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CLINICAL REPORT

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A novel *DNAH11* variant segregating in a sibship with heterotaxy and implications for genetic counseling

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Abstract

Background: Isomerism or heterotaxy syndrome is the loss of normal asymmetry of the internal thoraco-abdominal organs in the left-right axis and is associated with cardiovascular malformations. Mutations within *DNAH11* can be associated with primary ciliary dyskinesia and heterotaxy syndromes.

Methods: We report a family of healthy, nonconsanguinous parents with subsequent pregnancies demonstrating a novel likely pathogenic variant in *DNAH11* segregating in a sibship with varied presentations.

Result: The first affected pregnancy presented with right atrial isomerism. Further DNA testing identified three variants in *DNAH11* related to primary ciliary dyskinesia: a maternally inherited heterozygous variant of unknown significance (VUS) c.2772G>A (p.Met924Ile), a maternally inherited novel likely pathogenic variant c.11662C>T (p.Arg3888Cys) as well as a paternally inherited pathogenic c.1648delA variant (p.Arg550GlyfsX16). The second pregnancy inherited the same variants including the pathogenic and likely pathogenic *DNAH11* variants and presented with left isomerism and extracardiac abnormalities.

Conclusion: We present a novel likely pathogenic variant (c.11662C>T) in *DNAH11* that has manifested in heterotaxy with variability in phenotypes for subsequent pregnancies of common parents. This report demonstrates that sibship illustrates potential variability in phenotypes associated with the same pathogenic variants within a family and highlights the difficulty in genetic counseling due to the variation in clinical presentation.

KEYWORDS

ciliary dyskinesia, genetic testing, heterotaxy, isomerism, prenatal

1 | INTRODUCTION

"Situs solitus" is defined as the normal asymmetrical arrangement of internal organs in the body. Heterotaxy syndrome is the loss of normal asymmetry of the internal thoraco-abdominal organs in the left-right axis and is associated with cardiac malformations (Jacobs et al., 2007). Heterotaxy syndromes can be associated with increased morbidity and mortality (Bhaskar et al., 2015). Right and left isomerism can cause complex congenital heart disease (CHD) with 5-year survival rates ranging from 30% to 74% and 65% to 84%, respectively (Shiraishi & Ichikawa, 2012). Both survival rates

are substantially lower than other forms of CHD (Shiraishi & Ichikawa, 2012). Cilia function plays a critical role in organ laterality and pathogenic variants of functional proteins in cilia results in primary ciliary dyskinesia (PCD) (Sutherland & Ware, 2009). Many genes have been reported to be associated with heterotaxy. *DNAH11* (OMIM *603339) is one such gene, which codes for a dynein protein required for cilia motility. Pathogenic variants in *DNAH11* have been found to cause PCD and heterotaxy (Sutherland & Ware, 2009). The inheritance pattern of *DNAH11*-related Primary Ciliary Dyskinesia-7 (OMIM #611884) is autosomal recessive, whereas the forms of inheritance for other genes that cause PCD and heterotaxy are X-linked and autosomal dominant (Sutherland & Ware, 2009). A novel combination of a known *DNAH11* (NM_001277115.1) pathogenic c.1648delA variant with a likely pathogenic *DNAH11* c.11662C>T variant on the other allele in siblings presenting prenatally is described in this case report. This case reviews the phenotypic variability associated with the same gene mutations and highlights the challenges of genetic counseling. Informed consent was obtained from the patient and the hospital Research Ethics Board of Trillium Health Partners approved submission of this case for publication.

2 | CLINICAL REPORT

A 31-year-old G2P1 healthy female and 36-year-old healthy nonconsanguineous partner, both of Polish background with no family history of congenital heart defects, presented to Clinical Genetics with increased nuchal translucency of 4.6 mm in their pregnancy. First trimester screening was positive with a one in 45 risk for trisomy 21. Noninvasive prenatal testing showed low risk for trisomies 21, 18, and 13. Amniocentesis was completed, and QF-PCR revealed a male fetus without evidence of aneuploidy. Microarray showed a de novo 15q11.2 deletion of unknown significance (arr[GRCh37] 15q11.2(22652330_23226254)x1dn). It included *TUBGCP5, NIPA1, NIPA2* and *CYFIP1*. Detailed ultrasound at 18 weeks showed bilateral choroid plexus cysts, small collapsed stomach, midline liver, asplenia, possible branchial cleft cysts, and was concerning for cardiac anomalies (Figure 1). Fetal echocardiogram at 20 weeks confirmed the unbalanced atrioventricular septal defect (AVSD) and hypoplastic left ventricle. In addition, right atrial isomerism, pulmonary atresia and obstructed total anomalous pulmonary venous drainage were diagnosed. Due to the initial increased nuchal translucency measurement, Noonan syndrome panel

