Clinical Aspects of the CCM1 Common Mutation

Connie Lee, Psy.D.
President and CEO
Angioma Alliance

The Baca Family Historical Project
Genetics of the Common CCM1 Mutation

23 pairs of Chromosomes

One from each parent

CCM1 Common Mutation is on one copy of chromosome 7
Autosomal Dominant Inheritance Pattern

DAD HAS THE CONDITION

MOM DOES NOT HAVE THE CONDITION

WORKING GENE

NON-WORKING GENE

CHILDREN DO NOT HAVE THE CONDITION

50% OF CHILDREN DO NOT HAVE THE CONDITION

50% OF CHILDREN HAVE THE CONDITION

CHILDREN HAVE THE CONDITION
A Founder Mutation as a Cause of Cerebral Cavernous Malformation in Hispanic Americans

Murat Günel, M.D., Issam A. Aweid, M.D., Karin Finberg, B.S., John A. Anson, M.D., Gary K. Steinberg, M.D., Ph.D., H. Hunt Batjer, M.D., Thomas A. Kopitnik, M.D., Leslie Morrison, M.D., Steven L. Giannotta, M.D., Carol Nelson-Williams, B.S., and Richard P. Lifton, M.D., Ph.D.


Cerebral cavernous malformation is a vascular disorder of the brain characterized by abnormal vascular spaces lined by a single layer of endothelium without intervening neural parenchyma or identifiable mature vessel-wall elements. There is almost always evidence of prior hemorrhage, characterized by the accumulation of hemosiderin. This disease was recognized as a common clinical entity after the advent of magnetic resonance imaging (MRI), which demonstrates a characteristic lesion of variable signal intensity surrounded by a dark ring attributable to hemosiderin (Figure 1A and Figure 1B). Before the introduction of MRI, patients with cavernous malformation were typically classified as having an idiopathic seizure disorder or an angiographically occult vascular malformation. Both MRI and autopsy studies suggest a prevalence of cavernous malformation of 0.5 percent, although the prevalence of symptomatic disease is much lower.

Symptomatic disease typically begins in the third through fifth decades of life. Treatment ranges from therapy with antiepileptic drugs in patients with seizures to surgical excision of accessible lesions in patients with recurrent hemorrhage or intractable seizures.

Although the pathogenesis of cavernous malformation is unknown, a familial...
Losing the KRIT1 Protein

• There are many places in the body where KRIT1 plays minor or no role.

• But in capillary blood vessels in brain and spinal cord, it keeps junctions tight between endothelial cells.

• Without KRIT1, cavernous angiomas (cavernous malformation, cavernoma) form.

• Mulberry-shaped, thin-walled, leaky malformations. Slow blood flow.
Symptoms that lead to diagnosis

- Seizure – 50%
- Hemorrhage – 25%
- Focal Neurological Deficit – 25%

More than 20% of cavernous angiomas are discovered without symptoms. This number is growing with increased use of MRI and genetic testing.

At least half of those with the Common CCM1 Mutation never have a symptom.
When to consider MRI or genetic testing

- Focal seizures – uncontrolled movement in a limb or the face, smelling something that’s not there, staring.
- Limb weakness, tingling, burning
- Vision issues – double vision, jumpy vision, eye turning in, loss of part of visual field
- Balance or coordination problems, dizziness that won’t stop
- Facial paralysis that resembles Bell’s Palsy
- Diaphragm spasms (resemble hiccups) that continue for extended period. This is an emergency.
- Projectile vomiting, loss of consciousness are also emergencies.
General Symptoms That Overlap with Other Disorders

- Headache
- Fatigue
- Attention issues
- Learning disability
- Memory issues
- Social skills deficits
New Lesion Formation

- People with the Common CCM1 Mutation will develop more lesions over time.
- Average rate is 0.4 new lesions/year, so average 64-year-old will have 24 lesions.
- But, there is wide variation not always reflected in symptoms. Some older adults have 1 lesion and some have hundreds.
Why be diagnosed?

Actions that may help reduce risk of hemorrhage

- **Gut bacteria**, may have a direct impact on the number of lesions that develop and, possibly, on how active the lesions are.
- It is important to protect the lining of the gut to prevent bad bacteria from entering the system.
- To do this, reduce or eliminate **chemical preservatives and emulsifiers**.
- Chemicals like polysorbate-80, mono- and diglycerides, and carrageenan can compromise the mucous lining, making it more likely that bad bacteria will enter the system.
Why be diagnosed? Actions that may help reduce risk of hemorrhage

- Sleep apnea may have an impact on new lesion development.
- Mice with a CCM1 genetic mutation who were oxygen-deprived developed more lesions.
- In humans, this scenario is similar to sleep apnea.
- If there are symptoms of sleep apnea, it’s even more important for someone at risk for CCM1 to undergo a sleep study.
Why be diagnosed?

Actions that may help reduce risk of hemorrhage

- Vitamin D – make sure level is not low
- Cholesterol – not too high, but not too low (bad cholesterol)
- Weight – not too low
- Stay away from blood thinners like aspirin, unless benefit outweighs risk
- Reduce other controllable causes of inflammation, like smoking or flu
- Contact sports, roller coasters, hormonal birth control? Jury is out.
Access to Future Preventative Treatment

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<th>Category</th>
<th>Pre-Clinical</th>
<th>Phase One</th>
<th>Phase Two</th>
<th>Phase Three</th>
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Benefits

• Health monitoring for yourself and your family
• Early access to preventative treatments
• Reduce risk of misdiagnosis of symptoms which can lead to wrong and possibly harmful treatments or no treatment. Especially important for children.
Genetic Testing: What to Consider

Considerations

- Am I prepared to follow up with medical monitoring? We can help connect you to the UNM CCM Center of Excellence and our peer support groups in Albuquerque and other areas.
- Am I prepared to talk to my family? Genetic counseling is available at UNM and elsewhere.
- Is there a potential for impact on other areas: life insurance, military service?
Determine Your Risk By Completing and Submitting a Bowtie Pedigree Chart
Thank You!

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