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Case Report

Danon Disease Manifesting as Arrhythmogenic Right Ventricular Cardiomyopathy: A Case Report

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Abstract

Danon disease is a rare X-linked genetic disorder, manifesting as cardiac hypertrophy, myopathy, and intellectual disability. We report a rare case of arrhythmogenic right ventricular cardiomyopathy (ARVC) in a 28-year-old female with Danon disease. An electrocardiogram (ECG) showed sinus bradycardia and first-degree atrioventricular block; echocardiography revealed a right atrial thrombus, and computed tomography (CT) scan displayed an enlarged right ventricular outflow tract and right atrial thrombosis. Genetic testing identified a novel Lysosomal Associated Membrane Protein 2 (*LAMP2*) gene variant, confirming the diagnosis of Danon disease. The patient was administered anticoagulants and heart failure medications. This case underscores the importance of considering family history and genetic testing in diagnosing Danon disease with ARVC. This expands the disease's phenotypic spectrum beyond its conventional cardiac manifestations.

Keywords

arrhythmogenic; Danon disease; right ventricular cardiomyopathy; lysosomal associated membrane protein 2

Introduction

A rare X-linked genetic disorder, Danon disease is primarily characterized by cardiac hypertrophy, myopathy, and intellectual disability [1]. Although the majority of the patients with Danon disease exhibit cardiac hypertrophy on echocardiography, few cases manifest as dilated cardiomyopathy [2]. Here, we report a rare case of Danon disease with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Case Presentation

In 2018, a 28-year-old female experienced sudden palpitations and dyspnea. She underwent electrical cardioversion after an electrocardiogram (ECG) revealed ventricular tachycardia. After a few months, she received an implantable cardioverter-defibrillator (ICD) at a tertiary hospital. She experienced intermittent palpitations, abdominal bloating, and ascites over the following six years, which prompted her to seek treatment at several hospitals. In February 2022, she was admitted to the Department of Cardiology at Yueyang Central Hospital after experiencing palpitations, abdominal distension, and dyspnea.

She had a positive hepatojugular reflux sign and a blood pressure of 107/68 mmHg post-admission. The apical impulse was located in the fifth intercostal gap at the left midclavicular line, and the cardiac boundary was enlarged to the left. Her distended abdomen exhibited a 'frog-bellied' appearance, without any abdominal wall varicose veins. Her additional findings included hepatomegaly, a fluid wave tremor, and shifting dullness. Laboratory investigations showed 7.030 mg/L of D-dimer (normal range $<$0.5 mg/L), 0.240 µg/L of troponin I (normal range $<$0.023 µg/L), and 14,600.00 ng/L of N-terminal pro-brain natriuretic peptide (NT-proBNP, normal range $<$450 ng/L).

ECG findings revealed sinus bradycardia, first-degree atrioventricular block, and incomplete right bundle branch block (Fig. 1A), as well as ventricular tachycardia (Fig. 1B). Moreover, transthoracic echocardiography revealed a right atrium thrombus (Fig. 2). Computed tomography (CT) showed an enlarged right ventricular outflow tract (Fig. 3A) and right atrial thrombosis (Fig. 3B). An enlarged heart was observed on X-ray (Fig. 3C). Subsequently, she was diagnosed with ARVC. A familial predisposition to cardiac disease was observed as her grandmother died of heart disease at the age of 40, her sister died at 28 (unknown cause), and her son was diagnosed with ventricular preexcitation as well as hypertrophy, respectively. Exon-gene sequencing was performed on the patient as well as her mother and son post-family history, which revealed a pre-

