The Familial Intracranial Aneurysm (FIA) Study is one of the largest studies of the genetics of brain aneurysm in the world and has made tremendous contributions to our understanding of the why and who of brain aneurysm formation. Your participation in this important National Institutes of Neurological Disease of Stroke (NINDS) study has been critical to success of the study to this point.

The primary goal of the FIA study is to identify the gene or genes that lead to the formation and/or rupture of brain aneurysms.

The genome screen, which enables the identification of at risk genes across the chromosome, was performed at planned intervals since the study startup in 2002. The first was performed after the initial collection of 192 families. Possible evidence of chromosomal regions contributing to the formation and rupture of brain aneurysms were identified in 4 (chromosomes 4, 7, 8 and 12) of the 23 pairs of chromosomes in humans. We also found evidence that smoking interacts with specific regions of the chromosomes with regards to the risk of aneurysm.

The latest genome screen was performed in 333 participating families. In this expanded group possible evidence of chromosomal regions contributing to intracranial aneurysms was found in 2 chromosomal regions (chromosome 4 and 12) and a third (chromosome 7) with smoking interactions.

A high-density subsequent genome screen involving FIA subjects as well as subjects with and without aneurysms from other populations is ongoing with exciting preliminary results which await confirmation.

Conclusion to-date is that it is unlikely there is a single gene with a strong effect which is responsible for intracranial aneurysms in families. Rather, it likely that multiple genes of smaller to modest effect and environmental risk factors contribute to the susceptibility for intracranial aneurysms.

We are carrying this work forward and have applied for additional funding (FIA II) to the NIH to gather information and DNA from an additional 200 families and 1,800 sporadically occurring aneurysms without a significant family history. The hope is that this subsequent study will identify specific at risk genes not only in FIA families but in the general population.

Other significant findings resulting from the FIA study:

Screening for Brain Aneurysm in the Familial Intracranial Aneurysm Study: Frequency and Predictors of Aneurysm Detection: [Published article online version http://stroke.ahajournals.org]

In first degree relatives (parents, siblings, and children) of a person diagnosed with an intracranial aneurysm, it was found that 19.1% of the participants who received a study Magnetic Resonance Angiogram (MRA) had a previously undiagnosed aneurysm. Those diagnosed with an aneurysm were over the age of 30 years, female or had a history of smoking and/or high blood pressure. These findings provide guidance to health care professionals for screening high-risk individuals based on family and medical history.

Greater Rupture Risk for Familial as Compared to Sporadic Un-ruptured Intracranial Aneurysms: [Published article online version http://stroke.ahajournals.org]

113 subjects were found to have an un-ruptured aneurysm during the course of their participation in the FIA study. The main characteristic of these aneurysms was that the majority of these aneurysms, all but five, where classified as small less than 7 millimeters. However, the observed annual ruptured rate of these aneurysms was determined to be 1.2 percent. That’s approximately 17 times higher than the annual rupture rate for subjects with an un-ruptured intracranial aneurysm of similar size and no family history of intracranial aneurysm that has been previously reported in the International Study of Un-ruptured Aneurysm (0.069 percent). This information is very important in determining the management of an intracranial aneurysm in a person with a family history.
FIA I Close-Out Message and Plans for FIA II from the Principal Investigator
continued:

**Age at intracranial aneurysm rupture among generations: Familial Intracranial Aneurysm Study:**
[Published article Neurology, 2009;72:695-698]

Previous studies have suggested intracranial aneurysm occur at younger ages in subsequent generations of families with at least one case of ruptured aneurysm. But the FIA study found that when accounting for a similar length of follow-up in both generations, they actually tend to occur at an older age. Ruptured aneurysms were identified in the second generation 50 percent less often than the older generation of the family, but the FIA study findings suggest that the second generation will “catch up” in the number of aneurysm ruptures as that generation ages.

**The Effects of Study Participation in the Familial Intracranial Aneurysm Study on Cigarette Smoking:**
[Published article Journal of Stroke and Cerebrovascular Diseases, vol. 17, No. 6 (November-December), 2008: pp 370-372]

It was found that after 3 years of follow-up participants in the FIA study had significantly decreased their smoking rates, in both those with a diagnosis of intracranial aneurysm, and to a lesser degree those without a known aneurysm. This demonstrates that high-risk individuals can change their behavior to reduce their risk of a potentially life-threatening condition. Health care professionals should provide more aggressive risk factors education and smoking cessation strategies in this high risk group.

**Genome Screen to Detect Linkage to Common Susceptibility Genes for Intracranial and Aortic Aneurysms:**
[Published article http://stroke.ahajournals.org/cgi/content/full/40/1/71]

In addition to reporting brain aneurysms, families in the FIA study have also been reporting aneurysm elsewhere in the body including the chest and abdomen. The genome screen was completed in 29 of these families and the findings suggest that common genes maybe responsible for both brain aneurysms as well as abdominal aortic aneurysm. The two chromosomes involved include chromosome 11 (which has previously been reported in abdominal aortic aneurysms) and chromosome 6. The identification of the actual genes involved could one day allow a genetic screening test for families. Such a test will allow physicians to identify who is at risk for aneurysm development and who would benefit from further diagnostic testing.

None of these findings would have been possible without your participation and the hard work of the study investigators. We thank you for your generous participation.

This is the last newsletter for the FIA I study; however, the FIA website will continue on to provide future findings and hopefully as FIA II moves forward. You can access the website at [www.fiastudy.org](http://www.fiastudy.org)

As of July 31, 2009, FIA I will come to a close. At this time we will no longer be calling to conduct yearly follow up interviews.

Joe Broderick
Principal Investigator, FIA Study

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For more information on the FIA Study, please contact:

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All FIA participants are strongly urged to stay in close contact with their primary care physician. Your physician should be your point of contact for you and your families medical follow up, concerns and or questions.

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**Glossary**

- **Chromosome** – Structures found in the nucleus of a cell. Normal human cells contain 46 chromosomes, 22 pairs of autosomes and 2 sex chromosomes.
- **Genetics** – the scientific study of heredity.
- **Genome** – The substance of heredity. All the genetic material in the chromosomes of a particular organism.