

Somatic Mutations in Vascular Malformations

by

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Department of Molecular Genetics and Microbiology
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Date: _____

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Michael Hauser

Timothy Reddy

Craig Lowe

Dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in the Department of Molecular Genetics and Microbiology
in the Graduate School of Duke University

2021

ABSTRACT

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Abstract

Write your abstract here. You should not include references or mathematical notation.

If you want to dedicate your thesis to anyone do so here

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List of Abbreviations and Symbols

Symbols

Put general notes about symbol usage in text here. Notice this text is double-spaced, as required.

\mathbb{X}	A blackboard bold X . Neat.
\mathcal{X}	A caligraphic X . Neat.
\mathfrak{X}	A fraktur X . Neat.
X	A boldface X .
X	A sans-serif X . Bad notation.
X	A roman X .

Abbreviations

Long lines in the `sympollist` environment are single spaced, like in the other front matter tables.

AR	Aqua Regia, also known as hydrochloric acid plus a splash of nitric acid.
SHORT	Notice the change in alignment caused by the label width between this list and the one above. Also notice that this multiline description is properly spaced.
OMFGTXTMSG4ME	Abbreviations/Symbols in the item are limited to about a quarter of the textwidth, so don't pack too much in there. You'll bust the margins and it looks really bad.

Acknowledgements

Thank anyone you like here. It's good practice to thank every granting agency that's given you money since you've been ABD, any other school you visited during your research, and any professional society that's funded your travel.

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Introduction

1.1 Vascular Malformations

1.1.1 Common Genetic Mechanisms

1.2 Hereditary Hemorrhagic Telangiectasia

1.2.1 Genetics

1.2.2 Signaling of ACVRL1, ENG, and SMAD4

1.2.3 Relationship with Sporadic Arteriovenous Malformations

1.3 Sturge-Weber Syndrome

1.3.1 Mosaic Mutation of GNAQ p.R183Q

1.3.2 Function and Activity of GNAQ

1.3.3 Mutation of GNAQ in Other Diseases

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1.4.3 Two-Hit Mechanism

1.4.4 Signaling of the CCM Complex and its Downstream Effectors

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Two-Hit Mechanism of Hereditary Hemorrhagic Telangiectasia

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2.2.2 Somatic and Germline Mutations are Biallelic

2.2.3 Mutations are Consistent with Homozygous Loss of Function

2.2.4 Telangiectasia from the Same Individual Harbor Unique Somatic Mutations

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2.3.3 Necessary, but Not Sufficient

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2.3.5 Mutant Cell Metastasis

2.3.6 Two-Hit Mechanism for SMAD4 & JP-HHT

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DNA and RNA Extraction

Targeted Sequencing

Mutation Detection

Establishing Phase

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Reverse-Transcription PCR

Mutant *GNAQ* Alleles Produce Distinct Disease Phenotypes

- 3.1 Premise
- 3.2 Results
- 3.3 Discussion
- 3.4 Methods

MAP3K3 Mutations Seed Cerebral Cavernous Malformations

- 4.1 Premise
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5.3.3 Role of Clonal Expansion in Mutagenesis

5.3.4 Therapeutic Implications

5.3.5 Distinct Properties of PIK3CA vs. CCM/MAP3K3 Mutations

5.4 Methods

CCM Collection

Brain AVM Collection

DNA Extraction

Droplet Digital PCR

SNaPshot

Sequencing

Sequence Analysis

Single-Nucleus DNA Sequencing

Statistics

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Conclusion

6.1 Model for HHT Pathogenesis

6.2 Model for CCM Pathogenesis

6.3 Contribution of Somatic Mutations to Non-Cancer Diseases

Appendix A

Probability of Multiple Somatic Mutations

Biography

Your biography is limited to one page and must contain

1. Full name
2. Date and place of birth
3. Every degree you've earned, including this one, and where you earned it from.

Mostly, that information is to narrow down which John Smith wrote that dissertation on the mating habits of sea cucumbers. Sexy!

You may also include

1. Any awards you've won related to your discipline since your undergraduate degree.
2. Any fellowships you've held
3. Anything you've published (papers, books, book chapters). Don't be afraid to cite it here, so that the full bibliographic record of your article appears in the bibliography!
4. Where your next job will be, if you know