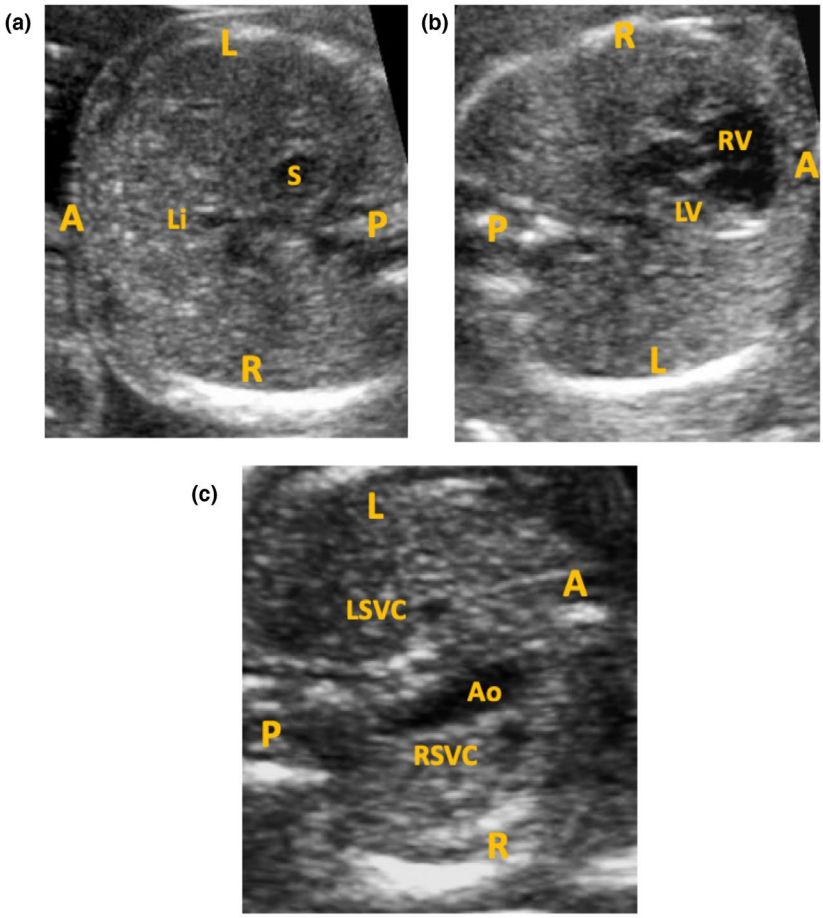

FIGURE 1 Still frame ultrasound images are shown diagnosing heterotaxy/right atrial isomerism. (a) A view of the fetal abdomen is shown with a midline liver and a small, collapsed stomach which is located more centrally than usual. (b) Cardiac imaging is shown with a normal size right ventricle and a hypoplastic left ventricle. The apex of the heart is towards the left. (c) The 3-vessel view is shown which shows the great vessels in transverse imaging in the chest. The aortic arch is seen and there are bilateral superior caval veins. A main pulmonary artery and ductal arch are not seen in keeping with pulmonary atresia. A: anterior, Ao: Aortic arch, L: left, Li: Liver, LV: left ventricle, LSVC: left superior vena cava, P: Posterior, R: right, RSVC: right superior vena cava, RV: right ventricle, S: stomach

was completed and the 13 genes (*BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1,* and *SPRED1*) tested were negative for pathogenic changes. Due to the initial question of branchial abnormalities, *EYA* and *SIX1* sequencing were completed and there were no disease-causing changes. Finally, due to the nature of congenital heart defects, a 15 gene congenital heart disease panel was completed. This identified a *NOTCH2* (NM_024498): exon 34 c.6858C>T p.Ser2286Ser variant of unknown significance (VUS) that was inherited from one unaffected parent. This variant was inherited from one unaffected parent and reported with a total allele frequency of approximately 0.0015% (out of 66,590 chromosomes) (Lek et al., 2016). While this is a synonymous amino acid change, it could create a new donor splice site based on the Alamut software that includes splicing predictions from SpliceSiteFinder-like, MaxEntScan, NNSPLICE, GeneSplicer and Human Splicing Finder. The family was counseled about the poor postnatal prognosis associated with hypoplastic left heart in conjunction with right atrial isomerism and obstructed pulmonary veins.

