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Cardiac Magnetic Resonance Imaging in Danon Disease Cardiomyopathy

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Danon disease (DD) is a rare, X-linked and highly penetrant vacuolar myopathy caused by the Lysosomal-Associated Membrane Protein-2 (LAMP-2) primary deficiency (1). The cardiomyopathy is the most common and high-risk manifestation of DD which can present with sudden cardiac death, arrhythmias and early-onset heart failure. DD cardiomyopathy is often misclassified as sarcomeric hypertrophic cardiomyopathy (HCM) in young boys and underrecognized in females who can present with isolated HCM or dilated cardiomyopathy (DCM) (2). Identifying DD may aid selection for ICD implantation, heart transplant and targeted gene therapy development (3).

The Natural History of Danon Disease is a global multi-center observational study approved by the University of California, San Diego Institutional Review Board (4). The largest DD cohort with cardiac magnetic resonance (CMR) to date is hereby presented (n=12, male 5 [42%], median age 13 yrs [10-15], BMI 23 ± 5 kg/m^2). DD diagnosis was performed with genetic testing and confirmed on muscle biopsy in genetic variants of uncertain significance. CMR scans were anonymized, centralized and analyzed by an experienced reader blinded to demographic and clinical parameters.

Phenotypical sex differences (**Figure, panel A**) and a particular pattern of extensive late gadolinium enhancement (LGE) with mid interventricular septum sparing (**Figure, panel B**) may help distinguish DD from other cardiomyopathies. While DD in males typically presents at a young age with various degrees of cardiac disease, myopathy and intellectual disability (1), heterozygotes females have variable X-linked expression and can present later in life without extra-cardiac symptoms, making their diagnosis additionally challenging (5). Recognizing DD imaging characteristics can aid clinical suspicion of this heterogeneous genetic syndrome.

The most frequent DD cardiomyopathy manifestation was LV hypertrophy (LVH) either isolated in 8 or with LV dilation in 2 (**Figure, panel A**). The remaining 2 DD patients had normal CMR. In DD males, LVH was typically concentric (3 in 4 males with LVH) with normal LV systolic function (ejection fraction [EF] 61 ± 5 %). Females presented with asymmetric LVH (5 in 6 with LVH), right ventricular hypertrophy and two different phenotypes: HCM (4 females) or DCM phenotype (2 females). Eleven DD had gadolinium-based contrast administered. Of these, 3 showed no LGE. All remaining (8, 73%) had various LGE patterns and distributions but LGE was always sparing the mid septum. Extensive LGE consistently sparing the mid septum may represent a specific sign of DD cardiomyopathy (**Figure, panel B**).

These findings define a crucial role of CMR imaging in DD. The proposed sex-related phenotypes and LGE sign may aid the difficult identification of DD cardiomyopathy.

