



# Angioma Alliance Newsletter

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Editor: Connie Lee

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Please note: In this newsletter, the terms “cavernous angioma” and “cavernous malformation” are used interchangeably.

**El angioma cavernoso**  
Información para los  
pacientes y sus familias



 107 Quaker Meeting House Road  
Williamsburg, Virginia 23188  
[www.angiomaalliance.org](http://www.angiomaalliance.org)  
[info@angiomaalliance.org](mailto:info@angiomaalliance.org)

## Announcing Our New Spanish Site and Brochure

We are very pleased to announce that the Angioma Alliance website, support forum, and brochure are now available in Spanish. Through the work of Norma Villa, our newest board member, and Wendy Burk, a professional translator, we are able to provide information to Spanish-speaking people affected by cavernous angioma both in the US and abroad.

To access our Spanish site, select the En Español choice on our main menu or go to [www.angiomaalliance.org/Espanol](http://www.angiomaalliance.org/Espanol). You may order the Spanish version of our brochure through the order form on the main page of our English site or through the order form on our Spanish site.

## Update of Latest Research Results

### The CCM2 gene has been identified!

Researchers at Duke University have announced the identification of the second of three genes responsible for the familial form of cavernous angioma. The team used the blood donations and MRI results of 27 families who did not have the KRIT1 mutation, but appeared to have the familial form of the illness. They painstakingly sequenced possible candidate genes in the area of chromosome 7 where the responsible gene was known to exist (7p15-p13). The team was able to identify 9 families of the 27 who had a mutation on a gene known as MGC4607. This gene is responsible for the production of a newly discovered protein which the Duke researchers have named malcavernin (using portions of the words malformation and cavernous). The function of this new protein is not yet known.<sup>1</sup>

It's a long way from gene identification to treatment, but the identification of CCM2 and its associated protein malcavernin gives researchers another approach to the problem. With time, researchers will be able to look at the KRIT1 protein and the malcavernin protein to see how they influence cavernous angioma cell development. It is likely that both proteins are part of the same system. The identification of the second gene and protein should speed up the process of understanding how this system functions.

Clinical testing is not yet available, but blood samples sent to the Duke University as part of a study enrollment can now be screened for the CCM2 mutation. The CCM2 mutation is thought to be the cause of the illness for 20% of individuals with familial cavernous malformations. The Duke researchers were struck by the fact that, of those individuals who had the CCM2 mutation, nearly 40% had no symptoms. This emphasizes the importance of broader blood screening for mutations, including among those who believe they have the sporadic form of the illness. It also highlights the need for MRI's to be performed on asymptomatic family members in families where the familial form of the illness is known to exist.

### KRIT1 and the Mexican-American founder mutation

In another one of the more important studies published this year, researchers worked with blood samples from 206 families with cerebral cavernous malformations (cavernous angiomas) in order to understand gain a greater understanding of the KRIT1 mutation.<sup>2</sup>

A gene can mutate in any number of ways, all causing the gene to stop functioning properly. Of note in this study was the finding that among Mexican-Americans in the study 86% of those with known familial cavernous malformations, as well as the 59% with what had been thought to be sporadic mutations, had a mutation in the exact same place on the KRIT1 gene, indicating that all of these individuals can trace their heritage back to a common ancestor. This is called a founder mutation. The founder mutation was not found in Mexican subjects who had not immigrated to the US. This appears to indicate that the founder mutation began fairly recently in the US, rather than in Mexico.

Perhaps the most significant finding of the study was the discovery that among 22 Mexican-Americans who were thought to have the sporadic form of the illness, 13 (59%) actually had the familial KRIT1 mutation. There are a number of conclusions which can be drawn from this. The first conclusion is that even the familial form of the illness can remain relatively asymptomatic in a sizeable proportion of affected people. This being the case, it seems that more individuals who are believed to have the sporadic form of the illness may actually have the familial form than was previously suspected. There is no research yet to determine whether this might be true outside of the founder mutation, but there is also no reason to believe that this is not the case.

