation. In our patient series with the ALMS1 c.7911dupC (p. Asn2638Glnfs*24) mutation, cardiomyopathy partially resolved in two cases (Patient D, G) while two

patients with the same mutation died despite maximal drug support. Similar to our results Mahamid et al [14] reported two brothers, 2 and 3 years of age, diagnosed with Alström syndrome during febrile respiratory infection who initially presented in infancy with severe dilated cardiomyopathy. The disease course in the older sibling has mainly resolved while cardiomyopathy in the younger sibling deteriorated despite maximal support with heart failure medications.

Our finding of LV systolic and diastolic dysfunctions in all the children are in accord with previous reports [15]. Phenotypic variation, such as differences in severity of cardiomyopathy among siblings with the same mutation, suggests that besides any variability due to the mutation itself, there is interplay between multitudes of potential genetic modifiers, with environmental factors leading to the range in severity of the Alström syndrome phenotypic spectrum [16].

In genotype-phenotype correlation studies, researchers have found no association between the location or type of ALMS1 mutations and T2D, body mass index (BMI), or the occurrence of dilated cardiomyopathy [10,17]. In another study, however, Ichihara et al. did identify a link between the polyglutamine repeat in ALMS1 and early onset myocardial infarct [18].

Despite advances in our knowledge of the spectrum of ALMS1 mutations, we still do not have enough evidence for prognostic predictions based on genotype. Histopathology of affected patients has shown diffuse interstitial fibrosis affecting the myocardium, a finding that was later confirmed by cardiac MRI [5,6]. Dilated cardiomyopathy (DCM) can occur suddenly in infancy (in first months of life) due to aberrant differentiation of cardiomyocytes [19, 20]. Histologic findings of infantile cardiomyopathy have not been presented yet, but there are studies in which mitogenic cardiomyopathy is described in patients with Alström syndrome [21,22].

Mitogenic cardiomyopathy is a very rare human phenotype. Shenje et al. showed homozygous or compound heterozygous mutations among six infants with Alström syndrome, suggesting that mitogenic cardiomyopathy is the main cause of lethal cardiomyopathy. They showed that ALMS1 is a key for cell cycle regulation in perinatal cardiomyocytes. The hearts of each of the individuals they studied were removed, either at the time of transplantation due to end-stage heart failure or after death from heart failure [21]. Although we did not perform autopsies, mitogenic cardiomyopathy may be posited as the cause of death of our patient with severe infantile cardiomyopathy. Restrictive cardiomyopathy develops slowly in adolescents and adults [23]. Our first adolescent case (Patient A) died because of restrictive cardiomyopathy, in line with previous reports.

Although intra-familial differences observed in the disease presentation of our patients carrying the same mutation (Patients B, C, D, E and F) complicated our notion about this recently recognized mutation, we suggest that there are mutations which tend to severe cardiomyopathy. Some authors have suggested that environmental and unknown genetic modifiers probably interact with ALMS1[13] children growing up in the same family with similar environmental factors to support expression patterns of genotype. Further to the evidence from our patients, Hollander et al. showed that the clinical course of Alström syndrome may vary with regard to cardiac disease manifestations even in monozygotic twins [24].

In a literature review of 44 patients from our country by Ozanturk et al, the authors reported death of two ALMS1 patients with unknown genetic mutation maybe linked to CMP [25]. Our patients had not been displayed in that study. In our ALMS1 cohort, cardiomyopathy appeared to be a primary manifestation.

However, the individuals in current cohort also displayed significant metabolic disturbances, including T2D, vision and hearing loss, elevated triglyceride and cholesterol levels, and obesity. These metabolic disturbances can themselves be significant cardiac risk factors over time. In a study made by Brofferio et al. there were subclinical strain echocardiographic abnormalities in nearly all patients in their cohort, suggesting the presence of myocardial disease in patients without overt cardiomyopathy, including those who have recovered from infantile cardiomyopathy [11]. Our findings of abnormal GLS with LV systolic dysfunction and restrictive cardiomyopathy of both ventricles support their results.