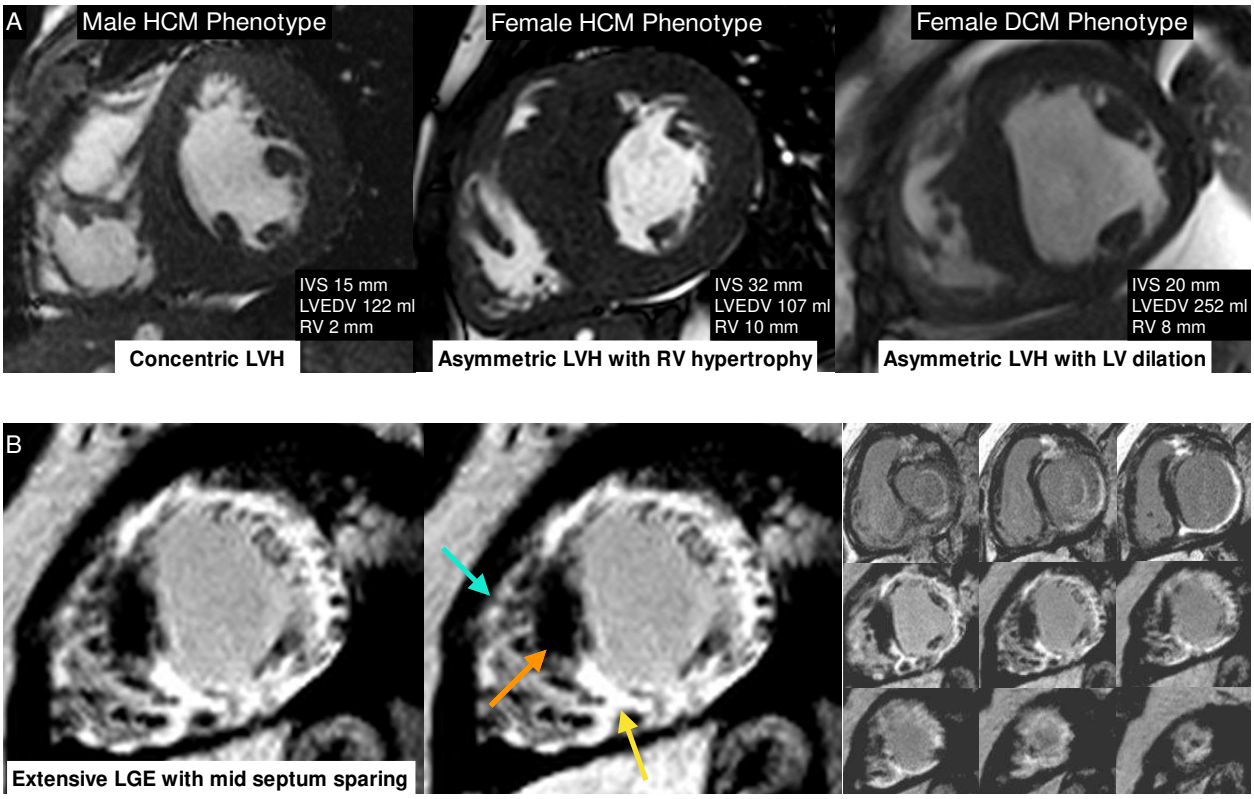

Figure. Proposed cardiac magnetic resonance (CMR) sex-related phenotypes and imaging sign of Danon Disease (DD) cardiomyopathy.

Panel A: The 3 sex-related phenotypes of DD cardiomyopathy are presented in the short-axis mid ventricular slice of three example patients. Concentric left ventricular hypertrophy (LVH) was the most common phenotype in males (*HCM phenotype – male*, 15y/o). Asymmetric LVH was more common in females and associated with right ventricular (RV) hypertrophy (*HCM phenotype – female* 12y/o). LV dilation with systolic dysfunction was present only in females (*DCM phenotype – female* 14y/o). *Panel B:* Late gadolinium enhancement (LGE) short-axis images in an example female DD with DCM phenotype. Although DD cardiomyopathy had various LGE patterns and distributions, LGE was always sparing the mid interventricular septum (**orange arrow,** 100% of LGE patients – proposed specific DD sign). Other common characteristics were the presence of LGE at the LV-RV insertion points (**yellow arrow**, 75% of

LGE patients) and RV-LGE in females (**blue arrow**). The presented CMR characteristics may help rise DD imaging suspicion in DCM and HCM phenotypes.

HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; LVH: left ventricular hypertrophy; IVS: interventricular septum thickness; RV: right ventricular free wall thickness; LVEDV: left ventricular end-diastolic volume. LGE: late gadolinium enhancement.

