Application of Clinical and Molecular Phenotyping to Pulmonary Hypertension Using the TriAxia Health Platform

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Rationale: TriAxia Health, an Illumina Accelerator enterprise dedicated to improving outcomes for rare disease patients, has, working with 5-academic pulmonary vascular disease programs, built a pilot version of their TriAxia Rare-disease Analytics Platform (TRAP) in Pulmonary Hypertension (PH). The platform combines clinical data with DNA and RNA isolated and sequenced from blood obtained from patients during right-heart catherization. The resulting data set integrates both longitudinal clinical and molecular data, offering a unique opportunity to better understand correlative biological and clinical aspects of PH. Methods: Enrollees underwent deep phenotyping including history and physical examination, cardiac and chest imaging, pulmonary function and six-minute walk testing, or exercise testing with gas exchange, and right heart catheterization. All blood samples were obtained at the time of right heart catheterization. RNA was bulk-sequenced and analyzed using limma with duplicate correlation. Genes with adjusted p-value <0.05 were considered significant. Results: To date, 650 patients have been enrolled, and 553 patients with PH had longitudinal clinical data, DNA (Whole Exome) and RNA processed. Differential expression contrasts of all five PH groups against healthy controls generated 5 down-regulated and 9 up-regulated genes (Figure 1). Of these, MAN1A1, involved in glycosylation, is up-regulated in PH compared to healthy controls (logFC of 0.37, adj.p<0.01). Most notably, MAN1A1 is shown up-related when separately comparing group-1 PAH (pulmonary arterial hypertension) and group-3 PH (due to lung disease) to healthy controls (logFC=0.36, adj.p<0.01 and logFC=0.39, adj.p<0.05, respectively). Conclusions: Advanced glycation end products (AGE) and its receptor (RAGE) and soluble RAGE (sRAGE) have been shown to be involved in the pathogenesis of PAH; here we find that it is a consistent marker in PAH and PH caused by lung disease. Since RAGE causes BMPR2 and PPARγ downregulation, promoting PAH‐PASMC proliferation, we speculate that the MAN1A1 gene is involved in the pathophysiology of groups 1 and 3. The long-term design is to bring all PH patients from these five health systems into the platform generating the most comprehensive database available in PH

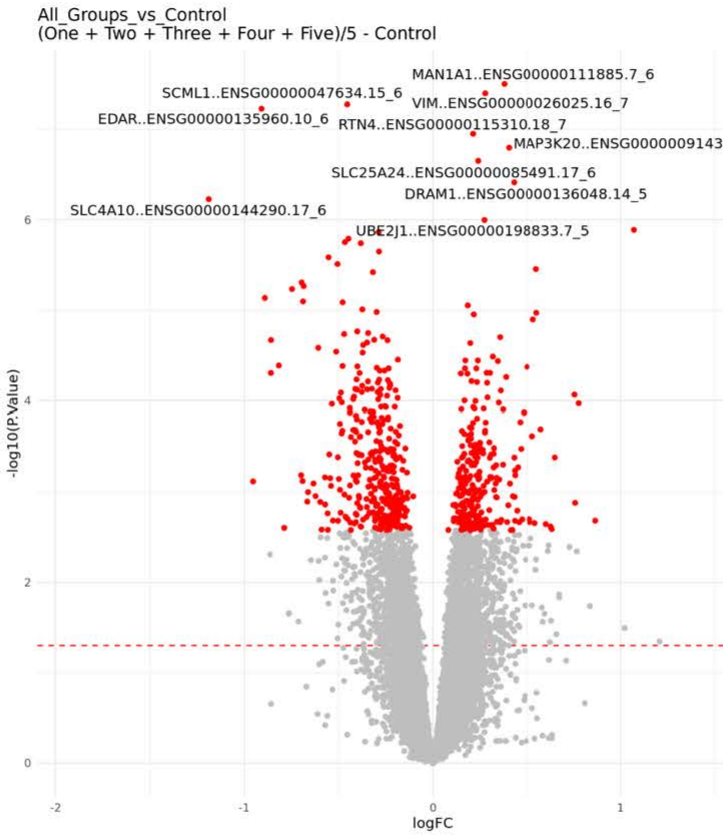

Figure 1. Differential expression of all 5 PH groups vs healthy controls. indicate gene with both large magnitude fold-changes and high statisti

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