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Highlighting cardiovascular manifestations of kleefstra syndrome: literature review and clinical insights

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Abstract

Kleefstra syndrome (KLEFS1) is a rare genetic disorder primarily caused by the deletion of the chromosome 9q34.3 genomic segment or pathogenic mutations in the euchromatin histone methyltransferase 1 (EHMT1) gene. It is characterized by intellectual disability or impairment, childhood hypotonia, and distinct facial features. Notably, cardiovascular defects especially congenital heart diseases also represent a major feature of KLEFS1. While the neuropsychiatric aspects of KLEFS1 have been extensively documented and researched, the cardiovascular manifestations have not received adequate attention. The majority of KLEFS1 patients often present with a spectrum of cardiovascular defects, including abnormal cardiac structure, arrhythmias, valve abnormalities, cardiomyopathy, and coronary artery abnormalities. Here, we systematically searched and reviewed previously published articles and case reports related to KLEFS1, conducting a comprehensive analysis of the existing literature to highlight the cardiovascular manifestations of this genetic disorder and explore the potential correlations between the cardiac phenotype and KLEFS1.

Clinical trial number: Not applicable.

Keywords Kleefstra syndrome, EHMT1, 9q34.3 microdeletion, Cardiovascular, Congenital heart disease

Introduction

Kleefstra syndrome (KLEFS1) (OMIM 610253), formerly known as 9q subtelomeric deletion syndrome (9qSTDS), is a rare genetic disorder caused by a microdeletion or pathogenic mutation in the euchromatin histone methyl-transferase 1 (EHMT1) gene located in the subtelomeric region 34.3 of the long arm of chromosome 9 (9q34.3) [1], which was also the first subtelomeric deletion syndrome to be identified. Among the reported cases, approximately 70% have a 9q34.3 microdeletion [2], while the remaining 30% of patients have EHMT1 mutations, including missense, nonsense, frameshift, splice site mutations, and deletions [3, 4]. According to our search, a total of 179 patients have been reported so far, including 127 patients with 9q34.3 microdeletion and 51 patients with EHMT1 mutations (Table 1).

The core features of KLEFS1 include intellectual developmental delay or disability, autism-like characteristics, childhood hypotonia, and distinct facial features. Additionally, the majority of KLEFS1 patients also have complex medical conditions affecting other systems. Cardiovascular defects, especially congenital heart defects (CHD) are prevalent in a significant number of KLEFS1 patients and represent another major phenotype of the syndrome.

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Table 1 Overview of reported Kleefstra syndrome cases

	9q34.3 deletion	EHMT1 mutation	Not described	Total
Reported cases summarized by Willemsen MH [9]	76	10	0	86
Cases reported by Willemsen MH [9]	16	13	0	29
Other cases reported so far	36	28	1	65
Total cases	128	51	1	180

With an increased number of case reports and the establishment of KLEFS1 disease cohorts, the proportion of patients exhibiting cardiac abnormalities can reach 30–50% [5–7]. Recent studies have shown a significant genotype-phenotype correlation in cardiac morphological abnormalities, which often occur in the context of 9q34.3 microdeletions or truncating mutations of the EHMT1 gene [7]. Among KLEFS1 patients with cardiac defects, a significant portion presents with CHD, particularly those with complex cardiac malformations. Additionally, some patients also experience atrial fibrillation and other arrhythmias [8]. However, in the literature reported so far, only a few cases have provided detailed evaluations of the cardiovascular system, with the majority focusing solely on the neurobehavioral symptoms of the patients, indicating a lack of emphasis on the cardiovascular aspect. Therefore, we provide a comprehensive literature review focused on the cardiovascular phenotype of KLEFS1, aiming to elucidate the cardiovascular manifestations of this complex disorder (Fig. 1).

Methods

As of March 1, 2024, a comprehensive literature search was performed on the PubMed database to retrieve all case reports, articles and reviews related to KLEFS1. In addition to English-language publications, non-English papers were also reviewed to ensure a thorough examination of the existing evidence. The search strategy employed a combination of keywords, including "kleefstra syndrome", "9q subtelomeric deletion syndrome", "EHMT1", and "9q34.3", to capture a broad spectrum of relevant studies. Due to the establishment of KLEFS1 cohorts such as the Radboudumc registry, GenIDA registry, and KLEFS1 local expertise center, previously reported cases may overlap, leading to potential duplication in statistics [5, 6]. Therefore, we did not include cohort data, focusing solely on currently reported cases and case series.