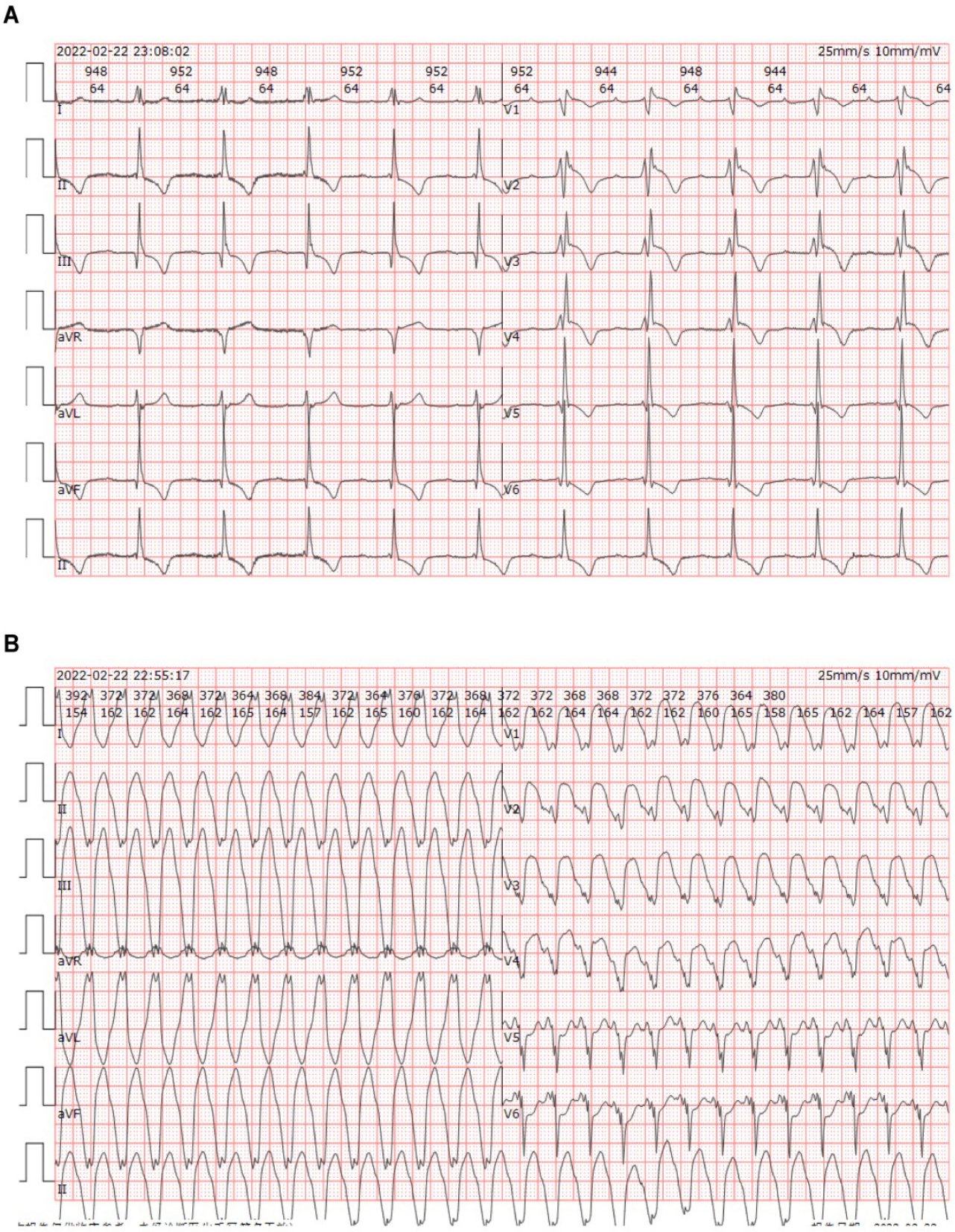

Fig. 1. Electrocardiogram (ECG) characteristics. (A) An ECG showed sinus bradycardia, first-degree atrioventricular block, and incomplete right bundle branch block. (B) ECG showed ventricular tachycardia with a left bundle branch morphology.

