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TBX5 variants and cardiac phenotype: A systematic review of the literature and a novel variant

Anne Kathrine Møller Nielsen [a,b], Anna Maria Dehn [a], Vibeke Hjortdal [a], Lars Allan Larsen [b,*]

[a] Department of Cardiothoracic Surgery, Rigshospitalet, Denmark
[b] Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark

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ABSTRACT

T-Box Transcription Factor 5 (*TBX5*) variants are associated with Holt-Oram syndrome. Holt-Oram syndrome display phenotypic variability, regarding upper limb defects, congenital heart defects, and arrhythmias. To investigate the genotype-phenotype relationship between *TBX5* variants and cardiac disease, we performed a systematic review of the literature. Through the systematic review we identified 108 variants in *TBX5* associated with a cardiac phenotype in 277 patients. Arrhythmias were more frequent in patients with a missense variant (48% vs 30%, $p = 0.009$) and upper limb abnormalities were more frequent in patients with protein-truncating variants (85% vs 64%, $p = 0.0008$). We found clustering of missense variants in the T-box domain. Furthermore, we present a family with atrial septal defects. By whole exome sequencing, we identified a novel missense variant p.Phe232Leu in *TBX5*. The cardiac phenotype included atrial septal defect, arrhythmias, heart failure, and dilated cardiomyopathy. Clinical examination revealed subtle upper limb abnormalities. Thus, the family corresponds to the diagnostic criteria of Holt-Oram syndrome.

We provide an overview of cardiac phenotypes associated with *TBX5* variants and show an increased risk of arrhythmias associated to missense variants compared to protein-truncating variants. We report a novel missense variant in *TBX5* in a family with an atypical Holt-Oram syndrome phenotype.

1. Introduction

Since the discovery of *TBX5* (T-Box Transcription Factor 5) in 1997, variants have been reported in both familial and sporadic cases of Holt-Oram syndrome (HOS, OMIM #142900). (Li et al., 1997; Basson et al., 1997) HOS is a rare autosomal dominant inherited disease with an estimated prevalence between 0.7 and 1 per 100.000 births (Barisic et al., 2014). Upper limb defects are obligate features of HOS with great phenotypic variability. In patients with HOS and a *TBX5* variant, a congenital heart defect (CHD) is present in 91% and rhythm disturbances are present in 30% (Vanlerberghe et al., 2019). Atrial septal defect (ASD) is the most common CHD, found in 62% of patients with HOS (Vanlerberghe et al., 2019).

TBX5 is a transcription factor and a member of the T-box family interacting in networks essential for cardiac development, in particular development of the conduction system, septation, and cardiomyogenesis (Steimle and Moskowitz, 2017). These multiple involvements in cardiac development, combined with differences in variant effect, may underlie the variable expression of the cardiac phenotype. To predict cardiac outcomes in patients with HOS, a genotype-phenotype correlation has been warranted, though still unidentified. More recent studies show specific phenotypes related to the type of variant in TBX5, suggesting that most patients with HOS have a Loss-of-Function (LoF) variant in *TBX5* resulting in haploinsufficiency (Barnett and Postma, 2014). Numerous missense variants have been identified as disease-causing, but the understanding of the molecular mechanism is incomplete. Postma et al. showed gain-of-function in a missense variant in a family with atrial fibrillation and HOS, suggesting that atypical cardiac phenotypes may occur in patients with missense variants. Furthermore, *TBX5* variants associated with a cardiac phenotype with no obvious or very subtle skeletal malformation have been reported, suggesting *TBX5* involvement in cardiac disease without HOS (Postma et al., 2008; Zhou et al., 2015).

Despite large efforts of finding *TBX5* variants in patients with HOS, there has been no systematic review of *TBX5* variants focusing on the cardiac phenotype. By reviewing the literature, we establish an overview of *TBX5* variants associated with cardiac features and find an association between *TBX5* missense variants and arrhythmia. In addition,

* Corresponding author. Blegdamsvej 3B, 2200, Copenhagen, Denmark.
E-mail address: larsal@sund.ku.dk (L.A. Larsen).

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we report a novel missense variant in *TBX5* in a family with ASD, conduction disturbances, arrhythmias, and subtle upper limb defects.

