

Research Update

Results, results, results!

The Spina Bifida Research Resource has been extremely busy! We have enrolled many new participants in the SBRR! This increase in participants has allowed us to start analyzing our genetic data. So we have results!

ENROLLMENT: We now have well over 500 individuals with spina bifida and their families enrolled in the SBRR! Thank you to all the families who are participating in the SBRR and also to those who have contacted us and are still considering participation.

Our goal, however, is to enroll 700 individuals and their families in the study. We need more participants in order to allow us to identify some of the risk factors that contribute to causing spina bifida.

Why do we need more participants? We need more in order to identify as many risk factors as possible. It is believed that several risk factors must act together to cause spina bifida, and each individual risk factor only

increases the chance that an individual will be born with spina by a small amount. The risk factors may vary from individual to individual. Therefore we need to study a large number of individuals in order to identify these factors.

We are working with local spina bifida associations to provide information about the SBRR to their members who may be interested in participating. Since the study can be done entirely by phone and by mail, we have participants from Maine to Alaska!

Thank you to all the SBAs who have worked with us, particularly the most recent groups - Colorado, Connecticut, San Diego, Greater Dallas, New Orleans, Austin and Tidewater.



Is there one single "spina bifida gene"?

NO. There does not appear to be one single gene which causes spina bifida all by itself. We keep hearing in the news about researchers discovering "the" gene for spina bifida. In most of these cases, researchers have discovered a gene that causes spina bifida (or a neural tube defect) in research animals like mice or frogs.

The genes *Lpp1*¹ and *Shroom*² are recent examples. Researchers have discovered that, in mice, having a mutation in either of these genes causes a neural tube defect. A mutation is a genetic change in a gene that damages the gene's ability to function properly. Since having a damaged form of the gene causes a neural tube defect, we can assume that having a normal version of the gene is necessary for normal development of the spine in mice. Once a gene is discovered to cause spina bifida in *animals*, the next step is to find out whether it plays a role in causing spina bifida in *humans*. Mutations in the gene *pax3*³, for instance, clearly cause spina bifida in mice but seem to play only a small role in causing spina bifida in humans.



1. Severe neural tube defects in the loop-tail mouse result from mutation of *Lpp1*, a novel gene involved in floor plate specification. Murdoch JN, Doudney K, Paternotte C, Copp AJ, Stanier P. *Hum Mol Genet*. 2001 Oct 15;10(22):2593-601.
2. *Shroom*, a PDZ domain-containing actin-binding protein, is required for neural tube morphogenesis in mice. Hildebrand JD, Soriano P. *Cell*. 1999 Nov 24;99(5):485-97.
Morphogenesis: *shroom* in to close the neural tube. Martin P. *Curr Biol*. 2004 Feb 17;14(4):R150-1.
3. Analysis of select folate pathway genes, *PAX3*, and human T in a Midwestern neural tube defect population. Trembath D, Sherbondy AL, Vandyke DC, Shaw GM, Todoroff K, Lammer EJ, Finnell RH, Marker S, Lerner G, Murray JC. *Teratology*. 1999 May;59(5):331-41
Absence of linkage between familial neural tube defects and *PAX3* gene. Chatkupt S, Hol FA, Shugart YY, Geurds MP, Stenroos ES, Koenigsberger MR, Hamel BC, Johnson WG, Mariman EC. *J Med Genet*. 1995 Mar;32(3):200-4.

Copies of these papers will be provided on request.



RESULTS!



We have published research journal articles about three different genes since our last newsletter! Now that we have so many individuals and families enrolled in the SBRR, we can continue to study other genes and to obtain more results as new samples are received.

What types of results do we expect? When we ask if a specific gene plays a role in causing spina bifida, we can expect one of the following answers:

1. No, the gene does not play a role in causing spina bifida
2. Yes, the gene does play a role in causing spina bifida. In addition the genetic change may have an effect when present in the baby OR when present in the mother OR only when present in both mother and baby.
3. Yes, the gene plays a role but only under certain circumstances (e.g. when other genetic or environmental factors are present).

How do we know whether or not a gene plays a role in causing spina bifida? We use statistical (math) tests to look for an association between having a certain form of a gene and having, or having a child with, spina bifida. Many normal genes have more than one "form". The different forms of a gene are called alleles. Sometimes one form (allele) of a gene does not work as well as others and so can affect the health of the person who has it.

1. A gene which appears to play a role in causing spina bifida when the genetic change is present in the mother.

"Maternal genetic effects" describes genetic changes in the mother that affect the kind of environment she creates for the baby. As an example, if the mother did not absorb or process folic acid well, her baby might not be getting enough. In fact, in this paper we report on two genes (MTR and MTRR) involved in how the body uses folic acid. If the mother has a particular form (allele) of either gene, she has an increased chance of having a child with spina bifida - as compared to a mother who does not have either of these alleles. If the baby has either of these genetic changes, it does not increase his or her risk of being born with spina bifida. The gene seems to influence how well the mother's body can make folic acid available to the baby.