In another study, while mild interstitial myocardial fibrosis was present in patients without a prior history of dilated cardiomyopathy, moderate-to-severe interstitial fibrosis was found in ALMS1 patients with history of dilated cardiomyopathy [4]. Progressive fibrosis along with cardiac risk factors (obesity, T2DM) can explain restrictive cardiomyopathy of our case (Patient A) diagnosed in adolescence with restrictive cardiomyopathy.

Conclusion

Early diagnosis of ALMS1 and genetic testing provide important prognostic information to the pediatric cardiologist and enable the family to consider likely outcomes. First, appreciation of the etiology of cardiomyopathy can guide appropriate management plans. Second, determining the exact causal mutation(s) in the index patient can clarify the pattern of inheritance. Thus, families can be counselled on the recurrence risk in future offspring and seek prenatal testing in subsequent pregnancies.

Our comprehensive evaluation of nine children with Alström syndrome suggests that cardiac function in ALMS1 patients with infantile cardiomyopathy has different clinical spectrums depending on the mutagenic allele. We suggest that the c.7911dup C (p. Asn2638Glnfs*24) mutation can be related with

Declarations

Ethics approval and consent to participate

This study was approved by Istanbul University-Cerrahpasa Institutional Review Board (November 3, 2020; 29430533-604.01-01-139311). Detailed informed consent was obtained from all patients or their parents/legally authorized representatives.

The authors declare that they have no competing interests, including specific financial interests, relationships and/or affiliations relevant to the subject matter or materials included.

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Author contributions

SD, ED, AG take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. SD designed the study, planned the concept, and prepared and edited manuscript. RD, ED, FO, GY, SD had roles in data acquisition and analysis. RD had a role in the literature overview and data analysis. All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of data and materials

Please contact author for data requests

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Tables

Table I. Echocardiographic parameters in nine children with Alström syndrome.

	Age at last examination	LV systolic functions		LV diastolic functions				RV systolic functions		Type of CMP
		Teicholz method (%) last examination	Speckle strain (%)	Pulsed Doppler (cm/s)			Tissue Doppler	FAC (%)	TAPSE (mm)	
		EF	Total GLS	e	a	e/a	e/e'			
A	17 y	24 (>55)		67	42	1.6	5.8 (5.4–9.3)	26	12	Restrictive CMP
B	17 y	48 (>55)	-18 -10[#]	84	35	2.38	6.28 (5.4–9.3)	40	15	DCM
C	5 y	43 (>55)	-13.2	74	67	1.1	6.3 (5.3–9.4)	38	17	DCM
D	7 y	55 (>55)	-15	121	63	1.93	8.1 (5.3–9.4)	45	17	DCM*
E	16 m	36 (>55)	-8	54	65	0.83	14 (6.8–14)	30	7	DCM*
F	22 m	35 (>55)	-9.5	61	51	1.1	15.9 (6.8–14)	30	6	DCM*
G	20 y	58 (>55)		74	36	1.5	5.2 (5.4–9.3)	47	18	DCM
H	16 y	55 (>55)		85	66	1.3	7.1 (5.4–9.3)	43	17	DCM*
J	18 m	29 (>55)		64	61	1.1	12 (6.8–14)	34	10	DCM*

Table II. Clinical features in patients with Alström syndrome.

Patient No	Weight (kg)	Obesity	Vision Loss	Hearing loss	Homa-IR	Hyperlipidemia (mg/dL)	Treatment	Other	EF % 1	EF % 2	
A	62	+	+	+	12.7	+	Enalapril Furosemid	Acanthosis Nigrikans, nephrocalcinosis	40	41	Ex 19 y
B	64	+	+	+			Enalapril Furosemid Spironolakton	Scoliosis	26	48	
C	17	+	+	-			Kaptopril Furosemid Digoxin		42	43	43
D	18	+	+	-	1.58	-	Captopril		59	55	
E	6	-	+	-			Enalapril Furosemid Spironolakton Digoksin Aspirin Metacartin		43	39	Ex in infancy
F	7	+	+	-			Digoxin Captopril Furosemid Spironolakton		25	35	Ex infancy
G	79	+	+	+			Enapril		59	58	Ex 17 y
H	72	+	+	+			Enapril		45	55	
J	11	-	+	-			Levosimendan Kaptopril, Spironolakton		40	29	

Table III. Confirmed mutations of Patients.