2. Methods

2.1. A systematic review of TBX5 variants and cardiac phenotype

We conducted a comprehensive search of the literature using the following 2 databases: Pubmed and Embase. We searched for English language abstracts published after 1996 (*TBX5* was identified and published for the first time in 1997) (Li et al., 1997; Basson et al., 1997) using keywords: *CHD*, *arrhythmias*, *heart diseases*, or *HOS* in combination with *TBX5* or *T-box domain proteins*. The search string is available in Table S1. We supplemented with articles cited in key papers. For further assessment, all abstracts were uploaded to Covidence (www.covidence.org), a tool for systematic reviews.

Inclusion criteria were articles with abstracts available, written in the English language, published after 1996, and addressing cardiac outcomes of patients with *TBX5* variants, including protein-altering variants (PAVs), duplications, deletions, insertions in exons, and junctional splice regions. Exclusion criteria were articles with no full text available, a language other than English, isolated animal studies, or no information on cardiac phenotype in study participants with *TBX5* variants. To minimize the risk of bias, 2 investigators independently completed the screening of abstracts and full texts. Conflicts in the screening process were solved by consulting a third investigator.

Data extraction from included papers covered *TBX5* variants and associated CHD, cardiac disease, skeletal malformations, and extracardiac features. We categorized variants as either missense, PAV (covering missense variants, in-frame duplications, or deletions), protein-truncating variants (PTV, frameshift variants, nonsense variants, and deletion of entire gene), and other (splicing variants, deletions/duplications of exons). We compared phenotypes between patients with missense and PTV variants.

2.2. Investigation of a family with septal defects

We identified a family with ASD in three generations and examined medical records to identify CHD and cardiac disease with a focus on arrhythmias, heart failure, cardiomyopathy, and pacemaker need. In addition, the family was examined with Holter monitoring, x-rays of the upper extremities, and syndromic features.

2.3. Genetic analysis

Peripheral venous blood was used for DNA extraction. Whole exome sequencing (WES) was performed by BGI Genomics, Copenhagen in 5 affected family members to identify the disease-causing variant. Sanger sequencing was used to investigate the carrier status of the variant in the rest of the affected family members >18 years of age.

2.4. Variant filtering and annotation

We filtered for very rare protein-altering variants, which were shared between the five affected family members. Thus, we included heterozygous variants with minor allele frequency (MAF) < 0.0001 in gnomAD (https://gnomad.broadinstitute.org/) and 1000 Genomes Project (1000 GP) (Auton et al., 2015). Shared rare variants within the 5 family members were annotated with CADD scores (Combined Annotation Dependent Depletion), MPC scores (Missense badness, PolyPhen-2, and Constraint), MVP scores (Missense Variant Pathogenicity Prediction), and REVEL scores (Lek et al., 2016; Kircher et al., 2014; Samocha et al., 2017; Qi et al., 2021; Ioannidis et al., 2016).

This study was approved by The Danish Committee on Health Research Ethics (jr. no.: H-19081483) with additional local approvals as required. Consent was obtained from patients according to applicable laws and regulations. Written informed consent has been obtained from the patients to publish this paper.

3. Results

3.1. A systematic review of published TBX5 variants

We imported 808 papers for screening. Eight duplicates were removed, leading to 800 papers eligible for abstract screening of which 122 studies were evaluated as eligible for full-text assessment. Finally, 60 articles were included in this review and data extraction.

In total, we identified 277 patients with *TBX5* variants associated with cardiac phenotype in the 60 included articles and our family. Among the 277 patients, we identified 108 unique variants of which 43 (40%) are missense variants, and 41 (38%) are PTVs.

The cardiac phenotype according to each unique variant is listed in Table S2. In 27 (24%) patients with arrhythmia, a pacemaker was implanted.

The phenotype was significantly different in patients with missense variants and PTVs. Arrhythmias were more frequent in patients with a missense variant (48% vs 30%, $p = 0.009$) and upper limb abnormalities were more frequent in patients with PTVs (85% vs 64%, $p = 0.0008$) (Table 2).

We found clustering of missense variants in the T-box domain, while PTVs were distributed evenly across the gene, without clustering in the T-box domain (Fig. 2.).