A male neonate was born at term and physical examination displayed a head circumference that measured 36 cm (at greater than the 50th percentile for 41 weeks and 1 day). There was note of periorbital fullness, mild micrognathia and overlapping second and third toes. Cardiac anomalies were confirmed. Overall findings were not typical of a single distinct common genetic syndrome. Due to the complexity of the heterotaxy, there was suspicion of an underlying etiology beyond the inherited VUS in *NOTCH2* and proband only exome sequencing with mitochondrial DNA testing from the cord blood was completed. Exome sequencing identified three variants in *DNAH11*: c.2772G>A (M924I) variant, c.11662C>T (R3888C) variant and a pathogenic c.1648delA variant. The c.2772G>A variant has been observed in 0.0586% (18/30712) of South Asian background alleles and 40/275992 total alleles in large population cohorts, with no individuals reported in a homozygous state (Lek et al., 2016). This variant results in a conservative amino acid substitution and is likely tolerated from in-silico analysis. Thus, it is not likely to impact secondary protein structure and is interpreted as a VUS. Neither c.11662C>T nor c.1648delA have been reported in large population database. The c.11662C>T variant causes a nonconservative amino acid substitution, is predicted to have a deleterious effect on in-silico analysis and the same residue with a different amino acid change has been described in an affected patient with PCD and situs inversus (Knowles et al., 2012). Thus, it is interpreted as a likely pathogenic variant. The c.1648delA variant causes a frameshift with a subsequent protein truncation due to a premature stop codon at position 16 of the new reading frame (p.Arg550GlyfsX16). This variant is likely to create a loss of normal protein function and is interpreted as a pathogenic variant. Since *DNAH11* is known to be associated with PCD in homozygous or compound heterozygous disease-causing state, parental testing was performed to understand if these changes were on the same or opposite alleles. The results of the parental testing showed that the pathogenic c.1648delA *DNAH11* variant was paternally inherited. The mother had the c.2772G>A variant of unknown significance and possessed the heterozygous likely pathogenic c.11662C>T change, prompting the laboratory to conclude the diagnosis of PCD being inherited in an autosomal recessive fashion with subsequent pregnancies having 25% chance risk of recurrence. The baby received compassionate care and died on the third day of life.

A year later, the couple presented with another pregnancy. Nuchal translucency at 12 weeks was increased at 8 mm. Chorionic villus sampling (CVS) testing was consequently performed, which showed normal quantitative fluorescence-polymerase chain reaction (QF-PCR), microarray and negative Noonan panel. Genetic testing revealed the fetus carried the same three variants in *DNAH11* including c.2772G>A and c.11662C>T as seen in their previous child. At 19 weeks, fetal anatomic survey revealed a normal nuchal fold, midline liver, left-sided stomach, dextrocardia, echogenic foci in the heart and an AVSD (Figure 2). No evidence of fetal hydrops was found, and the remainder of the fetal anatomy appeared normal.

At 20 weeks, a fetal echocardiogram was performed showing left atrial isomerism with dextrocardia, an AVSD variant with a common atrium, separate atrioventricular valves, an interrupted inferior vena cava with a hemiazygos continuation to the left superior vena cava and a right aortic arch. Fetal heart rate was at 110 beats per minute. The couple were counseled that the cardiac lesion was less severe and reviewed the possibility of biliary atresia, bowel malrotation, functional asplenia and potential lung and sinus problems associated with the gene mutations found. Given the congenital anomalies and gene mutations found, the couple ended the pregnancy at 22 weeks of gestation without an autopsy.

3 | DISCUSSION

Genetic counseling is difficult when there is heterogeneity in clinical presentation as highlighted by this case which presents two affected pregnancies with the same novel likely pathogenic c.11662C>T (p.Arg3888Cys) *DNAH11* variant segregating with a known pathogenic variant in the other allele. The pathogenic potential of this variant can be described in the manifestation of isomerism and CHD. To date, no literature has described the phenotype of the c.11662C>T likely pathogenic variant (Table 1). Previous studies have shown gene mutations causing primary ciliary dyskinesia (Table 1) associated with situs solitus (reference from table),

