Marinesco Sjogren Syndrome

NEWS

Summer 2006
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About the Newsletter

In this edition of the MSS newsletter, researchers from Jackson Laboratory tell us about "woozy", a mouse with mutations of the Sil1 gene that causes MSS. We also review our accomplishments of the past year and learn about the recent clinical genetics conference in San Diego.

Feel free to distribute the newsletter by email or to print copies for interested individuals. Email us if you wish to be added to or removed from the newsletter mailing list. Current and back issues of the newsletter are available at the website on the publications page. http://www.marinesco-sjogren.org/pubs.html

Introducing ….. *Woozy*

by
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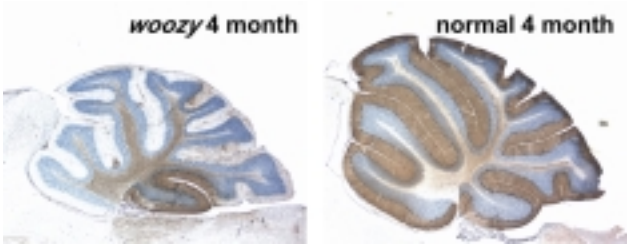
Prior to the identification of mutations in the *Si1l* gene as the culprit causing MSS, a naturally occurring mutation named woozy was associated with the mouse *Sil1* gene (Zhao et al., Nature Genetics, 2005 37:974-979). Although the disease manifestation in mice homozygous for the woozy mutation is not exactly the same as human MSS, a prominent symptom of the *Sil1*-deficient mouse is ataxia, or a loss of motor coordination. Pathological studies of the woozy mouse revealed early adulthood degeneration of Purkinje cells, nerve cells in cerebellum (the 'small brain') that coordinate body movement (the brown stained neurons in the figure below). Before Purkinje cells die, there is accumulation of misfolded proteins in the nucleus and endoplasmic reticulum of these cells. The nucleus contains the genetic material of a cell and also hosts the synthesis and processing of messenger RNAs, the molecules that encode proteins. It is currently unclear whether the misfolded proteins in the nucleus affect these functions. The endoplasmic reticulum is a membranous mesh around the nucleus that is involved in protein modifications and secretion. Accumulation of misfolded proteins in these two intracellular compartments could

compromise multiple cellular functions, leading to the demise of the cell.



The ataxia symptom appears around three months after birth in mice (laboratory mice have an average life span of 2-3 years), not unlike the childhood onset of MSS in humans. However, other symptoms of MSS are not apparent in woozy mice. For example, we have not observed cataracts in the eyes of woozy mice up to 1 year old. In older mice homozygous for the *Sil1* mutation, there is also no increase in incidence of cataracts. Overt muscle pathology is also not seen in woozy mice; however, we are currently investigating whether there are subtle or functional changes in muscles that are not amenable to regular pathological approaches.

We are just starting to understand how mutations in *Sil1* cause MSS. The SIL1 protein is a regulator of an important endoplasmic reticulum molecular chaperone, BiP. When proteins are initially generated, they form a linear "string" of amino acids. However, for proper function it is necessary for this structure to fold extensively into a particular conformation. Molecular chaperones are proteins that bind to unfolded proteins to prevent aggregation during the folding process, or that aid in the refolding or degradation of unfolded proteins. Many chaperones need additional proteins known as cochaperones for optimal activity. Without functional SIL1, BiP may be unable to refold unfolded proteins, or it may remain attached to unfolded proteins, and thus unable to help fold other proteins. This would lead to misfolded protein aggregation and eventually failure of cellular functions. However, whether protein aggregation directly causes cell death in Purkinje cells in woozy mice is still unclear.

The Jackson Laboratory is a research institution which studies mice to further understand the causes of, and treatment for, multiple human diseases including cancer, neurological syndromes, and diabetes. In addition, it is the world's largest repository of genetic mouse strains and supplies these genetic models to scientists around the world. Our current effort focuses on the mechanism underlying neuronal death in the woozy mouse, which will provide knowledge for future human therapy development for MSS.