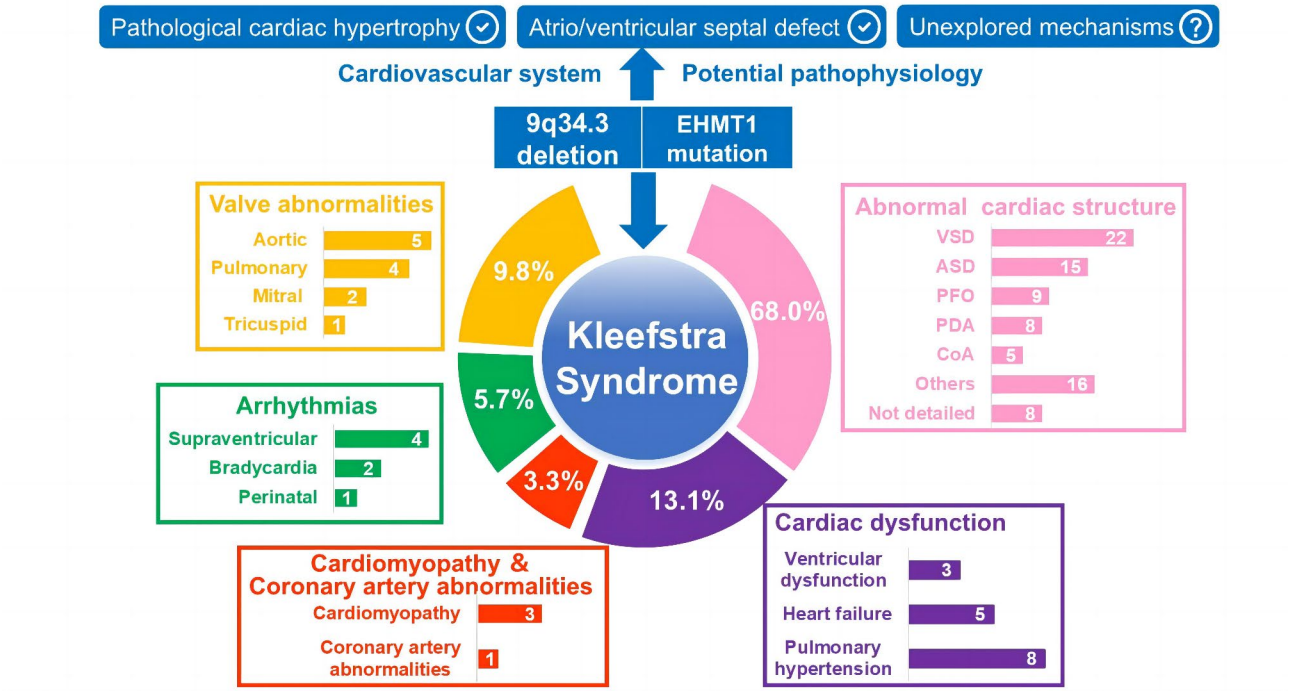

Fig. 1 The main cardiovascular manifestations and potential pathogenesis of Kleefstra syndrome. Kleefstra syndrome features diverse cardiac defects like structural abnormalities, arrhythmias, valve issues, cardiomyopathy, and coronary anomalies. The pathophysiological mechanisms are currently unclear, and further research is needed to elucidate the role of the EHMT1 in the cardiovascular system. ASD, atrial septal defect; CoA, coarctation of aorta; PDA, patent ductus arteriosus; PFO, patent foramen ovale; TOF, tetralogy of Fallot; VSD, ventricular septal defect

Literature review

Overview of clinical findings and mutations of KLEFS1

According to our search, a total of 180 patients have been reported so far, including 128 patients with 9q34.3 microdeletion and 51 patients with EHMT1 mutations (Table 1).

