Analysis of family histories suggests shared genetic risk for chronic thromboembolic pulmonary hypertension and venous thromboembolism

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Abstract
Chronic thromboembolic pulmonary hypertension (CTEPH) and acute pulmonary embolism (PE) are related phenotypes, however, previous reports have suggested that genetic risk factors for CTEPH and PE differ. Here we report that a family history of VTE is equally frequent in individuals with CTEPH and PE, suggesting that shared genetic variants may influence risk of both phenotypes. We also provide the first estimate of the frequency of familial CTEPH, which we identified in 2.2% of CTEPH patients in our cohort.

KEYWORDS
genetic epidemiology, pulmonary embolism, pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a devastating complication that occurs in approximately 3% of survivors of acute pulmonary embolism (PE).¹ CTEPH is thought to occur due to incomplete resolution of pulmonary thromboembolism, although the pathophysiology is poorly understood.² Although CTEPH and acute PE seem to be related phenotypes, genetic data have called this relationship into question. Common genetic variants that influence the risk of venous thromboembolism (VTE), such as the Factor V Leiden variant (observed frequency in CTEPH 5.0%–8.8%) and Prothrombin G20210A variant (observed frequency in CTEPH 2.5%–7.7%), are uncommon in CTEPH patients.³–⁶ The Factor V Leiden variant specifically seems to be less common in CTEPH patients than in patients with acute PE,⁵ suggesting that CTEPH and acute PE may have different genetic risk factors.

Risk of VTE—especially VTE that is not associated with an environmental risk factor—is highly heritable, with genetic factors estimated to account for 50%–60% of the variability in VTE risk.⁷–⁹ Known hereditary thrombophilias for which clinical testing is commonly available account for approximately 5% of the genetic risk for VTE,¹⁰ highlighting the limitations of clinically available genetic thrombophilia testing. However, an individual’s family history of VTE is a powerful marker of genetic risk for VTE, which can integrate risk derived from genetic thrombophilias that are as yet unidentified and/or cannot be tested for clinically. A history of VTE in a first-degree relative increases an individual’s risk for VTE by about 2.5-fold,¹¹–¹³ roughly comparable to the increased risk of VTE conferred by being a heterozygous carrier of the Factor V Leiden variant.¹⁴ An individual’s personal VTE risk is increased further if one of their first-degree family members experienced VTE at a young age, or if the individual has two or more first-degree family members that have experienced VTE,¹²,¹⁵ as these situations appear to identify families that are more likely to have a genetic basis for VTE. Indeed, an individual with two or more first-degree relatives with VTE has a
personal risk of VTE that is increased 50-fold relative to an individual with no family history of VTE,\textsuperscript{12} a degree of VTE risk which is comparable to that observed in individuals with Antithrombin deficiency.\textsuperscript{16}

To date, no comprehensive analysis of familial VTE risk has been undertaken in patients with CTEPH, leaving open the question as to whether individuals with CTEPH and individuals with acute PE share a similar profile of genetic risk for VTE. To address this knowledge gap, we performed a detailed analysis of the family history of VTE and CTEPH in a cohort of patients with CTEPH, and in a matched cohort of patients with a history of acute PE who did not develop CTEPH.

The cohorts included in this study have been described previously.\textsuperscript{5,17} Briefly, we enrolled consecutive patients with a diagnosis of CTEPH (n = 91) who were seen in the pulmonary hypertension clinic at Intermountain Medical Center between 7/1/2015 and 6/30/2019. CTEPH was defined using the previous hemodynamic definition of mean pulmonary artery pressure (mPAP) \(\geq 25\) mmHg and pulmonary capillary wedge pressure (PCWP) \(\leq 15\) mmHg, as this study began before the release of new guidelines recommending a lower mPAP threshold. The control cohort consisted of consecutive patients with a history of acute PE (n = 157) who were not suspected of having CTEPH, who were enrolled during scheduled visits at either the thrombosis or pulmonary hypertension clinics at Intermountain Medical Center. As described previously,\textsuperscript{5,17} PE subjects were matched to CTEPH subjects on age at first diagnosed VTE event (\(\pm 5\) years), lifetime history of DVT, and history of VTE not associated with an environmental risk factor (referred to as unprovoked VTE), since these factors are known to influence the likelihood of an individual with VTE carrying an inherited thrombophilia.\textsuperscript{15,18,19}

All enrolled subjects underwent a detailed interview aimed at eliciting their family history of VTE and CTEPH. This information was then used to construct a medical family pedigree for each enrolled subject. Any reported family history of CTEPH was corroborated through a detailed review of the subject’s family member’s medical records, after obtaining proper permissions. Due to constraints related to patient privacy, subjects’ reports of family members’ VTE histories were not corroborated through review of medical records. The study protocol was approved by the institutional review board at Intermountain Medical Center (IRB_1024723).

The clinical characteristics of the CTEPH and PE cohorts used in this study have been described previously.\textsuperscript{17} The cohorts were both nearly evenly divided between males and females, and >90% of subjects in both cohorts were Caucasian. Among the CTEPH subjects, 60.4% had undergone pulmonary thromboendarterectomy surgery, and 3.3% had undergone balloon pulmonary angioplasty.