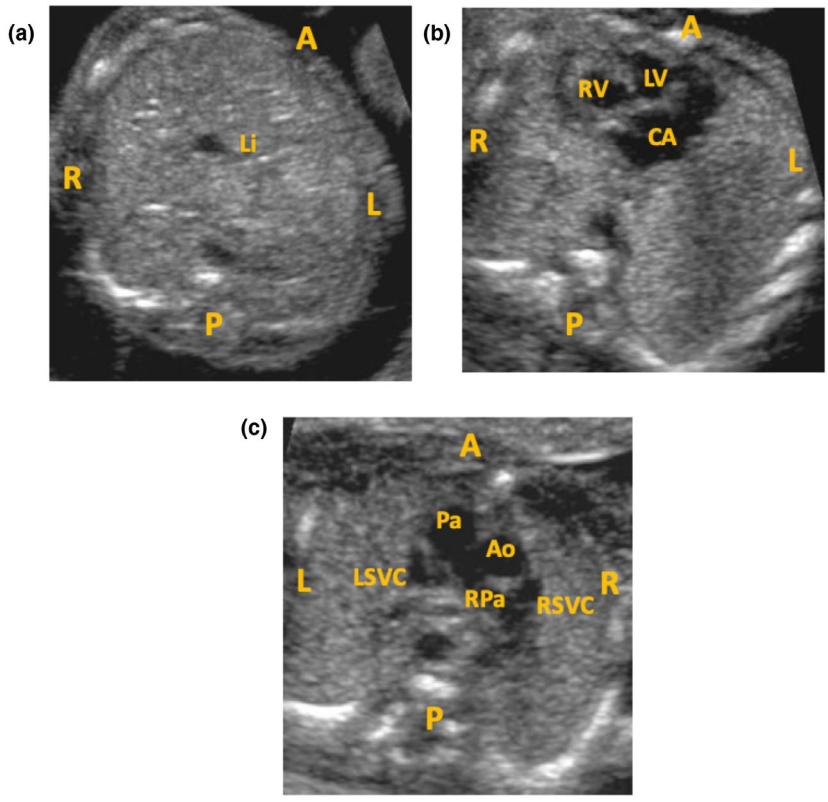

FIGURE 2 Still frame ultrasound images are shown diagnosing heterotaxy/left atrial isomerism. (a) A view of the fetal abdomen is shown with a midline liver; stomach is not shown in this still image but was found to be in normal position on the left side. (b) Cardiac imaging is shown with normal size right and left ventricles. A common atrium is seen. In addition, an azygous vein is seen left and posterior to the descending aorta which is usually seen in left atrial isomerism. The apex of the heart is towards the right in keeping with dextrocardia. (c) The 3-vessel view is shown which shows the great vessels in transverse imaging in the chest. The aortic, pulmonary artery and bilateral SVCs are seen. A: anterior, Ao: Aortic arch, Az: azygous veins, CA: common atrium, DA: descending aorta, L: left, Li: Liver, LV: left ventricle, LSVC: left superior vena cava, P: Posterior, PA: pulmonary artery, R: right, RPa: right pulmonary artery, RSVC: right superior vena cava, RV: right ventricle

situs inversus (reference from table) and heterotaxy (reference from table). Our cases are the first reported with *in utero* presentation of heterotaxy syndromes with gene mutations linked to primary ciliary dyskinesia. Both pregnancies were affected by the same two variants in *DNAH11* but presented with different forms of isomerism and significant variability in the complexity of the associated cardiac malformations, illustrating the variability in phenotypes associated with the same pathogenic variants within a family. One neonate had significant cardiac anomalies with high probability of poor outcome, while the second pregnancy was affected with milder cardiac anomalies. However, there was potential for an increase in severe extracardiac anomalies such as biliary atresia in the second pregnancy. In both pregnancies, there was the possibility of phenotypic presentation of PCD with variable severity. *DNAH11* variants were found previously to be associated with CHD and heterotaxy syndrome (Liu et al., 2019) and it is known that there is a substantial genetic component to isomerism (Bamford et al., 2000; Kaasinen et al., 2010; Kosaki, Kosaki, et al., 1999; Kosaki, Gebbia, et al., 1999; Mohapatra et al., 2008; Zhu et al., 2007). In addition, microdeletions in 15q11.2 have also been observed to be significantly associated with CHD (Vanlerberghe et al., 2015). This report of a novel gene mutation linked to both PCD and heterotaxy syndromes highlights the importance of discussing this association during prenatal counseling as PCD may increase risk of poor outcome in individuals with heterotaxy syndrome.