Pt No	Age at diagnosis	Consanguinity	Mutation: clinical Alström with
A	14 y	+	ALMS1 gene
B#¶	16 y	+	c.7911dup C (p. Asn2638Glnfs*24)
C#¶	1 y	+	c.7911dup C (p. Asn2638Glnfs*24)
D¶	3 y	+	c.7911dup C (p. Asn2638Glnfs*24)
E¶	10 m	+	c.7911dup C (p. Asn2638Glnfs*24)
F¶	1 m	+	c.7911dup C (p. Asn2638Glnfs*24)
G	10 y	+	homozygote c.7905-7906 Ins C (p. N2636Qfs*24)
H#	3 m	+	homozygote c.7316C>A (p.Ser2439*)
J#	1.5 m	+	homozygote c.7316C>A (p.Ser2439*)

Siblings, ¶ cousins

Table IV. Review of published mutations related with cardiomyopathy in Alstrom patients.

Article				CMP onset			
	Mutation	Patient no	Type	İnfant	adult	prognosis	outcome
JL Michaud / 1996 The Journal of Pediatrics (12)	NA	5	DCM	5		EF normal (1-10 y)	
JD Marshall et al/2005 Arch Intern Med (4)	mutations in at least 1 allele of ALMS1 69 2p13-specific haplotypes ,n 36	112	DCM	79 (1-16 m)	24 (5-36 y)		10 pt died
JC Smith et al /2007 Eur J Hum Genet (23)	Pathogenic mutation in the ALMS1 gene in 8 pt	15	DCM	4	3		NA
Ozantürk A /2015 Journal of Human Genetics (25)	c.4156insA p.Thr1386Asnfs*15 c.5311C>T p.Gln1769* c.5969C>G p.Ser1990* c.9749C>A c.12117+20delT (IVS19-8delT) p.Ser3250* c.11055ins(n)331 c.11870-3T>G p.Val3958fs*			8	8		
A Brofferio et al/2017 Molecular Genetics and Metabolism (11)	1 c.11316_11319delAGAG p.Glu3773Trpfs*18 c.11416CNT p.Arg3806* 3 c.10535GNA p.Trp3512* c.11291GNA p.Ser 3764* 5 c.4156dupA p.Thr1386Asnfs*15 6 c.10775delC p.Thr3592Lysfs*6 c.2234CNG p.Ser 745* 8 c.10775delC p.Thr3592Lysfs*6 c.10775delC p.Thr3592Lysfs*6 10 c.10775delC p.Thr3592Lysfs*6 c.10775delC p.Thr3592Lysfs*6 15 c.4885CNT p.Gln1629* c. 5923 CNT p.Gln 1975* 16 c.592CNT p.Gln198* c.1610_1611delTC p.Leu538Glnfs22 20 c.10849GNT p.Glu3617* c.10483CNT p.Gln3495* 23 c.11314dupA p.Arg3772Trpfs*10 c.10885CNT p.Arg3629* c.1903CNT p.Gln635* c.3579CNG p.Tyr1193*	38		10			
	13 c.10539_10557ins(n)19 p.Lys3545Asnfs*18 c.10539_10557ins(n)19 p.Lys3545Asnfs*18 19 c.6305CNA p.Ser2102* c.10775delC p.Thr3592Lysfs*6 21 c.10775delC p.Thr3592Lysfs*6 c.3716_3719del p.Ser1240Thrfs*23 24 c.5311CNT p.Gln1769* c.5311CNT p.Gln1769* 25 c.11651_11652insGTTA p.Asn3885LeufsX9 c.4817delA p.Lys1608ArgfsX9				5		NA
SA Hollander/2017 Am J Med Genet. (21)	First variant (c.2816T > A; p.Leu939*) Second variant (c.10837_10838delCA; p.Gln3613Alafs*2)	2	DCM	+			

Nerakh G/ 2019 The Indian Journal of Pediatrics (139	homozygous nonsense variant c.2816 T > A (p.Leu939Ter)	2	DCM	+	NA	
Mahamid j /2013 Pediatr Cardiol **(14)**	homozygous for a nonsense mutation in exon 10 of *ALMS1*, c.8008C>T (p.R2637X)	2	DCM	+		
Curent study	c.7911dup C (p. Asn2638Glnfs*24) (5 patient) homozygote c.7905-7906 Ins C (p. N2636Qfs*24) (1patient) homozygote c.7316C>A (p.Ser2439*) (2 patient)	9	DCM 8 Restrictive CMP 1	5		5 died (3 with the same mutation)

