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EXECUTIVE SUMMARY

Highlights of the 13th International Hereditary Hemorrhagic Telangiectasia Scientific conference

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The 13th International Hereditary Hemorrhagic Telangiectasia (HHT) Scientific Conference, held in San Juan, Puerto Rico, June 13–16 2019, was a gathering of clinicians, scientists, and patients focused on understanding, treating and curing this uncommon, underdiagnosed disease. HHT is characterized by development of cutaneous and mucosal telangiectases and solid organ arteriovenous malformations (AVMs), which can lead to epistaxis, anemia, stroke, or high-output heart failure [1]. HHT is an autosomal-dominant disease caused by mutations in *ENG* (HHT1), *ACVRL1* (encoding ALK1; HHT2), or rarely, *SMAD4* (JP-HHT). These proteins function in bone morphogenetic protein (BMP) signaling in endothelial cells.

Although no new causal genes were presented at this conference, Wooderchak-Donahue identified mutations in non-coding regions of *ENG* and *ACVRL1* that altered splicing, including a mutation hotspot in *ACVRL1* intron 9. There was consensus that this locus should be added to HHT genetic screening panels to improve diagnostic sensitivity.

The myriad clinical complications and varied presentations of HHT conspire to make these patients underdiagnosed, incompletely screened, and/or undertreated. Advances in clinical screening and treatment that were presented at this conference will improve this situation. A retrospective analysis of serious adverse events (SAEs) in children with HHT or suspected HHT suggested that screening children under 16 for pulmonary AVMs (PAVMs) with clinical assessment and pulse oximetry may be sufficient to identify children at risk for SAEs. Every child who suffered an SAE attributable to a PAVM had a screening SpO2 below 93%, and the majority of those had diffuse PAVMs.

MRI is emerging as a diagnostic modality of choice for liver and lung AVMs. The ability to measure flow through liver AVMs using phase contrast flow MRI and 4D flow techniques suggests that these tools may prove useful in monitoring response to therapy, and MR imaging of PAVMs is approaching the sensitivity of CT scans, without the risk of radiation. Another advance was the use of grayscale contrast echocardiography for PAVMs, which may eliminate the need to count bubbles as a quantitative measure of intrapulmonary shunting and may standardize the classification of PAVMs. Finally, the recognition of additional complications of HHT, such as hepatic encephalopathy and subaortic membranes, is rounding out the clinical description of this disease.

Sclerotherapy, as well as topical application of propranolol, tacrolimus, etamsylate, timolol, and bevacizumab, show promise in reducing epistaxis frequency and blood transfusion dependence. Results from trials of both local and systemic treatment are encouraging. The PATH study, examining the utility of oral pomalidomide in HHT, is about to launch and will be the first NIH-sponsored clinical trial for HHT patients. The tyrosine kinase inhibitor pazopanib is also showing promise. Reports on the efficacy of systemic bevacizumab, tranexamic acid, doxycycline, tacrolimus, nintedanib, and octreotide were discussed or planned.

Although repurposed drugs show some promise in treating HHT patients, there are currently no medications that directly target ENG-ALK1 signaling or AVM development, in part due to limited mechanistic understanding. Regarding ligand, two groups presented BMP10-deficient animal models, that, unlike BMP9-deficient models, exhibit HHT-like

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phenotypes. Choi demonstrated that global *Bmp10* depletion leads to retinal AVMs in neonates and wound-induced skin AVMs in adults. Capasso presented a zebrafish *bmp10/bmp10-like* double mutant that develops embryonic AVMs identical to *acvrl1*-mutants, and a *bmp10* mutant that exhibits vascular lesions in skin and liver and high-output heart failure in the juvenile-to-adult period. Arthur presented a somewhat similar phenotype in *Eng*-inducible knockout (iKO) adult mice, characterized by pelvic AVMs and high-output heart failure. As such, despite the biochemical redundancy of BMP9 and BMP10 as ALK1 ligands, BMP10 is emerging as the required ENG-ALK1 ligand pertinent to HHT. Additional advances in understanding ALK1-ENG signaling were presented by Kim, who reported that ENG overexpression failed to rescue AVM phenotypes in *Acvrl1*-iKO mice, while ALK1 overexpression inhibited AVM development in *Eng*-iKO mice. These data support the idea that ENG and ALK1 act in a linear signaling pathway.

Taken together, these new data regarding ENG-ALK1 signaling, combined with the promising preclinical results of BMP9 treatment for pulmonary arterial hypertension [2], suggest that enhancing ALK1 expression or BMP10-induced ALK1 signaling in HHT patients may have therapeutic potential. However, based on results presented by Snellings and Shaligram, ligand-based therapy may not be appropriate for all HHT patients. Snellings presented compelling data showing that HHT lesions are caused by somatic second hits (Fig. 1). In telangiectases, he identified low-frequency somatic mutations in the same gene as the causal germline mutation and showed that independent lesions from a single-patient harbor-independent somatic mutations. This finding suggests that a somatic mutation in the remaining wild-type copy of the inherited mutant gene is a necessary event in AVM genesis. In support of this idea, Shaligram presented evidence of clonal expansion of *Acvrl1*-null endothelial cells in brain AVMs. If null endothelial cells generated by somatic mutation do indeed seed HHT lesions, then ligand-based therapies may be appropriate for HHT1 patients but not for HHT2 and JP-HHT patients who lack the transmembrane signaling receptor or intracellular signaling mediator, respectively. Moreover, questions regarding effectiveness of ligand administration in the presence of high concentrations of circulating endogenous ligand and concerns regarding potential ligand toxicity will need to be addressed.

In sum, the outcome of this international gathering of HHT experts resulted in an impressive exchange of ideas, new insight into disease mechanisms, and improved approaches to diagnostic screening and therapy that will immediately translate to better care for HHT patients and ultimately lead to a cure for this vascular disease.

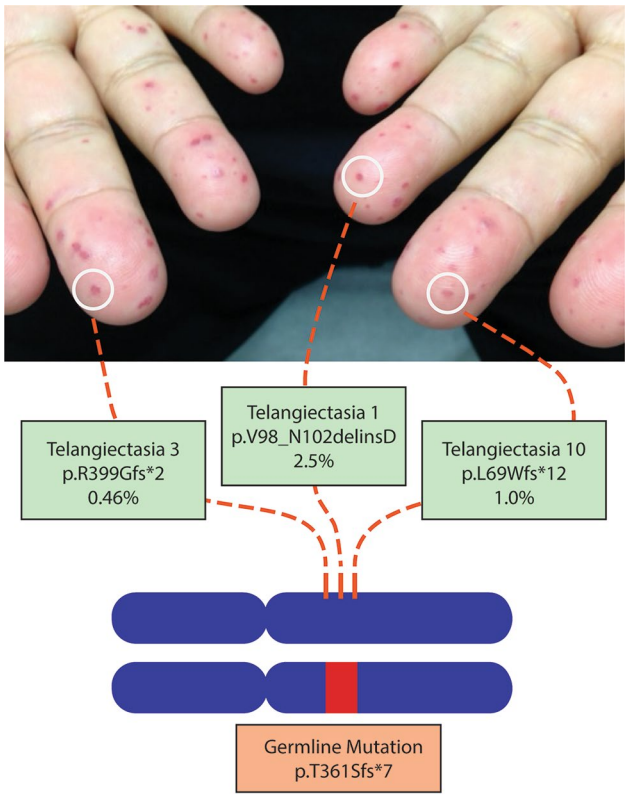

Fig. 1 Independent somatic mutations were found at low frequency (0.6–2%) in different telangiectases in an HHT patient with a germline *ENG* mutation

References

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