Prenatal genetic counseling must consider the phenotypic variations associated with gene mutations when reviewing possible outcomes with families. Specifically, isomerism demonstrates phenotypic variation, as in our case presentation, that may induce a greater negative emotional impact in the caregivers due to uncertainty. This necessitates genetic counseling that factors the psychological social and financial when reviewing a genetic diagnosis (Werner, Latal, Valsangiacomo Buechel, Beck, & Landolt, 2014). Werner et al. (2014) showed that the presence of a genetic disorder in a child with CHD significantly increased the perceived impact on the family (Werner et al., 2014). Parents of children with CHD report a lower quality of life than parents of healthy children (Lawoko & Soares, 2003). This reduction in the quality of life has been determined by factors such as care-giving time, sick-leave, financial difficulties,

TABLE 1 Literature review of patients with DNAH11 variants associated with primary ciliary dyskinesia-7 (CILD7)

Patient identifier from reference	Genotype	Age at test/ diagnosis	Cardiac features	Extra-cardiac features	Reference
Patient 1	Compound Heterozygote: Heterozygous DNAH11 c.2772G>A; p.Met924Ile Heterozygous *DNAH11* c.11662C>T; p.Arg3888Cys Heterozygous *DNAH11* c.1648delA; p.Arg550Glyfs*16	18 weeks (prenatal)	At 20 weeks: • Unbalanced atrioventricular septal defect • Hypoplastic left ventricle • Right atrial isomerism • Pulmonary atresia • Obstructed total anomalous pulmonary venous drainage	At 18 weeks • Bilateral choroid plexus cysts • Small collapsed stomach • Midline liver • Asplenia • Possible branchial cleft cysts At 41 weeks: (postnatal) • Primary ciliary dyskinesia	Current study
Patient 2	Compound Heterozygote: Heterozygous *DNAH11* c.11662C>T; p.Arg3888Cys Heterozygous *DNAH11* c.1648delA; p.Arg550Glyfs*16 Heterozygous *DNAH11* c.1648delA; p.Arg550Glyfs*16	19 weeks (prenatal)	At 19 weeks • Echogenic foci • Dextrocardia At 20 weeks • Atrioventricular septal defect • Dextrocardia • Left atrial isomerism • Atrioventricular septal defect variant with a common atrium • 110 bpm fetal heart rate • Separate atrioventricular valves • Interrupted inferior vena cava with a hemiazygos continuation to the left superior vena cava and a right aortic arch	At 19 weeks • Primary ciliary dyskinesia • Normal nuchal fold • Midline liver • Left-sided stomach At 20 weeks • Polysplenia • Bowel malrotation	Current study
Patient C.C	Homozygous *DNAH11* c.8554C>T; p.Arg2852* (603339.0001)	10 days old	At 10 days • Situs inversus • Dextrocardia	At 10 days • Visceral situs inversus with structurally normal spleen • Respiratory distress At 6 months • Cystic fibrosis • Primary ciliary dyskinesia with abnormal ciliary motion	Pan et al. (1998), Bartoloni et al. (2002)
Patient II-2	Compound Heterozygotes: Heterozygous *DNAH11* c.12384C>G; p.Tyr4128* (603339.0002) and heterozygous *DNAH11* c.13552_13608del; 57-BP DEL, NT13552 (603339.0003)	27 years old	• Situs inversus • Dextrocardia	• Primary ciliary dyskinesia with inflexible ciliary beating pattern and normal axonemal ultrastructure • Chronic respiratory infections (sinusitis, bronchitis)	Schwabe et al. (2008)

TABLE 1 (*Continued*)

Patient identifier from reference	Genotype	Age at test/ diagnosis	Cardiac features	Extra-cardiac features	Reference
Patient II-3		25 years old	• Situs solitus	• Primary ciliary dyskinesia with inflexible ciliary beating pattern and normal axonemal ultrastructure • Chronic respiratory infections (sinusitis, bronchitis, pneumonia)	
Patient II-4		24 years old	• Situs solitus	• Primary ciliary dyskinesia with inflexible ciliary beating pattern and normal axonemal ultrastructure • Chronic respiratory infections (sinusitis, bronchitis, pneumonia) • Bronchiectasis	
Patient II-6		20 years old	• Situs solitus	• Chronic respiratory infections (sinusitis, bronchitis, pneumonia) • Bronchiectasis	
Patient II-9		16 years old	• Situs solitus	• Primary ciliary dyskinesia with inflexible ciliary beating pattern and normal axonemal ultrastructure • Chronic respiratory infections (sinusitis, bronchitis, pneumonia)	
Patient II-11		12 years old	• Situs solitus	• Primary ciliary dyskinesia with inflexible ciliary beating pattern and normal axonemal ultrastructure • Chronic respiratory infections (sinusitis, bronchitis, pneumonia) • Bronchiectasis	
Patient #730	Compound Heterozygote: Heterozygous *DNAH11* c.8719C>T; p.Arg2907* (603,339.0004) and heterozygous *DNAH11* c.7793C>T; p.Pro2598Leu (603339.0005)	4 years old	• Situs solitus	• Primary ciliary dyskinesia with rapid, erratic dyskinetic ciliary beating but normal ciliary ultrastructure • Neonatal respiratory symptoms • Chronic cough • Rhinitis • Otitis	Lucas et al. (2012)
Patient 1	Compound Heterozygote: Heterozygous *DNAH11* c.2406G>A; p.Trp802* and heterozygous *DNAH11* c.846G>C; p.Met282Ile	3.8 years old	• Isolated right heart • Complete atrioventricular canal • Double outlet right ventricle • Atrial septal defect	• Heterotaxy • Abnormal ciliary function: immotile, discordant, and restricted	Liu et al. (2019)

