

Multigene panel for thrombophilia testing in chronic thromboembolic pulmonary hypertension

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Background: The contribution of inherited thrombophilia to chronic thromboembolic pulmonary hypertension (CTEPH) remains uncertain. Conventional testing for antithrombin, protein C, and protein S deficiencies and factor V Leiden and prothrombin G20210A variants identifies abnormalities in only 10 to 20% of CTEPH patients. Multigene panels allow broader evaluation of the coagulation system and have shown promise in acute venous thromboembolism, but their additional value in CTEPH remains unknown.

Aims: We aimed to characterize findings from a multigene thrombosis and hemostasis panel in unselected patients with CTEPH and compare its diagnostic yield with conventional thrombophilia testing.

Methods: We prospectively tested patients with CTEPH at the University Hospitals Leuven, Belgium, between July 2025 and February 2026, using a panel of 33 diagnostic-grade genes involved in thrombosis and hemostasis. Results were compared with conventional testing.

Results: We included 100 CTEPH patients (median age, 61.5 years [IQR, 51.5–71.0]; 51% women). Sixty-one had a history of acute venous thromboembolism. Conventional thrombophilia testing was positive in 23 patients, in 7 of whom results were likely affected by anticoagulation. The multigene panel identified 58 variants in 46 patients (46%): 29% carried at least one (likely) pathogenic variant, whereas 17% carried only variants of uncertain significance (Fig.1A). Variants in multiple genes were identified in 9% of patients (Figure 1B). The most frequently affected genes were *F2*, *F5*, *PROS1*, and *JAK2* (Fig.1C). Among 77 patients with negative conventional testing, the panel identified genetic variants in 27 (35%), including (likely) pathogenic variants in 12 (16%) (Fig.1D). Among 23 patients with positive conventional testing, the panel provided additional information in 13 (57%), by excluding false-positive conventional results or identifying additional variants (Fig.1E).

Conclusion: Multigene panel testing revealed variants in coagulation-related genes in nearly half of patients with CTEPH, supporting a genetic contribution to CTEPH.

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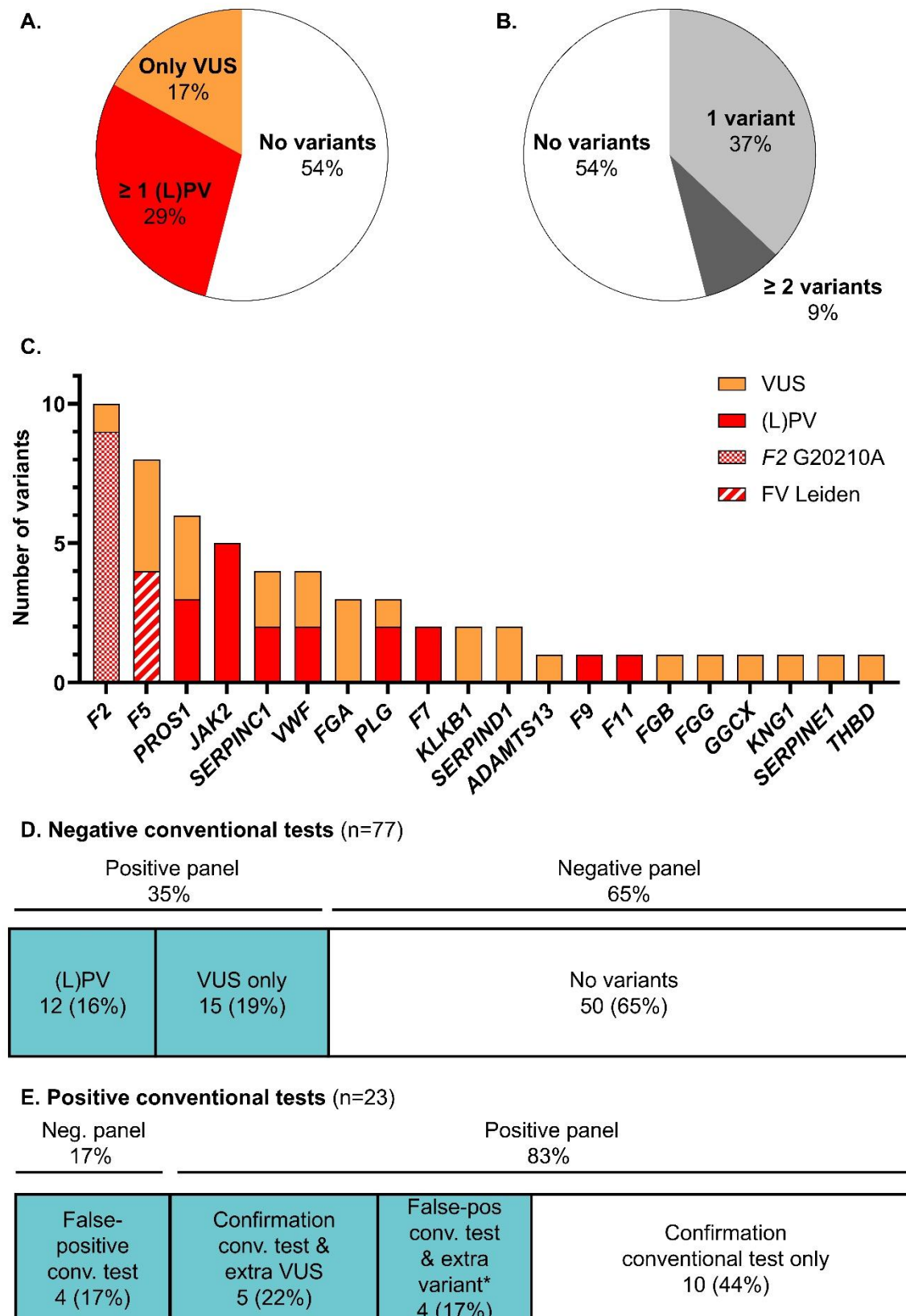


Figure 1. Multigene panel testing in CTEPH. A. Patients with ≥ 1 pathogenic or likely pathogenic variant ((L)PV), only variants of uncertain significance (VUS), or no variants. B. Number of variants per patient. C. Distribution of all 58 variants by gene and classification. D–E. Panel results in patients with negative (n=77) and positive (n=23) conventional tests. Blue indicates added diagnostic information from the panel.