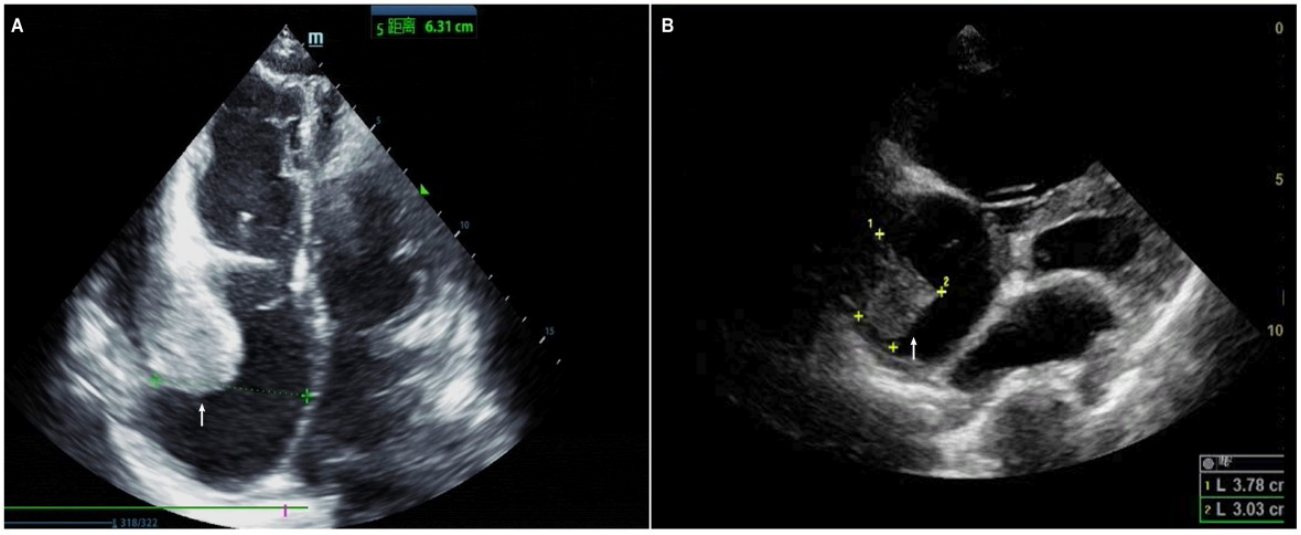

Fig. 2. An echocardiogram showed a right atrium thrombus. (A) Apical four-chamber view. (B) Subxiphoid four-chamber view. The white arrows in the Fig. 2A and B indicates a right atrial thrombus.