TABLE 1 (*Continued*)

Patient identifier from reference	Genotype	Age at test/ diagnosis	Cardiac features	Extra-cardiac features	Reference
Patient 2	Compound Heterozygote: Heterozygous *DNAH11* c.10379C>A; p.Thr3460Lys and heterozygous *DNAH11* c.13273G>A; p.Gly4425Ser	4.4 years old	• Congenital heart disease	• Heterotaxy • Abnormal ciliary movement: discordant and restricted	
Patient 3	Compound Heterozygote: Heterozygous *DNAH11* c.1339G>A; p.Gly447Arg and heterozygous *DNAH11* c.3470T>G; p.Leu1157Arg	5.4 years old	• Congenital heart disease	• Heterotaxy • Abnormal ciliary movement: immotile and restricted	
Patient 4	Compound Heterozygote: Heterozygous *DNAH11* c.6785T>C; p.Ile2262Thr and heterozygous *DNAH11* c.11398G>C; p.Asp3800His	3.6 years old	• Congenital heart disease	• Heterotaxy • Ciliary dysfunction: discordant and restricted	
Patient 5	Compound Heterozygote: Heterozygous *DNAH11* c.8275T>C; p.Phe2759Leu and heterozygous *DNAH11* c.13183C>T; p.Arg4395* and heterozygous *DNAH11* c.5470dupC; p.Ser1823fs	0.5 years old	• Congenital heart disease	• Heterotaxy • Ciliary dysfunction: immotile and restricted	
Patient 6	Compound Heterozygote: Heterozygous *DNAH11* c.10829A>T; p.Asp3610Val and heterozygous *DNAH11* c.727A>G; p.Ile243Val	8.6 years old	• Isolated right heart • Pulmonary atresia • Levo-transposition of the great arteries • Atrial septal defect	• Heterotaxy • Abnormal ciliary function: immotile and restricted	
Patient 11057	Homozygous *DNAH11* c.13183C>T; p.Arg4395Ter	3 years old	• Situs inversus	• Probable primary ciliary dyskinesia: immotile cilia, complete absence of outer dynein arms • Neonatal respiratory distress syndrome • Rhinitis • Sinusitis • Otitis • Bronchitis without wheezing	Boaretto et al. (2016)

TABLE 1 (*Continued*)

Patient identifier from reference	Genotype	Age at test/ diagnosis	Cardiac features	Extra-cardiac features	Reference
Patient 11174	Compound Heterozygote: Heterozygous *DNAH11* c.2753G>T; p.Gly918Val and heterozygous *DNAH11* c.12796_12801delinsATA; p.Phe4266_Asn4267delinsIle	10 years old		• Probable primary ciliary dyskinesia: normal ciliary ultrastructure, immotile and stiff cilia • Rhinitis • Sinusitis • Otitis • Bronchitis with wheezing • Cough • Asthma	
Patient 11228	Compound Heterozygote: Heterozygous *DNAH11* c.9304G>A; p.Gly3102Ser and heterozygous *DNAH11* c.4922C>G; p.Ser1641*	1 year old	• Situs inversus	• Probable primary ciliary dyskinesia: normal ciliary ultrastructure with atypical beating pattern • Rhinitis • Bronchitis without wheezing • Cough	
Patients A	Compound heterozygote: Heterozygous *DNAH11* c.883-1G>A and heterozygous *DNAH11* c.4145G>A; p.Trp1382*	15 years and 5 months old	• Situs inversus	• Primary ciliary dyskinesia: swollen and compound cilia, abnormal nonflexible ciliary beating pattern with reduced cilium bending capacity, hyperkinetic beat of cilia, and immotile cilia • Chronic respiratory symptoms • Neonatal purulent rhinitis with frequent relapses • Chronic rhinosinusitis • Otitis • Bronchiectasis • Bronchiectasis and atelectasis of the left middle lobe associated with fibrotic areas and pan-sinusitis	Pifferi et al. (2010)

TABLE 1 (*Continued*)

