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Genotype-phenotype correlation in a large cohort with HSPB1-related neuropathy

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HSPB1 has three domains: N-terminal (1-87aa), alpha-crystallin (ACD) (88-168aa), and C-terminal (169-205aa). In vitro studies show that variants in N-terminal might be less severe than variants in ACD and C-terminal. We performed a genotype-phenotype correlation study in patients with CMT due to heterozygous pathogenic variants in HSPB1.

We retrospectively gathered a minimal dataset of information in patients with pathogenic variants in HSPB1 at baseline and follow-up visits, across seven Italian centres and UCL (UK), including type of variant, motor milestones occurrence, and CMTES.

We included 106 patients with HSPB1-related neuropathy followed up for 9.2±4.8 years (276 visits overall): 43 patients had pathogenic variants in N-terminal domain, 50 in ACD, and 13 in C-terminal.

Disease onset occurred earlier in patients with variants in C-terminal (33±11.4 years), followed by those with variants in ACD (39±9.5), and N-terminal (48±10.8) (p=0.023).

We found that variants in N-terminal were associated to milder disease (CMTES 4.5±2.5), compared to those in the ACD (6.4±4.1) and C-terminal domain (7.4±4.4) (p=0.008). Accordingly, 28% and 26% of patients with variants in ACD and C-terminal, respectively, used AFOs (vs 9% of those with variants in N-terminal, p=0.040), 32% and 17% used stick (vs 6% p<0.001), 8% and 8% were wheelchair-bound (vs 0%, p=0.040), 40% and 42% had difficulties with buttons (vs 15%, p=0.014), and 29% and 27% presented with proximal weakness (vs 9%, p=0.032).

Similarly, disease progression (ΔCMTES/year) showed a direct gradient of severity from N-terminal (0.33/year), to ACD (0.55/year), and C-terminal (0.70/year) (p=0.040). Mean time from disease onset to stick use was 9 years for variants in C-terminal, 15 years for those in the ACD, and 32 years in the N-terminal domain.

Variants in ACD and C-terminal domain are associated to earlier disease onset, more rapid progression and severe disease burden compared to variants in N-terminal.