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# Genetically Identifying the "Thromboembolic" in Chronic Thromboembolic Pulmonary Hypertension

In this issue of the *Journal*, Liley and colleagues (pp. 1477–1485) report the largest genome-wide association study (GWAS) to date of patients with the rare disease of chronic thromboembolic pulmonary hypertension (CTEPH) (1). In a European and American endeavor, a total of almost 2,500 patients with CTEPH were recruited and genotyped for variants previously identified in the general population. More than 10,000 control subjects from Europe were used in a case-control analysis to tease out those variants enriched in patients with CTEPH compared with control subjects. The resulting genomic hits were ranked by *P* values. These were then coanalyzed together with *P* values retrieved from a GWAS of U.K. biobank patients with self-reported pulmonary embolisms or deep vein thrombosis (DVT) and with previously published GWAS results from patients with pulmonary arterial hypertension (PAH) (2).

The analysis of CTEPH samples on their own in comparison with control samples revealed a strong association with a SNP within the *ABO* blood group gene. Non–O-blood groups are a known risk factor for CTEPH development (3). Further genome-wide significant hits included the genes *FGG* (fibrinogen) and *F11* (coagulation factor XI), well known from the coagulation cascade. These findings lend credibility to the employed method because they are flagging known risk factors and genes related to thrombus formation. The same regions for the genes *ABO*, *FGG*, and *F11* were also identified in patients with pulmonary embolisms without CTEPH, already highlighting a shared underlying pathology.

A novel finding exclusively identified for patients with CTEPH was a GWAS hit near the *HLA-DRA* gene from the class II major histocompatibility complex. Given the role of inflammation in CTEPH pathobiology (4), these findings direct attention to a specific HLA gene. Its involvement in the CTEPH pathobiology could be explored in future studies. Interestingly, the neighboring *HLA-DPA1/DPB1* region on chromosome 6 also belonging to the class II major histocompatibility complex was the most significant hit of the previously published GWAS of patients with PAH (2).

When the CTEPH GWAS *P* values were coanalyzed in a second step with those from patients the U.K. biobank with self-reported pulmonary embolisms and/or DVT, further genes within the coagulation cascade were highlighted, such as *F2* (thrombin) and *F5* (factor V Leiden). Overall, these results seem almost expected and are reassuring, given the fact that roughly two-thirds of patients with CTEPH had a pulmonary embolism and more than one-third had a DVT before CTEPH diagnosis (5). The recent FOCUS study (Follow-Up after Acute Pulmonary Embolism: A Prospective Observational



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Multicenter Cohort Study) revealed a 2.3% incidence of CTEPH development up to 2 years after a pulmonary embolism (6), closely tying these disease entities together. In the present study, there was unfortunately no subcohort analysis of those patients with CTEPH with previous pulmonary embolisms or DVT. It would have been interesting to see whether this patient subset had shown an even greater genetic similarity to the DVT/pulmonary embolism cohort without CTEPH. In addition, the authors elegantly estimated the genetic similarity or correlation by linkage disequilibrium score regression between the pulmonary embolism and CTEPH cohorts, which again confirmed a significantly shared genetic basis.

In contrast, no genetic correlation could be identified for patients with PAH and patients with CTEPH. The PAH GWAS data were based on 2,085 patients with idiopathic, heritable, or anorexigen associated PAH (2). These results are a little surprising because PAH and CTEPH, both forms precapillary pulmonary hypertension, are both at least partly and to different degrees characterized by microvasulopathy and *in situ* thrombosis (3). The vessel occlusion in PAH, however, is driven largely by abnormal cell proliferation, migration, and apoptosis (7) and not by organized thrombotic material as seen in CTEPH (5).

Although Liley and colleagues could not reveal genetic similarities between CTEPH and PAH, this could also be due to limitations of the method. GWASs are based on previously described, preselected genetic variants. Thus, by design, rare, novel variants will not be considered in the analysis. Although risk factors for pulmonary embolisms and DVT can be as common as factor V Leiden mutation present in 2% of the population, idiopathic and heritable PAH are frequently caused by rare and novel pathogenic genetic variants absent in any control population (8). Thus, only a sequencing approach and not a genotyping approach could have revealed a potential enrichment of pathogenetic variants in shared genes such as the bone morphogenetic protein receptor 2 (*BMPR2*) gene. However, until today, only very few patients with CTEPH have been reported with *BMPR2* mutations (9) or familial aggregation (10). Because reoccurring pathogenic variants in *BMPR2* in unrelated patients with PAH are the exception, a shared haplotype to be picked up by a GWAS would have been very unlikely.

Overall, Liley and colleagues report novel GWAS signals such as the HLA region and confirm a genetic similarity of patients with CTEPH and patients who experienced pulmonary embolisms and/or DVT. The ongoing debate about potentially shared pathobiological features of PAH and CTEPH has received additional fuel; however, this cannot be conclusively clarified by the presented GWAS analysis and remains to be explored in future studies. ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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