A history of VTE in one or more first-degree relative (s) was observed with equal frequency in the CTEPH and PE cohorts (CTEPH: 42.9%, PE: 40.8%, \(p = 0.75\)) (Table 1). The two cohorts also had similar frequencies of individuals with VTE in two or more first-degree family members (CTEPH: 18.7%, PE: 15.9%, \(p = 0.58\)), or in one or more first-degree family members who were diagnosed with VTE at age 50 years or younger (CTEPH: 24.2%, PE: 22.9%, \(p = 0.82\)). Because not all subjects in the CTEPH cohort had a history of acute PE before their diagnosis of CTEPH, we performed a sensitivity analysis focused on the subset of CTEPH patients with a history of prior acute PE. Among this subset of CTEPH patients (n = 71), the frequency of a history of VTE in one or more first-degree relative(s) did not differ significantly from that observed in the PE cohort (CTEPH: 39.4%, PE: 40.8%, \(p = 0.85\)).

A family history of CTEPH was observed in 2 patients in the CTEPH cohort and 1 patient in the PE cohort, yielding a frequency of family history of CTEPH of 2.2% for subjects in the CTEPH cohort, and 0.6% for subjects in the PE cohort (Table 1). The two familial CTEPH

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### Table 1: Family history of VTE and CTEPH among subjects in the PE and CTEPH cohorts

| First-degree relative(s) with VTE (%) | PE (n = 157) | CTEPH (n = 91) | \(p\)-value |
|-----------------------------------|-------------|---------------|-------------|
| \(\geq 1\) first-degree relative with VTE (%) | 40.8 | 42.9 | 0.75 |
| \(\geq 2\) first-degree relatives with VTE (%) | 15.9 | 18.7 | 0.58 |
| First-degree relative diagnosed with VTE at age 50 years or less (%) | 22.9 | 24.2 | 0.82 |
| First-degree relative with CTEPH (%) | 0.6 | 2.2 | 0.28 |

Note: \(p\)-values reported are for comparison between the CTEPH and PE cohorts, and use the Chi-square test for proportions.

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism; VTE, venous thromboembolism.
pedigrees identified in this study have not been reported previously and are depicted in Figure 1. In pedigree A, the enrolled CTEPH proband, who underwent pulmonary thromboendarterectomy (PTE) surgery, had a grandfather with a history of recurrent PE who was treated at an outside facility, and died of complications related to right heart failure, with CTEPH confirmed at autopsy. Multiple additional family members in pedigree A had a history of DVT and/or PE without known CTEPH. In pedigree B, the enrolled CTEPH proband had a brother diagnosed with CTEPH who was also treated at our center. Although both brothers were deemed to be operable, both opted not to undergo PTE surgery due to patient preference. The CTEPH proband in pedigree B also had a daughter with PE, but no other first-degree relatives are known to have had VTE.

In this study, we have found that patients with CTEPH report a history of VTE in first-degree relatives with a similar frequency as do carefully matched patients with a history of acute PE not complicated by CTEPH. This corroborates our earlier work showing a similar relative risk of VTE in first-degree family members of VTE and CTEPH patients, based on analysis of a large genealogical database. These data suggest that overall genetic risk for VTE is similar in patients with CTEPH and acute PE, supporting the notion that genetic risk factors are likely to be shared between these two phenotypes.

We also describe two new familial CTEPH pedigrees and provide the first estimate of the frequency of familial CTEPH, with a family history of CTEPH observed in 2.2% of CTEPH patients in our cohort. It should be noted that this is a low-confidence estimate of the frequency of familial CTEPH since it is based on only two individuals in our CTEPH cohort having a family history of the disease. Confirmation in a larger CTEPH population will be necessary. Both familial CTEPH pedigrees described herein contained additional family members with VTE who were not known to have CTEPH. In both pedigrees, the index CTEPH case tested negative for both the Factor V Leiden and Prothrombin G20210A variants. The same is true of a prior familial CTEPH pedigree reported by our group, but not included in this analysis. These findings support the notion CTEPH and VTE risk are influenced by shared genetic factors. The segregation of CTEPH in these three pedigrees suggests a dominant inheritance pattern with incomplete penetrance.

Based on the findings of this study, we hypothesize that CTEPH and PE represent a spectrum of phenotypes that may be caused by the same genetic variants. However, based on the aforementioned data regarding the lower frequency of the Factor V Leiden variant in patients with CTEPH compared to those with acute PE, some of these shared genetic variants may differentially effect the likelihood of expressing one phenotype (i.e., CTEPH) compared to the other (i.e., acute PE not complicated by CTEPH). Future studies will be aimed at utilizing these familial CTEPH pedigrees as a resource for the discovery of gene variants that might influence CTEPH risk.

**AUTHOR CONTRIBUTIONS**

Mark W. Dodson, Meghan M. Cirulis, and C. Gregory Elliott jointly conceptualized the research, analyzed and interpreted the data, and wrote the manuscript.

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**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

**ETHICS STATEMENT**

The study protocol was approved by the institutional review board at Intermountain Medical Center (IRB_1024723). All subjects signed written informed consent.

**GUARANTOR**

MWD.
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