Finally, in looking at the many different ways that the KRIT1 gene can mutate, researchers saw that every type of mutation resulted in the KRIT1 gene losing its ability to function. This gives further support to the theory that a two-hit model is responsible for the development of cavernous malformations. In other words, familial cavernous malformations seemingly are caused when one copy of the KRIT1 gene has stopped working altogether, and the second copy of the gene has intermittently stopped working due to normal variations and mutations.

## Cavernous Malformations and Temporal Lobe Epilepsy

Cerebral cavernous malformations (CCMs) may appear anywhere in the brain, but they are most often found in the supratentorial region. This area includes the frontal, parietal, temporal, and occipital lobes as well as the thalamus, hypothalamus, and basal ganglia. Research has shown that 50 to 70% of supratentorial CCMs result in seizure disorders, and seizure is often the sole symptom in lesions of this location.<sup>3</sup> CCM-related seizures have a higher incidence than seizures induced by either arteriovenous malformations (AVMs) or gliomas. Additionally, CCM seizures are more likely resistant ("intractable") to medical therapy with antiseizure drugs .

The right and left temporal lobes are particularly vulnerable to seizure activity. There are a number of different types of seizure - the type of seizure most commonly associated with temporal lobe cavernous malformations are "simple partial" and "complex partial" seizures.

**Simple partial** – a type of seizure in which a person remains aware but is unable to stop their experience or behavior. The seizure behavior depends on the area of the brain affected. The seizure can result in such things as intense feelings, uncontrolled movements, vision problems, or speech problems. Simple partial seizures centered in the temporal lobe most commonly result in unexplained intense feelings.

**Complex partial** – a type of seizure in which there is a loss of awareness and the person engages in "automatisms" – behaviors such a chewing, swallowing, picking at clothes, or scratching. Seizures may "generalize" with frank loss of consciousness and convulsions, as a partial seizure spreads throughout the brain.

In each individual there are zones in the brain, called epileptogenic zones, which can cause seizure when irritated. The exact location of these zones is unique to each individual and is usually fairly small. Within each person, the locations of the zones remain stable over time. In other words, if an electroencephalogram (EEG) or magnetoencephalogram (MEG) were used to define the basic area of a person's

epileptogenic zone, this zone would not change or move over time.<sup>4</sup> Limitations of EEGs/MEGs, specifically placement of electrodes, make it impossible to define the exact boundaries of this zone within any give person.

Cavernous malformations can irritate epileptogenic zones, including those in the temporal lobes, in two different ways. First, cavernous malformations may exert pressure against an epileptogenic zone. Second, hemorrhages in cavernous malformations produce deposits of a substance called hemosiderin. Hemosiderin, a blood breakdown product, is a form of iron. These iron deposits do not go away, even if the cavernous malformation shrinks. If a hemosiderin deposit is in an epileptogenic zone, it can cause seizures.<sup>5</sup>

Once a seizure begins, it is not confined to the epileptogenic zone. Seizure activity spreads to a larger region which can be mapped using an EEG. Mapping these areas is helpful in generalizing the location of the epileptogenic zone and thus the origin of the epileptic seizure.<sup>3</sup> It's somewhat analogous to earthquake mapping where a seizure is akin to an earthquake of the brain. While an earthquake may be felt for hundreds of miles, the true epicenter of the quake may be determined from measurement locations quite distant from the epicenter itself.

Sometimes, epilepsy can result from sources other than cavernous malformation. Defining the boundaries of the epileptogenic zones can set the stage for determining whether a lesion, or some other process, is responsible for epilepsy. It's not as cut and dried as finding a lesion in one area and simply attributing epilepsy to the presence of the lesion alone. Other factors can play a role. These factors include such things as the number of lesions a person or the susceptibility/predisposition of the person to epilepsy. This susceptibility can vary greatly from person to person. For some people, the source of their epilepsy may never be determined.