Figures

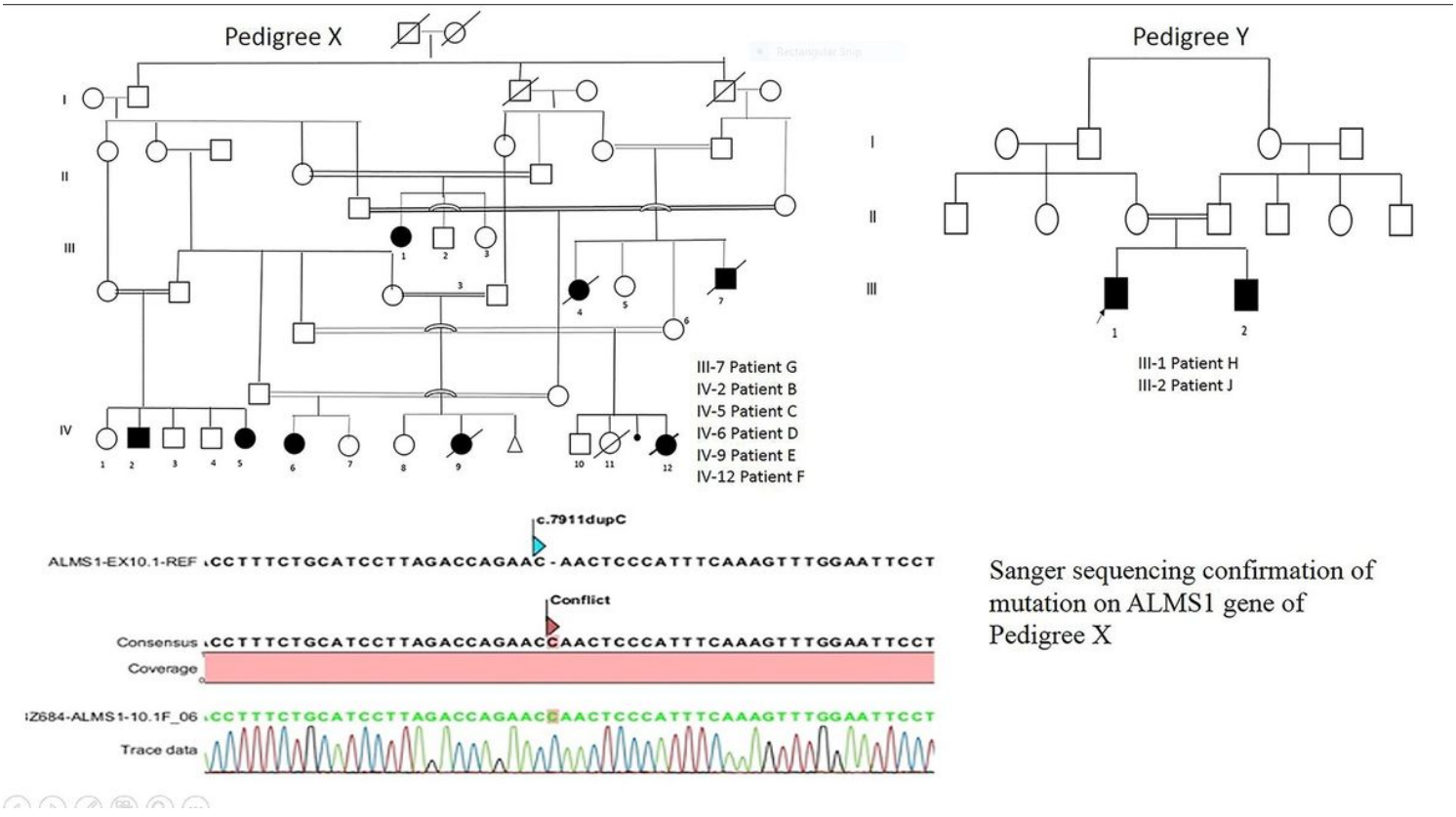

Figure 1

Pedigree of the patients, Sanger sequencing confirmation of mutation on ALMS1 gene.