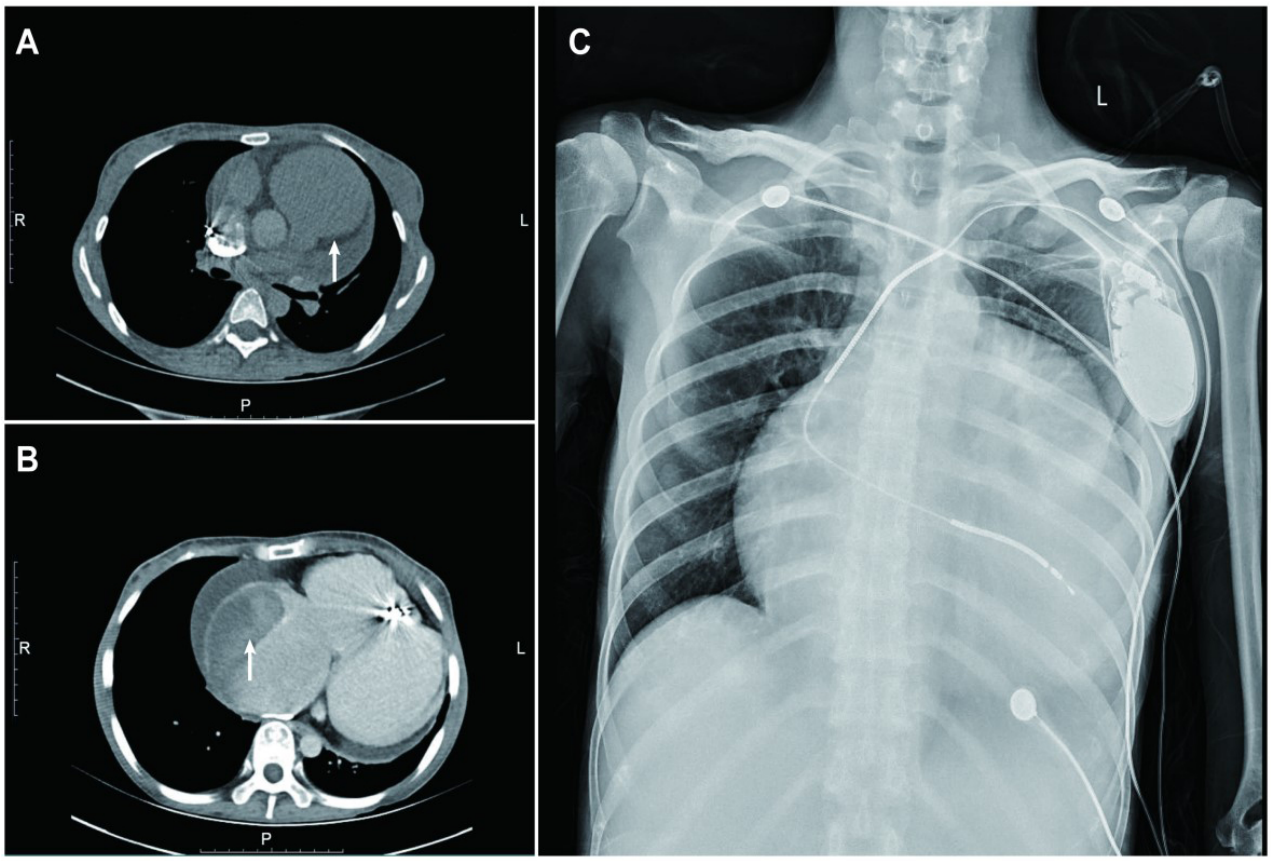

Fig. 3. Computed tomography (CT) and X-ray manifestations. (A) A CT revealed an enlarged right ventricular outflow tract (white arrow). (B) CT showed a right atrium thrombus (white arrow). (C) X-ray showed cardiomegaly. R stands for right, L for left, and P for posterior.

viously unreported Lysosomal Associated Membrane Protein 2 (*LAMP2*) gene variant: a nucleotide change (amino acid change) c.997A>T (protein sequence. Lysine 333*) on chromosome X in the patient's child (Fig. 4). A conclusive diagnosis of Danon disease was established based on the proband's cardiomyopathy manifestations and genetic findings.

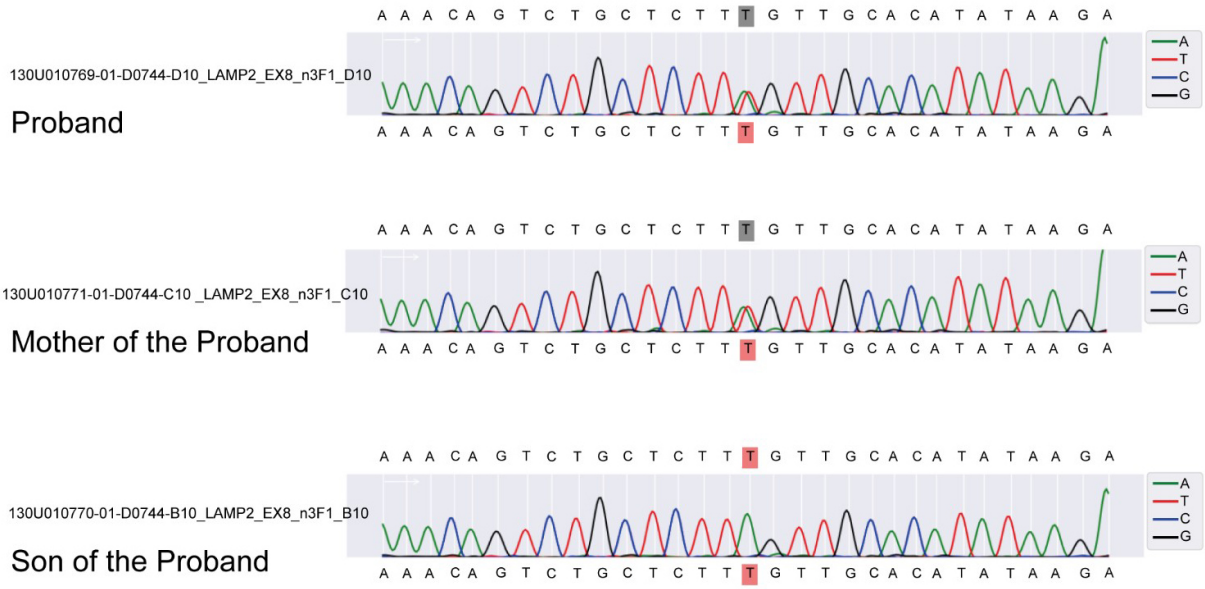

Fig. 4. Results of exon-gene sequencing of patient's family.

Abdominal paracentesis and drainage were performed for recurrent right heart failure and abdominal effusion. Because of the right atrial thrombus, rivaroxaban (15 mg) once daily was administered as an anticoagulant. Other medications included sacubitril/valsartan (50 mg) and torsemide (10 mg) twice daily, while bisoprolol fumarate (2.5 mg), amiodarone (200 mg), and spironolactone (20 mg) were administered once every day.