In the absence of surgical removal of the lesion, the most effective treatment method is through the use of anticonvulsants. The prospect for seizure control is excellent in most cases. Anti-convulsants have developed to the point where it is easier to achieve seizure control with fewer side effects than in the past. Also, CCM induced epilepsy that is completely controlled by medication probably does not warrant surgery unless other factors (mass effect, hemorrhage, lesion history/stability, etc.) necessitate it.<sup>6</sup>

For those patients with truly intractable seizures or those who do not respond fully to medications, surgery is the primary solution. Unlike most other CCM removal procedures, surgeries performed to stop CCM related seizures include removing a portion of healthy brain tissue stained by hemosiderin irritant. Without removing this stained tissue, seizure control is not nearly as assured. Of course, removal of healthy tissue cannot occur if the tissue is involved in functioning, or "eloquent". Functional MRI or other diagnostic "brain mapping" may be used to delineate eloquent from non-eloquent tissue.<sup>7</sup>

Of note, venous angiomas, regardless of location, rarely result in seizure activity. If a person who previously had been seizure free suddenly experiences partial seizures, an MRI in conjunction with EEG/MEG is strongly recommended to ensure that a cavernous malformation is not the root cause of the problem.

## Acknowledgments

Our thanks to Dr. Issam Awad, head of our scientific advisory board, for his review of the information in the previous articles.

## Spotlight: Duke University Medical Center Cavernous Angioma Research Lab

On September 29<sup>th</sup>, 2003, Angioma Alliance board member Jack Hoch and I were able to spend the day at Dr. Doug Marchuk's cavernous angioma research laboratory at Duke University Medical Center in Durham, North Carolina. We learned an enormous amount, and we'd like to share some of it here.

The Duke University laboratory highly encourages anyone with a cavernous angioma to contact them for screening. When individuals or families enter the CCM study, their blood is first screened for the KRIT1 mutation (also known as "CCM1"). The Duke lab sends an individual's blood to the lab at the Barrow Institute for this portion of the screening. If the individual does have the KRIT1 mutation, he or she is informed of the finding and offered screening for additional family members. If the individual does not have the KRIT1 mutation, the familial form of the illness may still be suspected because the genes for CCM2 and CCM3 have yet to be identified.

How is the familial form of the disease diagnosed? Any of the following are indications that the familial form of the illness may be present:

1. an individual has multiple cavernous angiomas,
2. multiple family members are affected
3. there is a history of unexplained neurovascular disease in the family.

In these cases, the lab will encourage as many family members as possible to submit blood samples so that the lab can perform "linkage" studies to determine whether the family may be linked to one of the other two possible genetic mutations causing cavernous angioma, CCM2 and CCM3. These families are particularly important because the CCM2 and CCM3 genes have not been definitively identified. Their participation in this study may help this process to move more quickly and is a real contribution to the research.

We started our day with Tracey Leedom, the genetics counselor for the laboratory. Tracey is the first point of contact for those individuals or families who sign up to participate in the study or who simply have questions about it. When you call the Duke laboratory, Tracey is the one who takes your medical history, either on the phone or via email. She will send out a blood sample kit, free of charge, to you and your family members if they also become involved. Tracey assigns each family who participates in the study a number so that information within the lab remains anonymous. Only she and Dr. Marchuk have access to the family files.

Because of the participation of Angioma Alliance members, we have become an important source of referrals to the Duke study. Since May of this year, 9 new families have received blood sample kits in order to enroll. Three of the families have returned their kits. All families that have called the lab directly, rather than through their physician or genetic counselor, have learned about the Duke study through our site.

The greatest challenge for Tracey in her job is encouraging families to return blood sample kits once they've been distributed. As Tracey notes, most people are very busy in their daily lives and getting blood drawn requires extra time and effort. The study will reimburse individuals for any costs associated with blood draws, and provides the shipping materials to return the blood kits via pre-paid FedEx overnight.