3.2. A novel TBX5 variant segregates with ASD, arrhythmia, and subtle limb defects

In a three generation family, all family members were diagnosed with ASD except two: one had a VSD, and one was examined with echo late in life showing no signs of CHD. A wide range of cardiac diseases is present in the family including 1st- and 2nd-degree AV-block, bradycardia, sinus node disease, atrial flutter and fibrillation, heart failure, and dilated cardiomyopathy (DCM) (Table 1). Patient II-2 needed a pacemaker because of sinus node disease and patient III-4 received a pacemaker at the age of 13 years because of recurrent syncope related to sinus node dysfunction. Patient III-4 also had an ICD implanted at the age of 30 because of ventricular fibrillation with syncope.

At the first visit, no obvious extracardiac features were noted, but the identification of a *TBX5* variant in this family raised suspicion of HOS, and a renewed examination was performed focusing on upper limb abnormalities. Clinical examination showed bilateral short fingers in all patients except one, who was not investigated. Two patients were unable to oppose the thumb to the 5th finger. X-ray of upper limbs was performed in seven family members, showing one case with abnormal scaphoid bone, one with a slightly shortened length of the humerus, and five without skeletal abnormalities.

In the investigated family we identified a novel missense variant c.694 T > C (p.Phe232Leu)(reference sequence NM_000192) within the T-Box encoding domain of *TBX5*. Genome coordinates of the variant is 12-114823342-A-G (hg19). The variant is not present in gnomAD, 1000 GP, or ClinVar. This novel variant is predicted damaging by in-silico algorithms (CADD score = 28.9, MPC score = 1.99, MVP score = 0.96, REVEL score = 0.938) and segregates with disease in an autosomal dominant pattern in three generations, affecting 10 family members investigated (Fig. 1). We classified the variant as “Pathogenic” according to ACMG guidelines (PP1-strong evidence, PM1-moderate evidence, PM2-supportive evidence, PP3-strong evidence, PP4-supportive evidence) (Richards et al., 2015; Pejaver et al., 2022).

4. Discussion

Since the discovery of the HOS disease gene in 1997 [1,2], many *TBX5* variants have been reported in patients with HOS. Through a systematic

Table 1
The cardiac phenotype of the family members.

Patient	CHD	Closure	1st-degree AVB (age)	2nd-degree AVB (age)	SND (age)	PM (age)	AF (age)	Other (age)
II-2	Unknown	Unknown	–	–	+	+	–	HF
II-4	ASD	Surgical	+	–	–	–	+[a] (60)	–
II-5	ASD	Spont.	+ (44)	+ (34) Intermittent	+ (44)	–	–	–
III-4	ASD	Surgical	–	–	+ (13)	+ (13)	+ Paroxysmal	TCI (28), DCM (29), VF (30)
III-5	ASD	Surgical	+ (42)	+ (42) Intermittent	–	–	–	–
III-7	ASD	Spont.	–	–	+ (33)	–	–	–
III-9	ASD	Surgical	–	–	+ (48)	–	+[b] (40) Intermittent	–
III-11	ASD	Surgical	–	–	+	–	–	–
III-12	ASD	Surgical	–	–	–	–	–	–
IV-10	VSD	Spont.	–	–	–	–	–	–

Abbreviations. AF, atrial fibrillation or flutter; ASD, atrial septal defect; AVB, atrioventricular block; CHD, congenital heart defect; DCM, dilated cardiomyopathy; HF, heart failure; PM, Pacemaker; SND, sinus node dysfunction; spont., spontaneous; TCI, transient cerebral ischemia; VSD, ventricular septal defect; VF, ventricular fibrillation. (+) indicates the presence of disease and (−) indicates disease is not present.
Age at diagnosis (years) is depicted in parentheses, if available from medical records.
[a] Patient II-4 has predominantly atrial flutter, but with episodes of atrial fibrillation.
[b] Patient III-9 has predominantly atrial flutter.

Table 2
Characteristics of patients included in the systematic review (present study included).