Discussion

An X-linked dominant genetic disorder, Danon disease is an autophagic vacuolar myopathy that manifests milder symptoms in females, compared to males [1]. This case described a patient with ventricular arrhythmias, the right ventricular outflow tract dilatation, and right atrium thrombus. While cardiac magnetic resonance imaging (MRI) helped to diagnose arrhythmias and cardiomyopathies [3], our patient did not undergo an MRI before ICD implantation. Moreover, this is the first documented instance of Danon disease, manifesting as ARVC.

Danon disease is associated with an enhanced risk of arrhythmias [4,5], ranging from ventricular pre-excitation and atrial fibrillation to ventricular tachycardia. Atrioventricular and bundle branch blocks are less common. This elevated arrhythmic risk is likely due to the *LAMP2* gene mutations. This results in myocardial cell dysfunction, as well as structural alterations like cardiac hypertrophy and fibrosis [6]. These factors can impair cardiac function and cause heart enlargement as well as heart failure. Additionally, the fibrous ring's extensive destruction in Danon disease creates an enlarged atrioventricular bypass tract [7]. However, our patient did not show these ECG correlations; we observed first-degree atrioventricular and incomplete right bundle branch blocks, respectively. Moreover, the right ventricular outflow tract's dilatation might have contributed to atrioventricular conduction delay.

A nationwide study suggested that the predominant features of Danon disease in males and females are cardiomyopathy, muscle weakness, and intellectual disability as well as cardiomyopathy, respectively [8]. Males with Danon disease develop symptoms at an early age, often showing hypertrophic cardiomyopathy, similar to the patient's son. Conversely, females develop symptoms at a later stage, with manifestations as either hypertrophic or dilated cardiomyopathies [9–11]. These varied cardiomyopathy presentations might stem from dysregulated autophagy [12,13]. Specifically, *LAMP2* deficiency in Danon disease patients disrupts cellular autophagy and causes overproduction of glycogen-filled intracellular vacuoles as well as other undigested cytoplasmic components, thereby causing cardiac cell hypertrophy. As seen in our patient's right ventricular enlargement, Danon disease can present as dilated cardiomyopathy, where progressive cardiac cell death and fibrosis cause muscle loss, weakened heart contractions, ventricular wall thinning, and chamber enlargement [10].

Until this instance, there was no explicit discussion of the benefits of anticoagulation therapy for Danon disease [1]. Our patient's substantial right atrial thrombus was likely linked to atrial arrhythmias; however, the right cardiac chambers' enlargement might have exacerbated blood stasis. Furthermore, the ICD implantation might have potentially increased the risk of thrombotic complications in the right-sided cardiac circulation. Hence, we prescribed rivaroxaban (15 mg) once daily as an anticoagulant to address these risks and ensure compliance.

Considering the patient's recurrent right heart failure, she was advised to have a heart transplantation. However, the patient refused this because of financial constraints. The prognosis for heart transplantation in Danon disease is similar to other conditions mandating heart transplantation. Hong KN *et al*. [14] reported an average left ventricular ejection fraction (LVEF) of 30% in 38 Danon disease patients with heart transplantation, indicating moderate to severe heart function impairment, with the youngest recipient being 15 years old. The increasing incidence of Danon disease has prompted the usage of several treatment approaches. Additionally, left ventricular assist devices (LVADs) are used in cases of unavailability of heart transplant donors. Kuroda K *et al*. [15] have described a case of a Danon disease patient who showed initial positive adaptation after LVAD implantation. However, LVAD implantation was not considered in our patient due to the presence of right heart failure.

Conclusions

This case underscores the crucial role of family medical history and genetic testing in the diagnostic process. For patients showing a familial predisposition to cardiomyopathy and various related clinical features, genetic testing is indispensable for establishing a definitive diagnosis. Hence, we should understand that Danon disease can also present as ARVC beyond the traditional findings of left ventricular hypertrophy or dilation.

Availability of Data and Materials

All of the material is owned by the authors and/or no permissions are required.

Author Contributions

DS, JY, GT, YX and GP participated in the conception and design of the study, data collection or analysis, and discussion and finalization of the manuscript. All authors have participated sufficiently in the work. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors 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.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki. For our article, we have got the written approval of participants and obtained rapid approval from the Ethics Committee of Yueyang Central Hospita. Ethics Approval No. (2024-053) from Yueyang Central Hospital.

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Conflict of Interest

The authors declare no conflict of interest. Guowei Tu is serving as one of the Editorial Board members of this journal. We declare that Guowei Tu had no involvement in the peer review of this article and has no access to information regarding its peer review.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.8125.

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