Patient identifier from reference	Genotype	Age at test/ diagnosis	Cardiac features	Extra-cardiac features	Reference
Patient B	Compound heterozygote: Heterozygous *DNAH11* c.883-1G>A and heterozygous *DNAH11* c.4145G>A; p.Trp1382*	9 years and 4 months old	• Situs inversus	• Primary ciliary dyskinesia: swollen and compound cilia, abnormal nonflexible ciliary beating pattern with reduced cilium bending capacity, hyperkinetic beat of cilia, and immotile cilia • Chronic respiratory symptoms • Recurrent wheezy bronchitis • Pneumonia • Pan-sinusitis and bronchioloectasis of the left middle lobe associated with fibrotic areas	
Patient C	Compound heterozygote: Heterozygous *DNAH11* c.8135A>G; p.His2712Arg and heterozygous *DNAH11* c.10284G>A; p.Gly3429Arg	8 years old	• Situs inversus • Partial interatrial defect	• Primary ciliary dyskinesia: swollen and compound cilia, abnormal nonflexible ciliary beating pattern with reduced cilium bending capacity, hyperkinetic beat of cilia, and immotile cilia • Neonatal respiratory distress • Recurrent otitis • Pneumonia • Fibrotic area in the left middle lobe, maxillary and sphenoid sinusitis with agenesis of frontal sinuses	
PCD623	Homozygous *DNAH11* c.4438C>T; p. Arg1480*	24 years old	• Situs solitus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Neonatal respiratory distress syndrome • Otitis • Bronchiectasis • Sinusitis	Knowles et al. (2012)

TABLE 1 (*Continued*)

Patient identifier from reference	Genotype	Age at test/ diagnosis	Cardiac features	Extra-cardiac features	Reference
PCD1022	Homozygous *DNAH11* c.4333C>T; Arg1445*	4 years old	• Situs solitus	• Primary ciliary dyskinesia: normal ultrastructure • Neonatal respiratory distress syndrome • Otitis • Sinusitis	
OP20-II:1	Homozygous *DNAH11* c.11663G>A; Arg3888His	12 years old	• Situs inversus	• Primary ciliary dyskinesia • Otitis • Bronchiectasis	
PCD108	Compound heterozygote: Heterozygous *DNAH11* c.4516_4517delCT; p.Leu1506Serfs*10 and heterozygous *DNAH11* c.7266+1G>A; p.Thr2379_Gln2422del	24 years old	• Situs inversus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic cilia • Neonatal respiratory distress syndrome • Otitis • Sinusitis	
PCD157	Compound heterozygote: Heterozygous *DNAH11* c.6244C>T; p.Arg2082* and heterozygous *DNAH11* c.11929G>T; p.Glu3977*	12 years old	• Situs inversus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Neonatal respiratory distress syndrome • Otitis • Bronchiectasis • Sinusitis	
PCD761	Compound heterozygote: Heterozygous *DNAH11* c.2275-1G>C; p.Tyr759_Glu889del and heterozygous *DNAH11* c.13213dC; p.Arg4405Alafs*1	30 years old	• Situs inversus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Neonatal respiratory distress syndrome • Otitis • Bronchiectasis • Sinusitis	

TABLE 1 (*Continued*)

Patient identifier from reference	Genotype	Age at test/ diagnosis	Cardiac features	Extra-cardiac features	Reference
PCD919	Compound heterozygote: Heterozygous *DNAH11* c.13065_67delCCT; p.4356delLeu and heterozygous *DNAH11* c.13075C>T; p.Arg4359*	8 years old	• Situs ambiguous	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Neonatal respiratory distress syndrome • Otitis • Bronchiectasis • Sinusitis	
OP98-II:1	Compound heterozygote: Heterozygous *DNAH11* c.7914G>C; p.Trp2604* and heterozygous *DNAH11* c.13333_34insACCA; p.Ile4445Asnfs*3	20 years old	• Situs inversus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Otitis • Bronchiectasis • Sinusitis	
PCD565	Compound heterozygote: Heterozygous *DNAH11* c.5778+1G>A; p.Val1821Thrfs*7 and heterozygous *DNAH11* c.13061T>A; p.Leu4354His	7 years old	• Situs inversus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Neonatal respiratory distress syndrome • Otitis • Bronchiectasis • Sinusitis	
PCD1077	Compound heterozygote: Heterozygous *DNAH11* c.3901G>T; p.Glu1301* and heterozygous *DNAH11* c.11804C>T; p.Pro3935Leu	2 years old	• Situs inversus	• Primary ciliary dyskinesia: normal ultrastructure • Neonatal respiratory distress syndrome • Otitis • Sinusitis	
PCD1126	Compound heterozygote: Heterozygous *DNAH11* c.12064G>C; p.Ala4022Pro and heterozygous *DNAH11* c.13504_05insGAAGA; p.Thr4502Argfs*14	42 years old	• Situs solitus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Bronchiectasis • Sinusitis	