Our second stop during the Duke research lab tour was with Christina Liquori, the post-doctoral fellow who is working to identify the CCM2 and CCM3 genes. Christina walked us through the very technical process of identifying a gene. We were able to see actual DNA in a test tube – a milky white substance that had been extracted from a blood sample. We saw large family pedigree charts which indicate family members affected by the illness and commonalities among their gene sections. It was both amazing and daunting to view the penetration of the mutation within these families.

One of Christina's wishes is for all family members in those families where there is a known familial cavernous angioma to undergo MRI screening. Many times family members who appear unaffected actually have a cavernous angioma but have no symptoms. Accurate identification of affected family members would make the work of identifying the CCM2 and CCM3 gene much easier.

Our next meeting was with Dr. Doug Marchuk. Dr. Marchuk explained to us some of the wider applicability of his lab's work. In particular, the identification of the CCM2 and CCM3 genes will enable easier identification and screening of families affected by familial cavernous angioma. His hope is that this will lead to more informed treatment choices and lower health care costs.

For example, when a simple blood test becomes the preferred and absolute method of identifying those with any of the three genetic mutations, MRI's can be performed selectively so that only those identified as having one of the mutations will be inconvenienced. Also, children can be screened at younger ages without undergoing sedation. Anyone with young children will certainly appreciate that!

A second facet of the Duke lab's work is to understand the mechanism by which these genetic mutations generate cavernous angiomas. Achieving an understanding of angioma formation may someday help in developing better treatments. In light of the findings of the recent genetic study of 206 families described in the "Latest Research" section above, Dr. Marchuk wanted to encourage as many people as possible to send blood for screening for familial genetic mutations. He expects that many more individuals who were thought to have the sporadic form of the illness will be identified as having the familial form. Because the familial form of the illness is an autosomal dominant disorder (meaning the child of one affected parent and one "normal" parent will have a 50% chance of inheriting the mutation; likewise if both parents are affected, there is 75% chance of inheritance), this becomes important for affected individuals who are parents or who anticipate becoming parents.

Our next visit was with Jon Zawistowski. Jon is a graduate student who is working to understand the role of the KRIT1 protein in the cell and to understand where in the body the KRIT1 protein is found. Jon is most impressed by the complexity of the systems involving KRIT1 synthesis and use. His most recent research has lead him to study cell-to-cell interactions, namely how the processes inside of one cell influence the metabolic processes of an adjacent cell. With each new discovery, this complex interrelationship has become more and more apparent. As the CCM2 and CCM3 genes and their corresponding proteins are identified, Jon and researchers in other labs who are addressing these questions will have much more information at their disposal.

Our final stop was with Nicholas Plummer. Nick is a post-doctoral fellow who is working to breed mice that have both the KRIT1 mutation and a clearly identifiable cavernous angioma. Nick told us that the KRIT1 mutation is known as a "loss of function" mutation since the KRIT1 protein is no longer synthesized properly inside the cell. While researchers don't know the exact purpose of KRIT1, they can tell that this loss of function inside the cell somehow results in the generation of anomalous blood vessels which gives rise to cavernous angiomas. The mice involved in this study are called "knockout" mice because one copy of the KRIT1 gene has been knocked out to produce the result. Oddly enough, to date no mice that harbor cavernous malformations have exhibited any unusual or overt neurological symptoms, regardless of lesion location in the brain.

Why mice, do you ask? Mice and human DNA are remarkably similar. Also the gestation period from mouse generation to generation is relatively short, allowing for multiple generations of mice to be produced within one year's time. The existence of mice with the disorder will allow for a much greater range of experiments than could be conducted on humans, possibly including experiments identifying hemorrhage factors or testing of pharmaceuticals that might address cavernous angioma symptoms.

