

Genetic, systemic and ophthalmic basis of vascular pathology in primary open angle glaucoma

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Glaucoma is the leading cause of irreversible blindness worldwide. The etiology of primary open angle glaucoma (POAG), the most common type of glaucoma in the US, is multifactorial and includes vascular dysfunction. Although genetic, systemic and ophthalmic studies separately support pathology contribution of vascular dysfunction to POAG, direct clinical evidence is lacking. Our previous work has demonstrated that both systemic and ophthalmic microvascular systems can be abnormal in patients with POAG. Furthermore, we showed a significant correlation between systemic and ophthalmic vascular pathology suggesting that a common etiology, such as genetic risk factors, may underlie vascular dysfunction relevant to glaucoma. Recently, 4 genes involved in vascular development have been associated with glaucoma, including POAG.

For this proposal, **we aim to establish a direct genotype-phenotype association of vascular pathology in POAG.** We will image the systemic and ophthalmic microvasculature in POAG patients and control subjects with existing genome-wide genotype data and determine if the severity of vascular pathology correlates with a genetic risk score (GRS) comprised of genetic variants from the POAG susceptibility loci involved in vascular development. We will also assess disease progression in POAG patients with the highest GRS quartile compared to those in the lowest quartile. The Harvard Catalyst grant will provide support for personnel and imaging costs. This study will define the role of vascular dysfunction in POAG and determine if disease-associated genetic variants are correlated with vascular abnormalities and progressive disease. Ultimately regulation of vascular function could be a novel therapeutic target for this blinding disease.