	Total cohort (n = 277)	Missense (n = 129)	PTV (n = 97)	PAV (n = 148)	Other[c] (n = 32)	Mis vs PTV p-value
CHD (%)	219 (79%)	96 (74%)	85 (87%)	108 (73%)	26 (81%)	0.02
Isolated septal defect[a] (%)	180 (82%)	77 (80%)	69 (81%)	89 (82%)	22 (85%)	1.0
Arrhythmias (%)	111 (40%)	62 (48%)	29 (30%)	69 (47%)	13 (41%)	0.009
Brady arrhythmias[b] (%)	74 (67%)	37 (60%)	22 (76%)	43 (62%)	9 (69%)	0.2
Other cardiac (%)	44 (16%)	20 (16%)	13 (13%)	23 (16%)	8 (25%)	0.8
Upper limb abnormality (%)	207 (75%)	82 (64%)	82 (85%)	93 (63%)	32 (100%)	0.0008
Familial (%)	203 (73%)	98 (76%)	63 (65%)	114 (77%)	26 (81%)	0.1

CHD, congenital heart defects Mis, missense; PAV, protein-altering variants (missense + in-frame deletion and duplications); PTV, protein-truncating variants.
[a] with co-existing persistent arterial duct, or persistent left superior vena cava in some cases.
[b] including conduction disturbances.
[c] splice site variants, and deletions/duplications of entire exons.

review of the literature on *TBX5* variants associated with cardiac disease, we identified new genotype-phenotype correlations suggesting that arrhythmias are more common and upper limb abnormalities are less common in patients with a missense variant compared to PTVs and clustering of missense variants in the T-box domain. In this study, we identified a novel missense variant in *TBX5* in a Danish family with septal defects, a wide range of cardiac diseases, and subtle upper limb abnormalities. This is, to our knowledge, the largest cohort describing patients with *TBX5* variants, and a cardiac phenotype identified through literature.

Surprisingly, we found that in 36% of patients with a missense variant, upper limb abnormalities were not reported. This expands on the concept of atypical HOS phenotype with a possibility of unrecognized mild upper limb abnormalities or non-syndromic cardiac disease associated with *TBX5* variants (Guo et al., 2016; Al-Qattan et al., 2015; Patel et al., 2012). Mild upper limb abnormalities like mobility defects in the shoulder and elbow, without skeletal involvement, can easily be overlooked by an inexperienced clinician, suggesting that upper limb abnormalities are underestimated (Vanlerberghe et al., 2019). This warrants further awareness of the diagnosis of atypical HOS phenotype, and in particular mild upper limb abnormalities.

In contrast, patients with PTVs displayed a higher frequency of upper limb abnormalities, indicating a likelihood of increased occurrence of patients with typical HOS diagnosis among patients with PTV. This is in accordance with previous findings demonstrating a higher frequency of nonsense and frameshift variants in patients with HOS (Vanlerberghe et al., 2019; Mcdermott et al., 2005; Basson et al., 1999).

The data suggest some phenotype-genotype correlation when comparing PAVs and PTVs, with PAVs significantly overrepresented in patients with arrythmia, while PTVs were significantly over-represented in patients with upper limb abnormalities. In addition, missense variants were clustered within the T-box encoding domain of *TBX5*, while PTVs were distributed evenly across the gene. We speculate that the observed phenotype-genotype correlation might suggest that haploinsufficiency of *TBX5* is necessary for display of the full HOS phenotype.

Extending on the phenotypical characteristics, we found that arrhythmias were more common in patients with missense variants compared to patients with PTVs. Of those patients with arrhythmias, bradyarrhythmia was more common among patients with PTVS compared to missense variants. This, again, suggests that patients with a PTV display more classical HOS symptoms, and patients with a missense variant display a more atypical phenotype. A study showed that in patients with HOS, missense variants are more likely to cause complex CHD than truncating variants, (Vanlerberghe et al., 2019) supporting our findings of a more atypical phenotype in patients with missense variants.

In the Danish family, the cardiac phenotype (ASD, VSD, both mild and severe arrhythmias with pacemaker need, heart failure, and DCM) corresponds to diagnostic criteria of HOS described in the literature, though the upper limb defects are less typical (Mcdermott et al., 2005). X-ray of upper limbs showed abnormal scaphoid bone in one patient and slightly shortened humerus in one patient, while X-rays of the rest of the investigated family members did not show abnormalities. Clinical examination showed a tendency of short digits of all family members, though not confirmed by X-ray. The normal length of digits in the general population varies and evaluation of short fingers in an X-ray is