TABLE 1 (*Continued*)

Patient identifier from reference	Genotype	Age at test/ diagnosis	Cardiac features	Extra-cardiac features	Reference
OP235-II:2	Compound heterozygote: Heterozygous *DNAH11* c.12697C>T; p.Gln4233* and heterozygous *DNAH11* c.12980T>C; p.Leu4327Ser	21 years old	• Situs inversus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Neonatal respiratory distress syndrome • Otitis • Bronchiectasis • Sinusitis	
OP41-II:1	Compound heterozygote: Heterozygous *DNAH11* c.350A>T; p.Glu117Val and heterozygous *DNAH11* c.7148T>C; p.Leu2383Pro	13 years old	• Situs inversus	• Primary ciliary dyskinesia: normal ultrastructure, dyskinetic and hyperkinetic beating pattern • Neonatal respiratory distress syndrome • Otitis • Sinusitis	
PCD812	Compound heterozygote: Heterozygous *DNAH11* c.5815G>A; p.Gly1939Arg and heterozygous *DNAH11* c.13373C>T; p.Pro4458Leu	8 years old	• Situs inversus	• Primary ciliary dyskinesia • Neonatal respiratory distress syndrome • Otitis • Sinusitis	

psychological problems (distress and hopelessness), and social isolation (Lawoko & Soares, 2002, 2003). The stress that a family endures when a child is born with a genetic disorder can be better managed through appropriate prenatal genetic counseling and expectation setting.

Prenatal detection rates of isomerism syndrome have improved drastically, and most cardiovascular anomalies can be defined with substantial accuracy by experienced fetal echocardiographers (Lim et al., 2005). It is crucial to identify extracardiac findings during prenatal screening as these extracardiac anomalies have been found to contribute significantly to morbidity and mortality (Gottschalk et al., 2016). Although the major contributing causes to mortality in fetuses with isomerism are cardiovascular malformations, extracardiac anomalies also have a significant impact on the outcome of newborns (Gottschalk et al., 2016). In conjunction with complex cardiac defects and heterotaxy, both siblings presented with extracardiac anomalies. The first affected pregnancy presented with asplenia, a small midline stomach with a central liver, while the second child was stillborn and presented with polysplenia and bowel malrotation. Another important and common extracardiac anomaly in heterotaxy syndrome patients is biliary atresia, which has been found to be the most important extracardiac contributor to postnatal outcome with a high mortality and morbidity (Gottschalk et al., 2016). Intestinal malformation, which has been seen in 70% of heterotaxy syndrome cases, was also suspected to cause midgut volvulus with potentially catastrophic consequences (Gottschalk et al., 2016).

Some challenges exist with prenatal screening including the failed detection of extracardiac anomalies such as bowel obstruction, biliary atresia, immune dysfunction and anomalous pulmonary venous return, despite thorough inspection (Lim et al., 2005) (Gottschalk et al., 2016). Prenatal diagnosis of biliary atresia is also very difficult because the morphology of the gallbladder is highly variable, and the usefulness of enzyme analysis in the amniotic fluid is not clear (Gottschalk et al., 2016). Finally, prenatal diagnosis of left isomerism has been reported to exist with a morphologically normal heart (De Paola et al., 2009), further strengthening the value of extracardiac findings. Genetic counseling in families with heterotaxy should emphasize the degree of uncertainty that exists with postnatal presentation. The summary and strengths of the cases presented are: 1) the significant association between isomerism and underlying genetics with the novel likely pathogenic c.11662C>T variant in *DNAH11* associated with disease, and 2) the importance of prenatal screening and genetic counseling once an abnormality indicating isomerism is detected during screening in order to ensure timely identification of genetic disease, as well as to allow for informative genetic counseling to aid in management decisions for the family.

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CONFLICT OF INTEREST

All authors declare that that there is no conflict of interest in connection with the work submitted.

AUTHOR CONTRIBUTION

VT, EG, and AN designed the work. VT provided the Figures 1 and 2. VT and EG provided the clinical information of the patient. AN compiled the summary of clinical information of the cases. AN and AE performed detailed literature review and developed the literature summary on Table 1. All authors offered a major contribution in the writing of the manuscript. VT and EG provided critical feedback on the manuscript. All authors approved the final version.

DATA AVAILABILITY STATEMENT

All available clinical data are shared in the article.

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