The core clinical phenotype of KLEFS1 is characterized by moderate to severe developmental delay/intellectual disability, hypotonia, and distinct facial features [9]. According to the current study, individuals with EHMT1 mutations and small 9q34.3 deletions (< 1 Mb) have similar clinical findings; whereas individuals with larger 9q34.3 deletions (≥ 1 Mb) may have more severe clinical problems, such as more severe mental retardation, congenital anatomical abnormalities, and respiratory problems [8]. KLEFS1 cases have been reported in various countries, including the Netherlands [9], Germany [10], Norway [11], Hungary [12], China [3], and Iran [13], without any clear geographic or ethnic predisposition. The literature has focused on classical phenotypes of KLEFS1, such as neurodevelopmental issues [14], autism and psychiatric problems [15, 16], and otopathology [17]. Pulmonary hypertension (PH) associated with 9q34.3 microdeletion has also been explored [18]. However, there is no systematic literature on cardiovascular manifestations in patients with KLEFS1.

Cardiovascular manifestations of KLEFS1

As case reports accumulate, heart defects are becoming increasingly prevalent among patients diagnosed with KLEFS1. In a recent study, Vasireddi SK et al. [5] evaluated two of the largest known KLEFS1 registries and found that the prevalence of cardiovascular abnormalities among KLEFS1 patients was 40%, with the majority being CHD. Our study demonstrates consistent findings through literature review of previously reported KLEFS1 cases, revealing an overall heart defect prevalence of 37.2% (67/180) (Table 2). Further stratification by genetic etiology revealed heterogeneity in heart defect rates across molecular subtypes. Cases with 9q34.3 deletions (39.8%) exhibited a relatively higher proportion of heart defects compared to those with EHMT1 mutations (29.4%).

The main cardiovascular manifestations that have been reported are diverse through literature review. Among them, cardiac structural abnormalities are the most common (69.2%), followed by cardiac function abnormalities (11.7%), valve abnormalities (10.0%), and arrhythmia (5.8%), while cardiomyopathy (2.5%) and coronary artery abnormalities (0.8%) are relatively rare (Table 3).

Table 2 Proportion of heart defects in reported Kleefstra syndrome cases by different etiologies

	Total cases	Heart defects
All causes	180	67 (37.2%)
9q34.3 deletion	128	51 (39.8%)
EHMT1 mutation	51	15 (29.4%)
Not described	1	1

CHD, congenital heart defects

Abnormal cardiac structure

Patients with KLEFS1 can present with a wide range of structural cardiac abnormalities, encompassing various types of cardiac abnormalities. These can include common abnormalities such as atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), patent foramen ovale (PFO) and tetralogy of Fallot (TOF), as well as rarer conditions like aortic constriction, double-outlet right ventricle, and Shone's complex, among others. There are 49 patients with structural cardiac abnormalities reported, and their prevalence is around 33%. Among the cardiac structural abnormalities, the most common type was VSD, followed by ASD, PFO, and PDA. This highlights the variability and diversity of cardiac abnormalities that can be associated with KLEFS1. Each patient may present with a unique combination of structural cardiac abnormalities, and the prevalence of specific abnormalities may vary among different cohorts of KLEFS1 patients.

The majority of KLEFS1 patients with structural cardiac abnormalities have only one simple defect, but a significant number of reported cases have complex and severe structural heart disease, which tends to occur in neonates and infants. Neas KR et al. [23] reported three cases of KLEFS1 with complex and severe structural heart disease, all of which eventually died. Campbell CL et al. [29] reported a neonatal patient with KLEFS1 who had severe hypoplastic left heart syndrome including moderate valve hypoplasia, mild hypoplastic left ventricle not reaching the apex, thickened dysplastic aortic valve with decreased excursion. There was also a large conoventricular septal defect, moderate dilatation of the main pulmonary artery, and dilatation of the coronary sinus. The child eventually died after palliative care due to severe cardiovascular disease that prevented surgery and dialysis. However, it is not always the case that complex cardiovascular manifestations lead to death or a poorer prognosis. Kohli U et al. [27] reported a case of a neonatal patient with both KLEFS1 and Shone's complex, who had a typical parachute-type mitral valve with mitral stenosis, dysplasia of the aortic arch combined with aortic constriction, and a narrowing of the left ventricular outflow tract. The patient also had a moderate-sized ASD and VSD. The patient underwent arterial conduit stenting and bilateral pulmonary artery palliation on the 12th day of life, after which he developed atrial arrhythmias that were well controlled with digoxin therapy. An asymptomatic patient with complex CHD has also been

Table 3 Reported Kleefstra syndrome cases with specific cardiovascular manifestations

	Cardiac manifestations	N*	References
Abnormal cardiac structure (*N* = 83) (68.0%)	VSD	22	[18–30]
	ASD	15	[1, 18, 23–27, 31–36]
	PFO	9	[18, 22, 25, 26, 34, 37–39]
	PDA	8	[18, 22–24, 26, 27, 31, 40]
	Coarctation of aorta	5	[12, 18]
	Aortic arch hypoplasia	3	[23, 29]
	TOF	2	[23, 25]
	Double outlet right ventricle	2	[18, 22]
	Pulmonary artery dilation	2	[19, 29]
	Absent right superior vena cava	1	[41]
	Endocardial cushion defect	1	[36]
	Right ventricular hypertrophy	1	[19]
	Conotruncal heart defects	1	[13]
	Coronary sinus dilatation	1	[29]
	Hypoplastic left heart syndrome	1	[29]
	Shone's complex	1	[27]
	Not detailed	8	[9]
Arrhythmia (*N* = 7) (5.7%)	Perinatal arrhythmias	1	[32]
	Atrial arrhythmias	3	[9, 27, 42]
	Bradycardia	2	[4, 43]
	Supraventricular tachycardia	1	[44]
Valve abnormalities (*N* = 12) (9.8%)	Pulmonary stenosis	4	[1, 23, 25, 37]
	Mitral stenosis	2	[22, 27]
	Tricuspid valve dysplasia	1	[22]
	Bicuspid aortic valve	2	[23, 25]
	Aortic stenosis	3	[12, 22]
Coronary artery abnormality (*N* = 1) (0.8%)	Coronary artery fistula and dilation	1	[26]
Cardiomyopathy (*N* = 3) (2.5%)	Dilated cardiomyopathy	1	[17]
	Hypertrophic cardiomyopathy	1	[45]
	Left ventricular muscle bundle abnormality	1	[9]
Cardiac dysfunction (*N* = 16) (13.1%)	Pulmonary hypertension	8	[18, 19, 21, 23]
	Ventricular dysfunction	3	[17, 23, 27]
	Heart failure	5	[17, 19, 23, 27, 41]
Undescribed cardiac defect		8	[3, 11]

*N: the count of occurrences of each specific cardiac defect among the included reported cases. Some of these reported cases involved multiple patients with various cardiac defects, whereas a patient might also have various cardiac defects. VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; PFO, patent foramen ovale; TOF, tetralogy of Fallot

Table 4 Reported Kleefstra syndrome cases classified by congenital heart defects complexity

	Simple CHD	Complex CHD	Unclassified*
9q34.3 deletion	19	20	12
≥ 1 Mb	3	12	3
< 1 Mb	12	2	5
Unknown	4	6	4
EHMT1 mutation	6	0	9
Not described	0	0	1

*Unclassified: reported cases that did not provide detailed information on cardiac defects or only had arrhythmias or cardiomyopathy, thus making it impossible to classify them based on the CHD complexity. CHD, congenital heart defects

reported in the literature [26] as a 3-month-old infant with multiple coronary microfistulas, mild dilatation of the left coronary artery, multiple small VSD, as well as hemodynamically non-significant PDA and PFO. At the age of 20 months, it was observed that most coronary artery fistulas spontaneously regressed and there were still free of associated symptoms.

Grouping CHD by complexity, our study found that patients with 9q34.3 deletions larger than 1 Mb tend to exhibit more severe and complex congenital cardiac structural defects (Table 4). On the other hand, patients with smaller deletions (< 1 Mb) generally present with milder defects, or may even be asymptomatic or experience spontaneous healing. Notably, all classifiable CHD

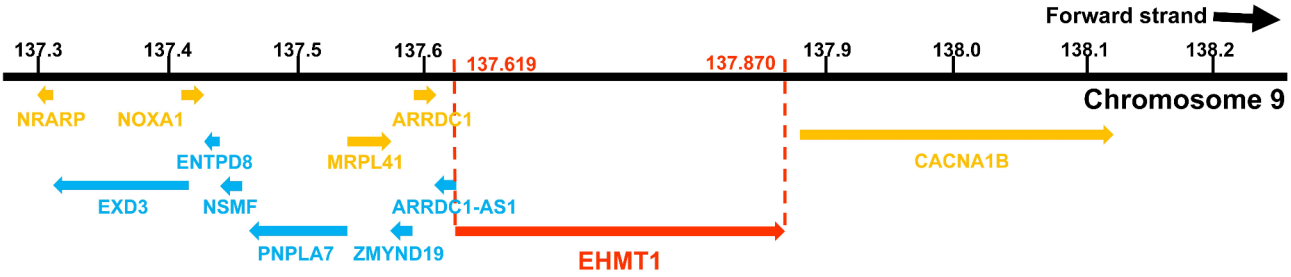

Fig. 2 The EHMT1 gene and its neighboring genes in the chromosome 9q34.3 region. Genes listed (e.g., CACNA1B, ZMYND19) are co-localized with EHMT1 in the chromosome 9q34.3 critical region (coordinates chr9:137,300,000-138,200,000, GRCh38/hg38)

cases in EHMT1 mutation carriers demonstrated simple defects. This finding aligns with previous studies that have reported more severe clinical problems in individuals with larger 9q34.3 deletions (≥ 1 Mb) [9]. However, it is important to note that this does not imply that patients with smaller deletions or EHMT1 mutations are exempt from complex cardiac defects. For instance, the case reported by Vargiami E et al. [26] involved a patient with a deletion of just 0.55 Mb who experienced complex CHD including multiple coronary artery microfistulas, mild dilatation of the left coronary artery, VSD, ASD and PDA, despite not exhibiting any current cardiac-related symptoms. Another case reported by Kleefstra T et al. [25] also involved a patient with a sub-1 Mb deletion diagnosed with TOF, but no further details were provided. Furthermore, we also found that due to severe cardiac problems, these patients with large 9q34.3 deletions (≥ 1 Mb) tend to be recognized in the neonatal or infantile period and have a relatively poor prognosis. Therefore, it cannot be determined whether EHMT1 is the sole or primary gene influencing the prevalence of heart defects in KLEFS1. EHMT1 mutation is the primary driver of KLEFS1, while potential modifiers may contribute to phenotypic variability. Further research is required to determine whether additional genes within the 9q34.3 region contribute to the phenotypic severity, particularly in driving complex cardiac malformations. Figure 2 presents the EHMT1 gene and other nearby genes located in the chromosome 9q34.3 region. It is worth noting that genetic risk plays a significant role in CHD, with over 400 genes estimated to contribute to its development [46]. As the definitive pathogenic gene responsible for KLEFS1, EHMT1 is strongly implicated in heart defect pathogenesis through its critical involvement in this phenotype [7]. However, there is currently no conclusive evidence identifying EHMT1 as a causative gene for CHD [46]. In addition, many previously reported cases did not specify the type of heart defect, which to some extent affected the exploration of the specific cardiac phenotype of KLEFS1 related to 9q34.3 deletion and EHMT1 mutation. Therefore, future research is necessary to delve deeper into this topic.

Arrhythmia

The occurrence of preexisting arrhythmias in KLEFS1 patients is relatively rare, with only 7 reported cases so far, accounting for approximately 5% of the total cases. Among these cases, two were reported to have presented with arrhythmias during the neonatal period [32, 43], but specific details were not provided. The earliest reported case of a KLEFS1 patient with an arrhythmia was by Schimmenti LA et al. [44]. They described a 5-month-old infant who presented with paroxysmal supraventricular tachycardia. The cardiac ultrasound showed no abnormalities, and no delta waves were detected on the ECG. However, esophageal electrophysiology revealed the presence of an insidious accessory connection leading to a positively tuned reciprocating tachycardia. The report did not provide information regarding the treatment of the supraventricular tachycardia, only mentioning that the patient was eventually discharged from the hospital. Another case reported by Rump A et al. [4] involved a 3-year-old KLEFS1 patient who exhibited bradycardia. However, their echocardiography results were normal, indicating no structural abnormalities in the heart. Verhoeven WMA et al. [42] described a 59-year-old KLEFS1 patient with paroxysmal AF who underwent pacemaker implantation. However, the report did not provide detailed information about the cardiac aspects of the patient, as their main focus was on the behavioral and neuropsychiatric characteristics of KLEFS1. Another report by Willemsen MH et al. [9] mentioned a 41-year-old KLEFS1 patient with atrial flutter, but no specific details were provided. Regrettably, the aforementioned cases hardly mention family history related to arrhythmias and other predisposing factors.