A Genetics Update

by
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The three laboratories are finishing up their work looking for mutations in the Sil1 gene. Results from my laboratory will be released fairly soon to the families. We are still interested in receiving more samples. Not all patients with typical MSS have mutations in the Sil1 gene. There is another gene for MSS. Genetic disorders are defined by the findings the patients have, not by the gene. There are many conditions caused by more than one gene.

Although the Sil1 mouse model is not completely identical to the human disorder, it is similar enough to be used for testing potential therapies. Interestingly, the same storage granules are seen in the cultured skin cells of many humans with MSS and the brain cells of the mouse.

Annual Review of Accomplishments and Goals

It's time to sit back and take a look at what we have accomplished over the past year.

(1) The MSS gene (Sil1) was identified in September 2005. Congratulations to the researchers from German and Finland and their teammates on this exciting discovery. We are just beginning to learn what MSS is all about and what this gene discovery means to all of us.
(2) We continued to expand our network of families, adding new members from Germany, Canada, Australia, and the United States.
(3) We established a listserv/discussion group to provide more frequent updates on MSS and to allow easier communication between our families.
(4) We developed and circulated a one-page MSS questionnaire to help us better understand the characteristics of our group and match families with each other. If you have not responded yet, please do so. Contact us by email if you need a copy of the questionnaire.
(5) We participated in the ACMG conference (see article below)
(6) We initiated efforts to translate portions of the MSS website into other languages. See the home page of the MSS website for a link to German language translations. Thank you very much to our new German family for this excellent work! Contact us if you can help translate from English to any other language or help review translated materials.

Here are our goals for the future.

(1) Become a 501(c)3 non-profit corporation so that we can do fundraising and become eligible to receive grants. Let us know if you would be willing to serve as a board member, help write the articles of incorporation, or have good fundraising ideas.
(2) Participate in more medical and genetics conferences, e.g., American Society of Human Genetics (ASHG), American College of Medical Genetics (ACMG), and Child Neurology. Would you be willing to help exhibit at a conference location close to your home?
(3) Start planning an international research and family conference.
(4) Create family-friendly materials for dealing with MSS-related medical, therapy, educational issues, and transition-to-adult issues. Let us know if there are any particular topics you feel would be helpful to families.

ACMG Conference

Colleen Yinger attended the American College of Medical Genetics (ACMG) Conference in San Diego, CA, March 23-26, 2006 as one of nine participants in the ACMG and Genetic Alliance Advocacy Training Partnership Program.

Two of the most relevant sessions to our group were collaborative research efforts and genetic testing issues for very rare disorders. The collaborative research session talked about the success of the children's cancer network in improving treatment outcome and how those approaches can be applied to rare disorders by establishing multi-center research groups.

The genetic testing session addressed the challenges of balancing quality and availability of clinical genetic testing since any given laboratory analyzes very few samples each year for a particular rare disorder. Solutions include clinical lab confirmation of mutations identified in research labs, efforts to promote the translation of tests from the research to the clinical setting, and the emergence of commercial genetic testing including rare disorders.

One of the most exciting aspects of the conference was the opportunity to network with other advocacy group leaders. The participants shared ideas for increasing awareness of their

disease, engaging researchers, hosting conferences, creating family-oriented publications, fundraising, and more. It was incredibly motivating to see the dedication and accomplishments of these groups, even those representing very rare disorders. We really can make a difference!

MSS Technical Publications

Van Raamsdonk JM, "Loss of function mutations in SIL1 cause Marinesco-Sjogren syndrome", Clinical Genetics, May 2006. (This is a summary of recent MSS publications on the SIl1 gene.)

Parsian, A, "Marinesco-Sjögren syndrome (MSS) maps to chromosome 5q31 and is caused by a mutation in BAP/SIL1 gene in an extended pedigree", 11th International Congress of Human Genetics
http://www.ichg2006.com/abstract/399.htm

MSS Discussion Group

The MSS listserv/discussion group is up and running. The listserv provides MSS updates in a timelier manner than the newsletter and is a good opportunity for families to share information, advice, and concerns. Families, friends, therapists, caregivers, medical professionals, or anyone else with an interest in MSS is welcome to participate. It is a low-volume list. