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Exome Sequencing Defines the Molecular Pathogenesis of Vein of Galen Malformation

Daniel Duran; Jungmin Choi; Xue Zeng; Charuta G. Furey; Jonathan Gaillard; Jinwei Zhang; Carol Nelson-Williams; Michelle Sorscher; Julio D. Montejo; Jennifer Klein; Charles C. Matouk; Joseph M. Zabramski; Andrew F. Ducruet; Darren Orbach; Edward R. Smith; Beverly Aagaard-Kienitz; Georges Rodesch; Alejandro Berenstein; Murat Gunel; Richard P. Lifton; Kristopher T. Kahle

Introduction

Vein of Galen malformations (VOGMs) are morbid and often lethal developmental arteriovenous malformations, with poorly described genetic underpinnings (1). Despite improvement in endovascular treatment, mortality from this disease remains high (2). VOGM has been reported as a rare finding in Capillary Malformation-Arteriovenous Malformation Syndrome (*RASA1*; OMIM #605384) and Hereditary Hemorrhagic Telangiectasia (*ENG, ACVRL1*; OMIM #187300 and #600376, respectively) (3-4). This paucity of genetic data results from intrinsic limitations of patient recruitment in a frequently deadly disease, and constraints of traditional targeted genomic techniques. Collaborative recruitment and unbiased whole-exome sequencing (WES) are poised to overcome these barriers.

Methods

Germline DNA was isolated from 50 unrelated probands harboring radiographically-confirmed VOGMs. Both parents were available for 48/50 probands. Targeted exome capture, followed by paired-end WES was performed on DNA samples from all participating individuals (n=148). Data was bioinformatically analyzed to identify rare de-novo and transmitted mutations, and short insertions/deletions. Unbiased binomial analysis tested for exome-wide statistical significance of mutational burden. Transient transfection of constructs harboring VOGM mutations in HEK293 cells followed by immunoprecipitation and immunoblotting were performed.

Results

Mutations in previously reported VOGM-associated genes were found in only 2/50 patients (4%; *RASA1* n=1; *ACVRL1* n=1) in our cohort. Exome-wide significant enrichment of rare damaging mutations was found for a member of the EPHB receptor tyrosine kinase family (**Fig 1**; n=4; 8%; p = 3.64x10-7, 72.12-fold enrichment). Novel damaging mutations were found in five other genes of the ephrin family, and in a close paralog of the HHT-causing *ACVRL1*, never previously implicated in human disease. In vitro assays demonstrate VOGM-related EPHB mutants exhibit reduced tyrosine autophosphorylation and Ras GAP binding (**Fig 2**), leading to dysregulated RAS/MAPK/ERK1/2 and PI3K/AKT/mTORC1 signaling (**Fig 3**).

Figure 1. EPHB4 mutations in VOGM

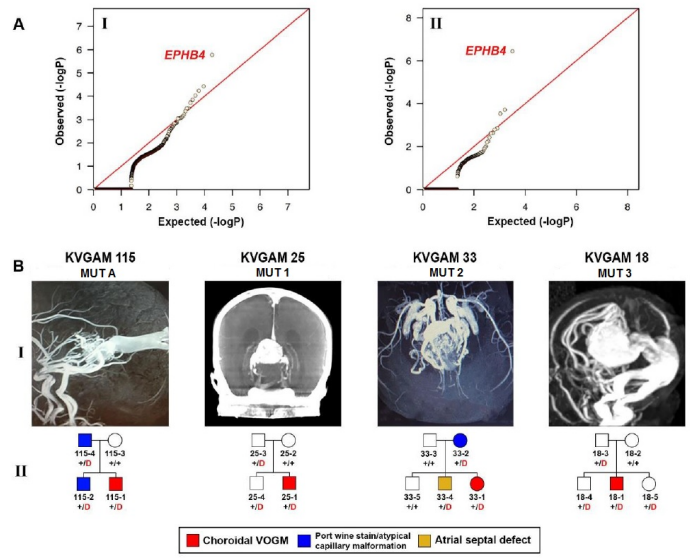
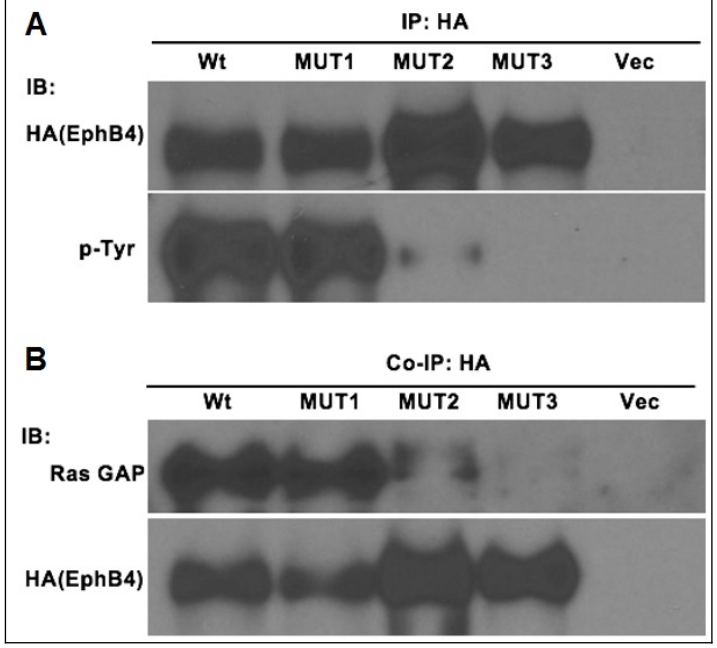


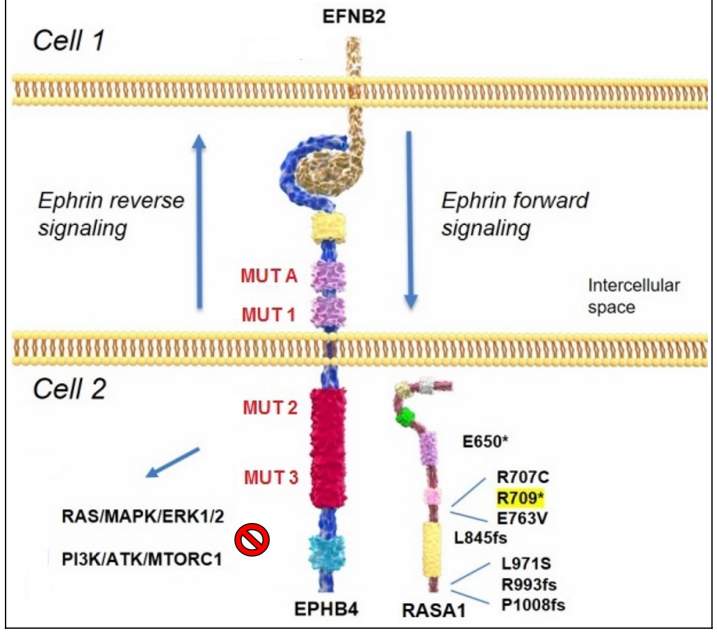
Figure 2. Biochemical implications of EPBH4 mutation



Conclusions

This work represents the largest phenotyped and exome-sequenced VOGM cohort in the world. Our findings uncover genetic determinants and molecular mechanisms of VOGM pathogenesis, provide novel insight into vascular developmental biology, and identify potential therapeutic targets.

Figure 3. Ephrin signaling dysregulation in VOGM



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