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Retinol binding protein 4 as a screening biomarker for hereditary TTR amyloidosis in African American adults with *TTR* V142I

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The *TTR* V142I variant (previously known as V122I), associated with hereditary transthyretin amyloidosis (hATTR), is the most common *TTR* variant worldwide, with recent prevalence estimates of 1 in 330 individuals (1). Up to 4% of African American (AAs) in the U.S. are heterozygous for V142I (i.e., V142I+) (2), which, in part, is thought to explain the observation that cardiac amyloidosis (CA) is four times more common among AA than European descent patients over 60 years of age (3). .Non-cardiac clinical features of hATTR such as carpal tunnel syndrome, spinal stenosis and polyneuropathy ("red flags") can precede CA by several years, and have been observed in undiagnosed V142I+ individuals absent heart failure (HF) symptoms (4). Nevertheless, the clinical diagnosis of hATTR in V142I+ individuals is typically only made after they develop overt CA and HF.

Retinol binding protein 4 (RBP4) is a lipocalin retinol carrier that binds 1:1 with transthyretin in serum, functioning as an endogenous transthyretin stabilizer (5). Circulating RBP4 levels depend on the interaction of RBP4 and transthyretin, and are reduced in hATTR. RBP4 levels have been shown to discriminate between V142I CA and non-CA HF in AA patients 60 years or older when integrated with other clinical parameters (6). However, RBP4 has not been studied in undiagnosed or younger V142I+ individuals without CA to inform preclinical hATTR. Here, we hypothesized that RBP4 levels would differentiate younger undiagnosed V142I+ individuals without overt CA from V142I- individuals, indicating circulating destabilized transthyretin and potentially enabling earlier risk prediction for hATTR.

V142I+ and V142I- individuals were identified from the Bio*Me* Biobank in NYC, which links exome sequencing to longitudinal electonic health record (EHR) data (2, 4), and

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includes banked plasma samples from participants at enrollment. We obtained plasma from 40 self-reported AA V142I+ individuals without any diagnosis codes related to cardiomyopathy, HF, or amyloidosis (heart healthy). V142I+ individuals were aged 40–60 years at enrollment, were 60% female, and 50% had at least one red flag (based on diagnosis codes related to carpal tunnel syndrome, spinal stenosis, and polyneuropathy). V142I+ individuals were age-, sex-, and race-matched with 80 heart-healthy V142I- individuals from Bio*Me*. We conducted manual chart reviews blinded to V142I status, and excluded 9 individuals (2 V142I+ and 7 V142I-) who had evidence of HF, significant valvular disease, or reduced (≤ 50%) ejection fraction. Plasma samples were randomized and analyzed in duplicate for target protein concentrations using a solid phase sandwich enzyme linked immunosorbent assay for human RBP4 (Quantikine ELISA kit, R&D Systems, Minneapolis, MN, USA). All samples were assayed in technical duplicate and standards were included for calibration of readouts against both positive and negative controls. Optical density measurements from ELISA readouts were converted to concentrations (ng/mL) using the standard curve generated during the assay run. Values more than three standard deviations from the mean were excluded from analyses. A two-tailed Student's t-test (heteroscedastic) was used to compare distributions of protein expression.

We analyzed RBP4 levels from 111 (38 V142I+ and 73 V142I-) heart-healthy AA individuals aged 40–60 years. Mean RBP4 levels were significantly lower in V142I+ *vs.* V142I- individuals (N=106; 18.89 μg/mL vs. 24.69 μg/mL, $P=1.1\times10^{-4}$), and this difference was observed in both females (N=61; 17.05 μg/mL vs. 23.54 μg/mL, $P=6.8\times10^{-4}$) and males (N=45; 21.41 μg/mL vs. 26.25 μg/mL, $P=3.4\times10^{-2}$; Figure 1A). Mean RBP4 levels were similarly low among V142I+ individuals with and without red flags (18.12 μg/mL *vs.* 19.65 μg/mL, P=0.43, Figure 1B). Although the exact relationship between RBP4 and destabilized transthyretin in hATTR is not known, pathogenic variants in *TTR* such as V142I, which destabilize transthyretin, may increase RBP4 clearance (6). Our findings suggest that circulating destabilized transthyretin may be elevated in young V142I+ individuals preceding CA and even preceding non-cardiac red flags related to hATTR. Given this, RBP4 could be more useful to identify presymptomatic V142I+ individuals at risk of hATTR than clinical screening for red flags alone. This study extends upon previous findings that RBP4 levels can discriminate between hATTR and non-amyloidogenic HF in older AA individuals, and identifies RBP4 as a potential biomarker for hATTR in younger individuals and those without CA.