Recently, a sizable study by Vasireddi et al. [5] have probed the cardiovascular manifestations of KLEFS1 by examining patients from the two largest KLEFS1 registries. Notably, their findings revealed a substantial prevalence of cardiac arrhythmias, with 8% of patients affected, and atrial tachyarrhythmias specifically, occurring in 6 out of 213 patients (3%), including atrial fibrillation (AF). Moreover, at least 4 cases of atrial fibrillation/atrial tachycardia were found to occur in the absence of

structural heart disease. Our own study, employing a systematic case review approach, yielded similar results, implicating supraventricular arrhythmias as a significant and hitherto underappreciated phenotype of KLEFS1.

However, arrhythmias may have various underlying causes, and thus currently it is still uncertain whether arrhythmias are part of the KLEFS1 phenotype or secondary to heart defects. While heart defects are a well-known phenotype in KLEFS1 patients, the initial focus during evaluations often lies on neurologic and neuropsychiatric issues, potentially leading to the underdiagnosis or oversight of cardiovascular problems such as arrhythmias. It is crucial for clinicians to be more attentive to the cardiac rhythm problems of KLEFS1 patients in order to provide comprehensive care. This includes actively investigating whether the arrhythmia is due to secondary factors or if it is directly related to KLEFS1. This evaluation should ideally be conducted by a cardiologist who can perform a thorough assessment, including electrocardiograms, echocardiograms, and other cardiac tests as needed. If necessary, specialized treatment options, such as medication, pacemaker implantation, or radiofrequency ablation, should be considered and implemented based on the individual patient's needs. To improve our understanding of arrhythmias in KLEFS1 patients, it is important for more reports and studies to be conducted on this subject. This will help increase awareness among healthcare providers and contribute to the development of appropriate management strategies.

Valve abnormalities

There have been several case reports documenting the presence of congenital valve abnormalities in patients with KLEFS1, accounting for approximately 8% of total cases. These abnormalities encompass a range of valve malformations, including pulmonary stenosis, mitral stenosis, tricuspid dysplasia, bilobed aortic valve, and aortic valve stenosis. In current reports, it has been observed that some KLEFS1 patients with valvular abnormalities exhibit only mild problems detected on imaging, without experiencing clinical symptoms including mild peripheral pulmonary artery stenosis [1, 37] and mild aortic valve stenosis [12, 22]. However, a subset of patients may require hospitalization due to severe cardiac problems, which are primarily attributed to concomitant combined structural abnormalities rather than valvular issues [22, 23, 27].

Additionally, there have been cases of asymptomatic bicuspid aortic valve detected on imaging in KLEFS1 patients [23, 25]. Bicuspid aortic valve is a complex and heterogeneous disorder with a prevalence ranging from approximately 0.5–1.4% [47]. Only two cases of KLEFS1 patients with bicuspid aortic valve have been reported so far, and therefore, the evidence supporting bicuspid aortic valve as a phenotype of KLEFS1 is insufficient. Notably, bicuspid aortic valve is highly heritable, with up to 89% of cases having a genetic basis [48]. Mutations in genes such as NOTCH1, the GATA gene family, and GATA5 have been identified as possible causes of bicuspid aortic valve [49]. It is worth mentioning that the two reported cases of KLEFS1 patients with bicuspid aortic valve had 9q34.3 deletion rather than EHMT1 gene mutation. This raises the question of whether other genes on 9q34.3 may be associated with bicuspid aortic valve, and further investigation is needed to determine this. Similarly, more studies, including animal models and clinical research, are necessary to elucidate the relationship between the EHMT1 gene and other genes in the 9q34.3 region, specifically regarding congenital valve abnormalities and valve development. These efforts will contribute to a better understanding of congenital valve disease and the cardiovascular phenotype specific to KLEFS1.

