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Expanding cohort of individuals with p.V142I homozygous alterations suggests presentation onset similar to heterozygotes

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Introduction

Hereditary transthyretin amyloidosis (hATTR) is a progressive autosomal dominant multisystem disease caused by the abnormal formation and extracellular deposit of transthyretin protein fibrils in various tissues, including the cardiovascular, nervous, and ocular organ systems. Pathogenic alterations in the *TTR* gene result in a misfolding of the transthyretin protein and lead to the accumulation of abnormal fibrils throughout the body. hATTR can present in a spectrum of phenotypes. Specific disease-causing *TTR* alterations tend to associate with one of three broad phenotypes: polyneuropathy amyloidosis, cardiac-dominant amyloidosis, and leptomeningeal amyloidosis. Recent advances in disease treatment have resulted in slowing down the progression of nerve cell damage, decreasing cardiovascular mortality and hospitalizations, and improving quality of life. An accurate and early diagnosis of hATTR is crucial to achieving optimal patient outcomes. One pathogenic alteration associated with a cardiac-dominant amyloidosis subtype, p.V142I (also known as V122I), is carried by approximately 3% of Black individuals, making hATTR the cause of a substantial portion of cardiomyopathies in this population. Given the relatively high prevalence of this alteration, individuals with homozygous p.V142I genotypes have been reported as having a more severe and earlier onset of disease compared to p.V142I heterozygotes; however, these reports have been limited by small, predominantly male cohorts. Here, we aim to report on the clinical and demographic characteristics of a cohort of patients with p.V142I who were enrolled in the COMPASS hATTR genetic testing program to compare heterozygote vs homozygote characteristics and determine if there is a difference in manifesting symptoms and age of onset.

Methods

We retrospectively reviewed testing outcomes and clinical features submitted on testing requisition forms for genetic testing of patients in the United States and Canada with clinical suspicion of hATTR or a family history of hATTR. Individuals underwent one of three genetic tests as chosen by their clinicians as determined by their presenting features. Genetic test offerings include an 81-gene panel associated with inherited neuropathies, a 92-gene panel

associated with inherited cardiovascular disorders, or a targeted analysis of the *TTR* gene. Individuals with homozygous V142I, heterozygous V142I, and other pathogenic or likely pathogenic (P/LP) alterations in *TTR* were analyzed for demographic and reported clinical features. Age of onset was available for a subset of patients (n=311). Statistical analysis was run by Fisher Exact test or Chi-square.

Results

In total, we identified 43 individuals with homozygous *TTR* p.V142I alterations, 980 individuals with *TTR* p.V142I in the heterozygous state, and 205 individuals with other P/LP *TTR* alterations. Other commonly recurrent P/LP alterations identified include p.T80A (n=64) and p.V50M (n=49) (see table 1).

We compared individuals who were homozygous for p.V142I to individuals who were heterozygous for p.V142I and found homozygotes had an earlier average age at testing (testing 64.84 years homozygotes vs. 67.62 years heterozygotes) and an earlier average age of onset (58.92 years homozygotes vs. 60.94 years heterozygotes), but these differences were not statistically significant (p=0.473 for reported age of onset before 50 years and p=0.3614 for onset before 60 years). Individuals with non-p.V142I P/LP alterations did have a significantly earlier onset (p=0.0002, OR = 3.12 (95% CI: 1.69 -5.76), for reported onset before 50 years) compared to individuals with p.V142I in a homozygous or heterozygous state. We further compared non-p.V142I P/LP alterations vs. any zygosity of p.V142I by gender. In males, there is no difference in age of onset (p=0.15, OR = 1.92, 95% CI: 0.79-4.69). However, in females, non-p.V142I P/LP carriers had a significantly earlier onset compared to any p.V142I carriers (p=0.0001, OR =5.11, 95% CI: 2.11-12.38), suggesting females with p.V142I alterations present later than their male counterparts.

Cardiac features (p<0.001) and imaging or histological evidence of amyloid (p<0.001) were reported more commonly in both p.V142I homozygotes and heterozygotes compared to individuals with non-p.V142I alterations; however, there was no significant difference between homozygotes and heterozygotes (p=0.105 for cardiac features and p=0.077 for imaging/histological evidence). Sensory neuropathy was more commonly reported in individuals with non-p.V142I P/LP alterations (p=0.0006).

Conclusions

Homozygous p.V142I was the fourth most common molecular diagnosis in this cohort, accounting for a substantial portion of individuals with molecularly confirmed hATTR. This data suggests that p.V142I homozygotes present earlier compared to heterozygotes as previously

reported, but the difference may not be significant. Age of onset in females with p.V142I alterations is later than in females with other hATTR-causing alterations. Genetic testing can impact clinical management and accurate recurrence risk counseling. Family members of individuals with hATTR are at risk for developing features of hATTR, and therefore should be screened and managed appropriately.

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Table 1: Number of individuals with reported *TTR* pathogenic/likely pathogenic alterations

Number of individuals	**980**	**64**	**49**	**43**	**8**	**7**	**6**	**5**	**4**	**3**	**2**	**1**
Pathogenic/likely pathogenic TTR alteration(s)	V142I (het)	T80A	V50M	V142I (hmz)	P44S	I127V	F84L I88L S97Y	D58A T80I V52A	L78H S70R	E81A I104S V40I	E109V E81G F53L G67A G67V H108R L32V	A101V A117S A140S A45S A65V D38G D38N D58H E109K E74Q F64S S97F Y98F