hATTR diagnosis is frequently missed or delayed in AA individuals harboring V142I, which potentially contributes to worse HF outcomes. With the emergence of new hATTR therapies, strategies for screening and early detection of disease are paramount. In the ATTR-ACT trial comparing efficacy of the transthyretin stabilizer tafamidis against placebo in CA, the overall positive outcome of reduction in all-cause mortality and cardiovascular-related hospitalizations was driven by the response in the least symptomatic group (those with NYHA Class 1 or 2 HF) (7). These observations have led experts to propose use of tafamidis in V142I+ individuals as early as possible. Noninvasive tools are needed to enable early identification of preclinical hATTR when treatment is likely to be most efficacious. RBP4 levels were previously found to be lower in individuals with hATTR-CA compared to those with non-CA HF; here, we show that RBP4 levels are lower in undiagnosed V142I+

individuals without CA compared to matched V142I- individuals. RBP4 may serve as a useful biomarker to signal preclinical hATTR, permitting early diagnoses and expedited care delivery in patients at high genetic risk of HF, especially in AA populations where there is an urgent need to address existing health disparities. Longitudinal studies are needed to define the discriminative capacity of RBP4 for predicting red flag and CA manifestations of hATTR.

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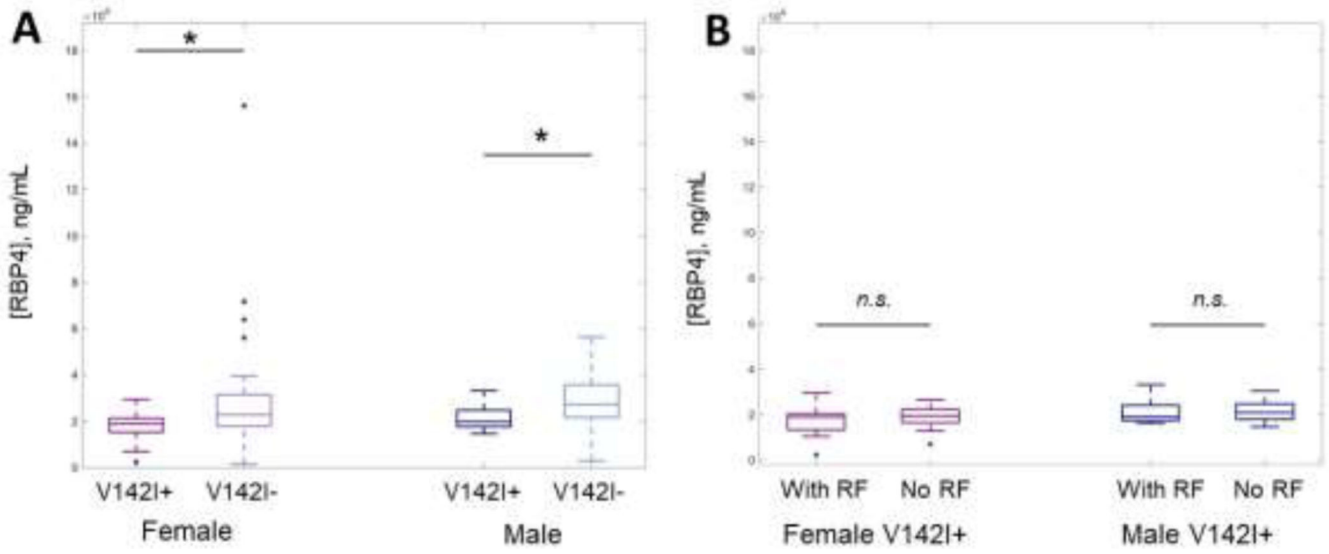

Figure 1.

A) Retinol binding protein 4 (RBP4) concentrations in African American individuals harboring *TTR* V142I (V142I+) are significantly lower than in age-, sex- and race-matched V142I-individuals; B) RBP4 levels are similar in V142I+ individuals regardless of presence/absence of red flag (RF) diagnoses. † $P < 0.001$; * $P < 0.05$; n.s. = not significant.