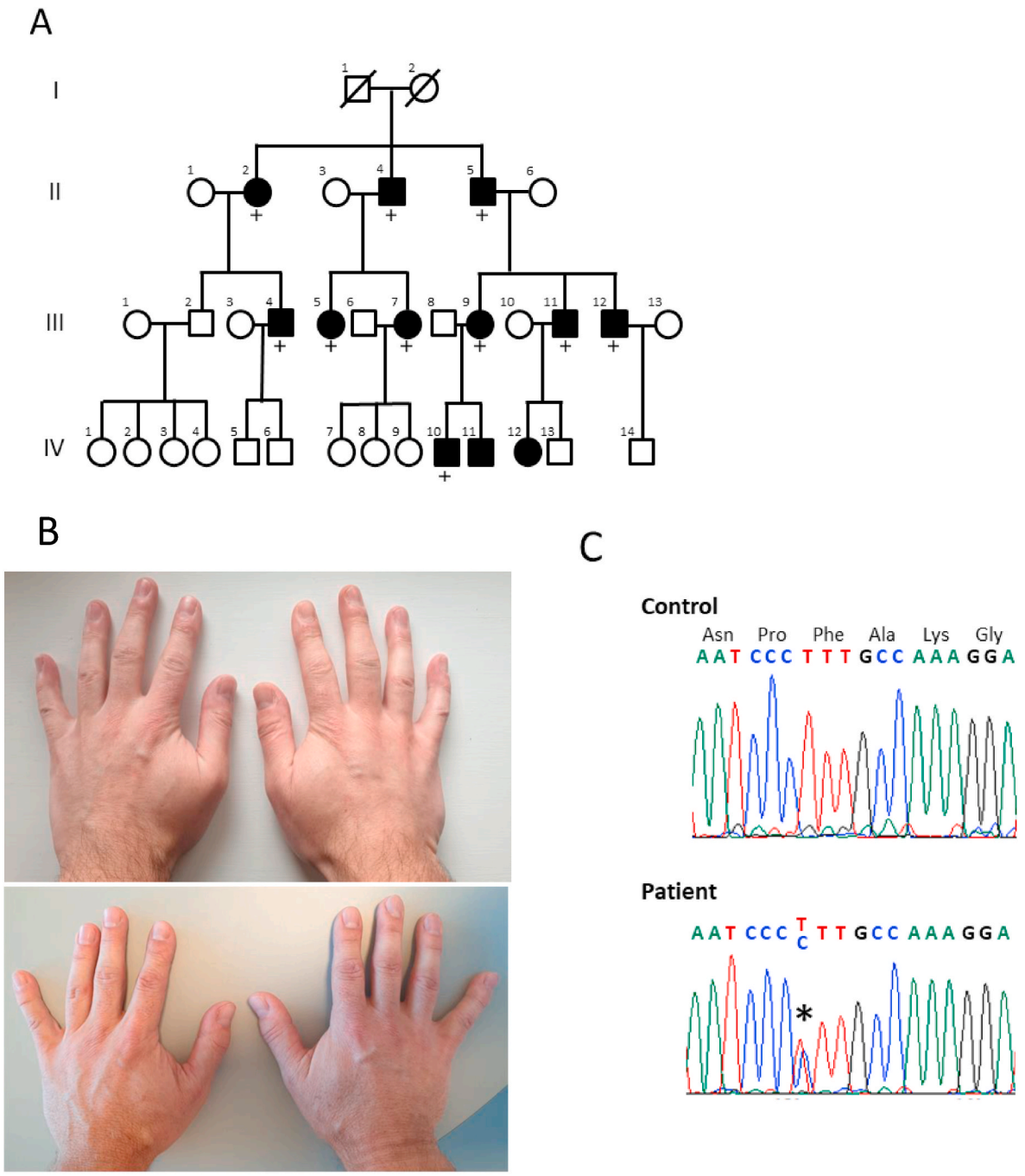

Fig. 1. A family with a novel p.Phe232Leu variant in *TBX5*. A. Pedigree of the family. + indicates a carrier of p.Phe232Leu, black circles and squares indicate affected members with a septal defect, arrhythmia, dilated cardiomyopathy, or heart failure. **B.** Clinical photos of hands showing shorter fingers in family member III-11 and III-12. C. The chromatogram of a patient and control.

challenging. Consequently, it is questionable whether p.Phe232Leu justifies the diagnosis of HOS in this family, keeping strict phenotypical criteria in mind (Mcdermott et al., 2005). A few studies have also observed missense variants in families with mild skeletal deformations and AF, suggesting an atypical HOS phenotype (Postma et al., 2008; Guo et al., 2016; Patterson et al., 2020).