Maternal Genetic Effects, Exerted by Genes Involved in Homocysteine Remethylation, Influence the Risk of Spina Bifida. M-T Doolin, S Barbaux, M McDonnell, K Hoess, AS Whitehead, LE Mitchell. American Journal of Human Genetics 71:1222-1226. 2002.

2. A gene which appears to play a role in causing spina bifida when the genetic change is present in the baby.

In this paper we report preliminary evidence that an individual who has a particular form (allele) of the gene NOS3 has an increased the risk of being born with spina bifida. The NOS3 gene produces a "chemical" that may affect cell growth in the neural tube and may also affect the level of homocysteine in the blood. (The role of homocysteine was described in newsletter # 3, Winter 2000). Data from more individuals is needed to clarify the role this gene plays in causing spina bifida.

Evidence that the Risk of Spina Bifida is Influenced by Genetic Variation at the NOS3 Locus. KS Brown, M Cook, K Hoess, AS Whitehead, & LE Mitchell. Birth Defects Research (part A) 70:101-106, 2004. Birth Defects Research (Part A) 70:101-106, 2004.

3. A gene which does NOT appear to play a role in causing spina bifida.

We report that the ABCC2 gene does not appear to play a role in causing spina bifida. The ABCC2 gene is involved in moving folate (folic acid) out of cells.

A Common ABCC2 Promoter Polymorphism is not a Determinant of the Risk of Spina Bifida. L Jensen, AM Wall, M Cook, K Hoess, C Thorn, AS Whitehead, & LE Mitchell. Birth Defects Research (Part A)

Copies of these papers will be provided to anyone who requests them.

Please remember that these are preliminary results! Our results must be confirmed by other research groups and/or in larger numbers of participants before they are can be used for clinical care. These results cannot at present be used to predict recurrence of spina bifida in the family or for prenatal diagnosis.

SBRR on the road...

MEETINGS:

Dr. Mitchell attended the Third International Conference on Neural Tube Defects organized by Dr. Richard Finnell, director of the Institute of Biosciences and Technology at The Texas A & M University.

Scientists from many different areas of research attended the conference to discuss their research findings and to establish ways to work together for future research. Dr. Mitchell presented research on maternal genetic effects. The overall goal of these International Conferences is to find ways to prevent spina bifida and other neural tube defects.

Katy Hoess attended the 47th Annual Scientific Meeting of the Society for Research into Hydrocephalus and Spina Bifida hosted by Dr. Stephen Kinsman of the University of Maryland School of Medicine.

Barbara Weyland attended Spina Bifida Association of Colorado Annual Meeting.

Katy and Barbara attended the National Spina Bifida Association of America Conference in Crystal City, MD. They were delighted to meet, in person, many of the people who have participated in the SBRR research! Many meeting attendees who were not yet SBRR participants signed up to be contacted about the SBRR. We welcome all our new participants!

Spina Bifida Associations!

**Have you included information about the SBRR in a mailing?
Would you like to have a description of the SBRR and a contact form
provided to the members on your mailing list?**

**The SBRR will pay the cost of a one-time mailing that includes information
about our study, if arrangement is made in advance.**

Please contact Barbara Weyland at 1-866-521-SBTX to make arrangements.

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We need blood!

We are able to get DNA from cheek swabs, but we get much more DNA from blood samples.

If you are willing to provide a blood sample, please call 1-866-275-SBRR or 1-866-521-SBTX

Welcome to our new families!

We want to thank the members of the SBAs of Austin, Colorado, Connecticut, **San Antonio**, Dallas, San Diego, and the Tidewater SBA for their participation in the SBRR!

We also want to thank all of you who have found us through the Internet!

The SBRR is The SBRR welcomes the participation of any individual with spina bifida, regardless of geographical location.

We have over 500 families enrolled but need your help to reach our goal of 700 families.

Please tell you friends about us or write us up for your SBA newsletter!

HABLA ESPANOL?

Ahora tenemos información sobre el estudio de espina bifida y formas de participación en español. Si usted habla español y necesita literature en su lengua, llame a Barbara Weyland, gratis, a 1-866-521-7289. ¡Gracias!

Still thinking?

Have you contacted us about the study but have not yet sent in your consent form? If the materials we sent you are in that "to do" pile, we would still love to hear from you!

If you have any questions or if you can't remember whether you did enroll, please contact Katy Hoess at 1-866-275-SBRR or Barbara Weyland at 1-866-521-SBTX.

You are welcome to receive the newsletter whether or not you chose to enroll in the study.

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