Jack and I were exceedingly impressed with the commitment, knowledge and professionalism exhibited by the Duke lab staff. While they are not the only team, there is no doubt that they are one of the preeminent teams in the world studying this disease. With a little more time and help in the form of blood samples from affected patients, the Duke team is confident that they can identify CCM2 and CCM3. This in turn will clear the way for ultimately understanding the genetic mechanism leading to CCM formation as well as the development of enhanced screening tools, and possibly a future cure.

## Welcome to New Board Member Norma Villa



Angioma Alliance is pleased to introduce our newest Board of Director's member, Norma Villa. Norma Villa is first-generation American, born of Mexican immigrants. She is married and has two teen aged-children; a son 19, and a daughter, 17. In 1992, her daughter was diagnosed with multiple cavernous angiomas--the largest and most threatening being on the pons of the brainstem. Although not medically confirmed, it is suspected to be the familial form of the disease. At the time, diagnosis at the age of 6 was rare. In 1994, her daughter underwent surgery that partially removed the brainstem angioma. There have been many discoveries and advancements in the past 11 years. Given her family situation, Norma is particularly interested in recent identification of a mutation founder gene responsible for familial cavernous angiomas in Mexican-Americans. Norma's educational background is in social work/human relations. She has joined the board of Angioma Alliance to help with outreach projects, especially those extending to the Latino/Hispanic population.

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## Tidbits

### Are You Facing Surgery? Talk to us about tissue donation.

Angioma Alliance would like to become more actively involved in facilitating cavernous angioma tissue donation to research laboratories. Research laboratories have an immediate and long term need for cavernous angioma tissue that has been surgically removed. Currently, labs are using the tissue to gain understanding of the process of cavernous angioma formation and hemorrhage. This is important work that will have an enormous impact on future treatment options for this illness.

Over the next few months, Angioma Alliance will be publishing descriptions of the individual research projects in the US that require cavernous angioma tissue on our website. We hope this will aid you in choosing a lab to receive your tissue donation. We would like to encourage anyone facing surgery in the US who would like to

donate their angioma to call us at our new toll-free number, 1-866-HEAL-CCM, so that we can help to make arrangements. The process is very simple and primarily involves filling out and signing a few forms. Your donation could make a big difference in the pace of research progress.

### Toll-Free Number

Angioma Alliance now has a business line, 757-258-3355, and a toll-free number, 1-866-HEAL-CCM! This line has been established primarily to facilitate tissue donations, but please feel free to call if you have other needs or concerns. Connie Lee will be answering the phone from her home, and will not be keeping regular office hours. However, if you leave a message on voicemail, she will try to get back to you within 24 hours.

### American Academy of Neurologists Convention in San Francisco

Angioma Alliance will be exhibiting at the annual convention of neurologists which is being held from April 26-April 29 at the Moscone Convention Center in San Francisco. This is an opportunity to introduce neurologists from all over the US to the work of our organization and to help them become more familiar with the issues which are important to those affected by cavernous angioma. **If you live in the Bay area and could provide housing for 1, 2 or 3 Angioma Alliance exhibit staff during this week, we would be very grateful.** We may also have a need for people from the Bay area to help staff our booth or assist with set-up and breakdown. We would like to begin compiling a list of folks who may be available. Please let us know by emailing [info@angiomaalliance.org](mailto:info@angiomaalliance.org).

### Igive.com

As you approach your holiday shopping, please consider making your online purchases through Igive.com and designating Angioma Alliance as your charity. Igive.com provides a simple way for you to earn money for Angioma Alliance without cost to you. Simply go to [www.igive.com](http://www.igive.com) and register. Each time you shop, go through the Igive.com site to get to your retailer, and a percentage of your purchase price will be given to us. There are hundreds of stores, including most major retailers, that participate in this program. You do not pay any more for your items, and this helps us to continue providing a website, producing educational materials, and increasing awareness of cavernous angioma.

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