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Identifying Genetic Risk Factors for Chronic Thromboembolic Pulmonary Hypertension

INTRODUCTION AND BACKGROUND:

Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating condition caused by chronic obstruction of the pulmonary arteries by thromboembolic material arising from incomplete resolution of pulmonary embolism (PE). Existing data suggest that the majority of CTEPH cases go undiagnosed, and when a correct diagnosis of CTEPH is made there is often an unacceptably long diagnostic delay. There are two major reasons for this. First, CTEPH occurs in only a small percentage of PE survivors (approximately 3%), making screening of all PE survivors for subsequent development of CTEPH inefficient. Second, the mechanisms leading to incomplete thrombus resolution after acute PE are not well understood, and thus no clinically useful biomarkers of future risk of CTEPH have been identified.

The goal of this proposal is to identify genetic markers associated with CTEPH risk. These genetic markers could ultimately be integrated into a risk prediction model for CTEPH, which may improve case recognition by allowing for the triage of high-risk patients to more intensive surveillance for CTEPH after acute PE. In a recently published manuscript, our group has used the Utah Population Database (UPDB), a unique genealogical database that includes a majority of families in the state of Utah, to show that patients with CTEPH are significantly more related than would be expected by chance. These data provide the strongest evidence to date that genetic factors influence CTEPH risk. In this proposal, we aim to use unique Utah genetic resources to gain further insight into the types of genetic variants that are associated with CTEPH, and then use both candidate-based and unbiased screening methods to identify CTEPH predisposition genetic variants.

HYPOTHESIS:

The unifying hypothesis of this proposal is that genetic factors influence CTEPH risk, and that these genetic factors are distinct from the common inherited thrombophilias that influence the risk of acute uncomplicated VTE. We hypothesize the existence of a set of genetic variants that specifically predispose to VTE events that do not resolve and thus predispose to CTEPH. This set of genetic variants contrasts with the common inherited thrombophilias (including the Factor V Leiden mutation), which we hypothesize predispose to VTE events that are likely to resolve and thus unlikely to lead to CTEPH.

SPECIFIC AIM 1:

Determine the frequency of the Factor V Leiden mutation in patients with CTEPH and in carefully matched patients with acute uncomplicated PE in whom CTEPH is not suspected.

SPECIFIC AIM 2:

Use the UPDB to determine whether CTEPH high risk pedigrees are also VTE high risk pedigrees, and whether probands from these pedigrees carry common inherited thrombophilias.

SPECIFIC AIM 3:

Use a powerful pedigree-based whole genome sequencing approach to identify and validate novel candidate genetic variants underlying CTEPH risk in Utah high risk CTEPH pedigrees.

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