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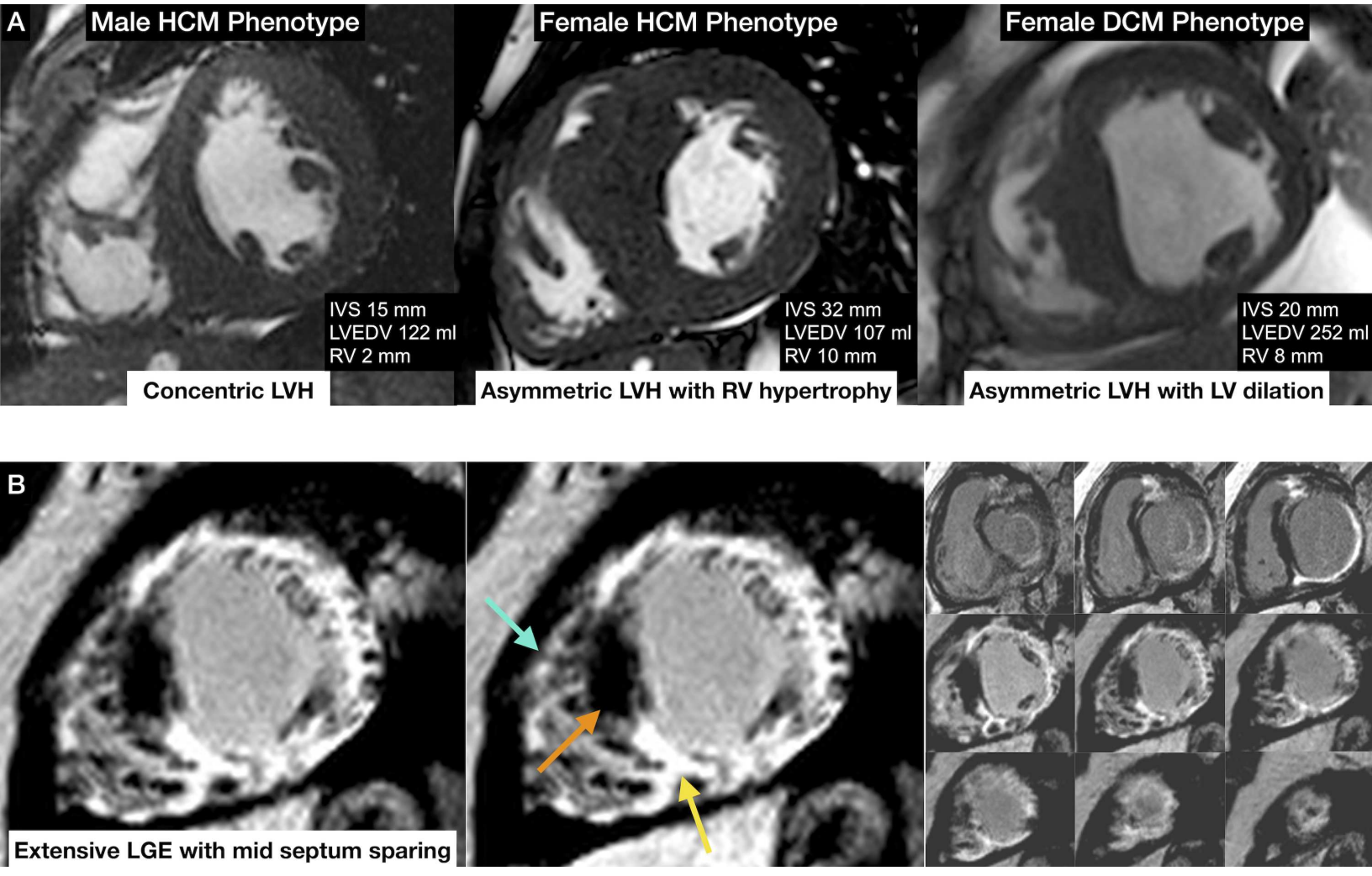
A
Male HCM Phenotype
IVS 15 mm
LVEDV 122 ml
RV 2 mm
Concentric LVH
Female HCM Phenotype
IVS 32 mm
LVEDV 107 ml
RV 10 mm
Asymmetric LVH with RV hypertrophy
Female DCM Phenotype
IVS 20 mm
LVEDV 252 ml
RV 8 mm
Asymmetric LVH with LV dilation
B
Extensive LGE with mid septum sparing