In the Danish family presented in this study, one patient was diagnosed with DCM at an early age, and this adds to recent findings, showing an association of DCM and LVNC with *TBX5*-related heart disease, warranting increased awareness of DCM in patients with *TBX5* variants (Zhou et al., 2015; Patterson et al., 2020; XL et al., 2015; SB et al., 2018).

4.1. Limitations

Our study is limited by a retrospective design, therefore certain precautions should be taken. First, published variants are often novel in either functional analysis, phenotype, or variant, to be published. Hence already-known phenotypes and variants are more likely unpublished. This bias could skew the information and make the cases in this review more unique, and not representative of the general population of patients with *TBX5* variants. This should be considered when used in a clinical setting.

Second, included papers use different genetic testing methodologies (mutation analysis of *TBX5*, NGS gene panels, WES, MLPA), and clinical

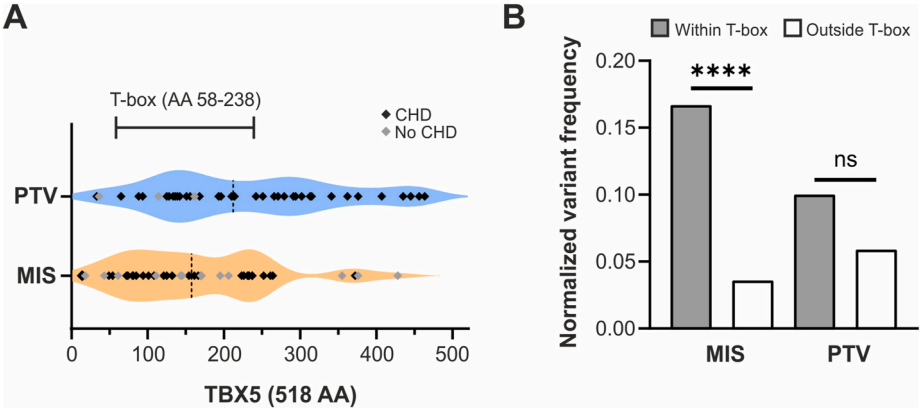

Fig. 2. Distribution of missense and protein-truncating variants in *TBX5*. **A**. The position of missense (MIS) and protein-truncating (PTV) variants within *TBX5* are shown with diamonds (black: variants associated with congenital heart defects (CHD), grey: variants not associated with CHD). The violin plots indicate the density of unique variants along the *TBX5* protein. The median of the distribution is marked with a dotted line. **B.** Normalized variant frequency within (grey) and outside (white) the T-box region of TBX5. Normalized variant frequency was calculated as the number of unique variants divided by the number of amino acids (AA) within or outside of the T-box (180 AA and 338 AA, respectively). Fisher's exact test was used for statistical analysis. Asterisks indicate P-values: ****$P < 0.0001$. ns: not significant.

examinations of cases vary. Thus, relevant clinical information is lacking in some patients, and we speculate if the presence of upper limb abnormalities might be underreported in the literature. In addition, details of arrhythmia were lacking in some papers and could not proceed further analysis.

Despite these limitations, our literature review provides an overview of variants in *TBX5* associated with a cardiac phenotype which can be used in a clinical setting when evaluating patients with *TBX5* variants. We raise awareness of subtle skeletal features in patients with familial CHD and arrhythmias, as skeletal features can be absent or difficult to acknowledge, and propose cardiac follow-up on patients with a *TBX5* variant, even without classic HOS features. The present review showed that *TBX5* variants reported in the literature display great variability in cardiac phenotype, with arrhythmias more common in missense variants compared to PTVs. Awareness of an association between missense variants and arrhythmia is important because missense variants are more likely to be classified as variants of uncertain significance (VUS) compared to PTVs.

5. Conclusion

To conclude, we identified a novel p.Phe232Leu variant in *TBX5* in a family with atypical HOS phenotype. We provided an overview of published *TBX5* variants associated with cardiac disease and showed that patients with missense variants are more likely to develop arrhythmias, compared to patients with PTVs. Our results add to the current knowledge of *TBX5* variants and are important in a clinical setting when evaluating a patient with a *TBX5*.

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Anne Kathrine Møller Nielsen: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing, Visualization. **Anna Maria Dehn:** Data curation, Formal analysis, Writing – review & editing. **Vibeke Hjortdal:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. **Lars Allan Larsen:** Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2024.104920.

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Further reading

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