Cardiomyopathy

Indeed, there have been several rare cases reported of myocardial abnormalities in patients with KLEFS1. Okayasu et al. [17] reported on an 18-year-old male patient with a 9q34.3 microdeletion who had dilated cardiomyopathy with ventricular systolic dysfunction, ultimately resulting in heart failure and death. Harada et al. [45] described a case of a patient with KLEFS1 who had hypertrophic obstructive cardiomyopathy, a condition characterized by abnormal thickening of the heart muscle. Willemsen et al. [9]reported on a patient with KLEFS1 who had left ventricular muscle bundle abnormalities, a common feature in hypertrophic cardiomyopathy and a risk factor for left ventricular outflow tract obstruction [50]. Although the types and severity of myocardial abnormalities in these cases vary, these findings still highlight the importance of assessing myocardial abnormalities in KLEFS1 patients. It is also worth noting that all these three cases were caused by 9q34.4 deletion, not by EHMT1 mutation. This seems to suggest that it is not the EHMT1 gene, but other genes in the 9q34.4 region that play an important role in cardiomyopathy. However, due to the limited number of related cases, more cases and research are still needed to further explore the relationship between the chromosomal 9q34.3 region and myocardial diseases.

Coronary artery abnormalities

Only one case of coronary abnormalities has been reported so far, involving a 20-month-old female patient with KLEFS1 which was caused by a 9q34.3 microdeletion (0.55 Mb) [26]. The patient was found to have multiple coronary microfistulas and mild dilatation of the left coronary artery, along with ventricular and atrial septal defects, during a routine pediatric follow-up examination

at the age of 3 months. While it is not possible to definitively establish coronary abnormalities as phenotypes of KLEFS1 based solely on this report, it does highlight the importance of conducting coronary-related investigations in patients with KLEFS1. Ancillary assessments for coronary abnormalities may be included in the cardiac evaluations of affected individuals. Further research is needed to better understand the relationship between the 9q34.3 chromosomal region and coronary artery development.

Cardiac dysfunction

Any of the aforementioned structural cardiac abnormalities or arrhythmias can lead to abnormal cardiac function. Previously reported cases of KLEFS1 have documented cardiac functional abnormalities, including pulmonary hypertension (PH), ventricular dysfunction, and heart failure [17–19, 23, 27, 41]. Okur et al. identified three KLEFS1 patients with PH and systematically reviewed previously reported PH cases in this population [18]. All cases were caused by 9q34.3 deletions and exhibited CHD, irrespective of its structural complexity. No new PH patients have been identified in subsequently reported cases. Further research is still needed to clarify whether the 9q34.3 deletion or EHMT1 mutation affects pulmonary vascular development and leads to congenital PH, or whether PH arises secondary to CHD. Heart failure, a complex clinical syndrome that commonly occurs in various heart diseases, arises from structural or functional impairments in ventricular filling or blood ejection [51]. There have been some reports of KLEFS1 patients with heart failure, which often occurs in patients with complex CHD or cardiomyopathy [17, 19, 23, 27, 41]. Consequently, assessing cardiac function in individuals with KLEFS1 is crucial. It is noteworthy that a significant number of patients have been reported without any mention of their cardiac function, highlighting the importance of addressing this aspect in future studies.

EHMT1 gene expression and its role in the circulatory system

EHMT1 is located within the chromosomal region 9q34.3 and encodes a histone methyltransferase that specifically adds methyl groups to the lysine-9 position of histone H3 (H3K9me1 and H3K9me2) in hyperchromatin, leading to transcriptional repression of MYC- and E2F-responsive genes involved in the G0/G1 transition of the cell cycle [52]. Additionally, EHMT1 is a key component of the PRDM16 transcriptional complex, which stabilizes PRDM16 proteins and regulates the thermogenesis program in brown adipocytes [53].