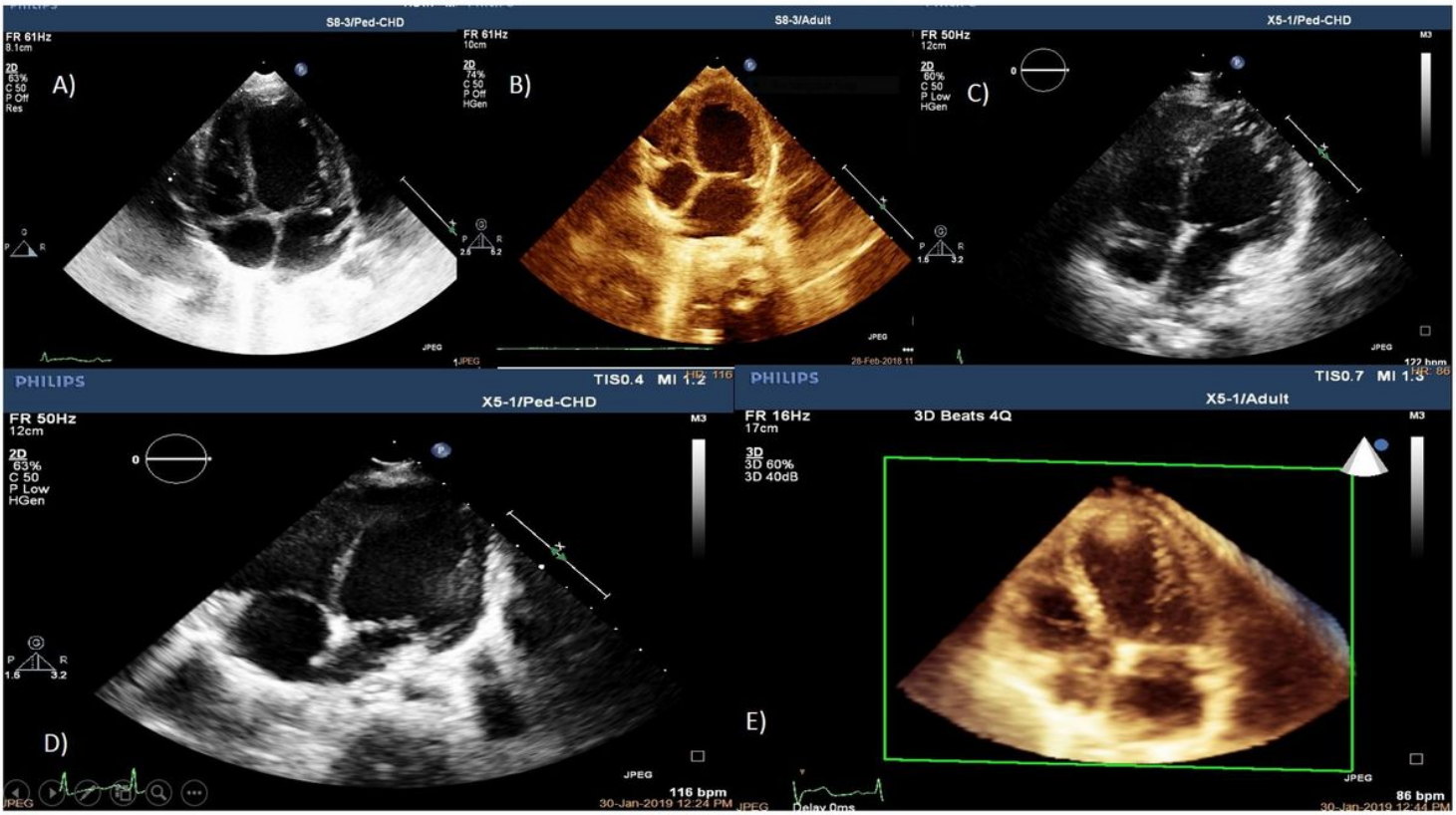

Figure 2

Left ventricular dilatation of patients with Alström syndrome on echocardiography. a) Patient C, b) Patient B, c) Patient C, d) Patient E, e) Patient F