EHMT1+/- mouse models that have been discovered so far recapitulate the developmental characteristics of core KLEFS1 phenotypes [54]. However, there is limited research on the role of EHMT1 in the cardiovascular system. Some studies have suggested that Ehmt1/2 may protect cardiomyocytes and prevent pathological cardiac hypertrophy. Chatzieleftheriadis K et al. [55] conducted in vitro and in vivo experiments on rats found that inhibiting Ehmt1/2 promoted proliferation of neonatal rat cardiomyocytes, while also resulting in a decrease of the repressive histone mark H3K9me2. Thienpont B et al. [56] conducted in vitro and in vivo experiments on mice found that the downregulation of miR-217 leading to the suppression of Ehmt1/2 has been implicated in pathological cardiac hypertrophy, with similar findings observed in humans. In another mouse study, Prdm16 and Ehmt1/2 were found to interact and inhibit the function of the pro-hypertrophic transcription factor Myc, thereby reducing the expression of reactivated fetal genes in hypertrophic hearts [57]. A study on genetic analysis of CHD found that EHMT1 mutations may be related to the pathogenesis of atrioventricular septal defect, but the underlying pathophysiological mechanisms remain unclear [58]. A recent cohort study provided a comprehensive clinical and molecular spectrum of KLEFS1 disease, finding that the SET domain of the EHMT1 gene may play a key role in cardiac development [7]. Mutations in this domain are associated with a significant prevalence of congenital heart defects, even in the absence of the typical KLEFS1 phenotype. Further experiments are needed to investigate the specific associations between the SET domain of EHMT1 and the different cardiac defects observed in KLEFS1, as well as their underlying mechanisms.

Currently, research on the association of EHMT1 with congenital cardiac structural abnormalities and cardiac electrophysiology is still limited, and there have yet to be experimental animal models specifically targeting the cardiovascular manifestations of KLEFS1. While there is growing recognition of the cardiovascular phenotypes in KLEFS1 patients, the role of EHMT1 in the cardiovascular system has not been adequately explored.

Conclusion

Cardiovascular abnormalities are a significant phenotype in individuals with KLEFS1, especially congenital structural heart defects. Earlier case reports primarily focused on the neurological system, but it is encouraging that defects in the cardiovascular system are now gradually receiving more attention. Therefore, we recommend that all KLEFS1 patients undergoing genetic testing for diagnosis, regardless of their predominant clinical features, undergo routine cardiovascular screening, including electrocardiography and echocardiography. Further evaluation, such as cardiac magnetic resonance imaging, may be warranted to assess any potential cardiac issues. Understanding the spectrum of cardiac abnormalities in

KLEFS1 is crucial for appropriate management and treatment. This will help ensure timely detection and management of any cardiac abnormalities, which can have significant implications for the patient's overall health and well-being. Similarly, for individuals with either common or rare cardiac phenotypes with extracardiac anomalies suggesting a genomic disorder, genetic testing should be conducted to exclude KLEFS1. Moreover, future studies should encompass additional animal and clinical trials to elucidate the role of the EHMT1 gene and the 9q34.3 region in the occurrence and progression of cardiovascular diseases. These endeavors will contribute to a better understanding of the relationship between cardiovascular abnormalities and genomic disorders, particularly KLEFS1.

Abbreviations

AF	Atrial fibrillation
ASD	Atrial septal defect
CHD	Congenital heart defects
CNVs	Copy number variations
EHMT1	Euchromatin histone methyltransferase 1
KLEFS1	Kleefstra syndrome
PDA	Patent ductus arteriosus
PH	Pulmonary hypertension
PFO	Patent foramen ovale
TOF	Tetralogy of fallot
VSD	Ventricular septal defect
9qSTDS	9q subtelomeric deletion syndrome
9q34.3	Subtelomeric region 34.3 of the long arm of chromosome 9

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Author contributions
The conceptualization of the study was led by H.X and L.Q. The investigation was carried out by H.X., and resources were provided by W.M. Data curation was handled by H.X. The original draft preparation was undertaken by H.X., and the writing—review and editing was completed by L.Q. Visualization efforts were led by P.K and Q.S. Supervision of the project was conducted by Y.G, Y.Z and L.Q, while project administration was managed by L.Q.

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Data availability
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Declarations

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Not applicable.

Consent for publication
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Competing interests
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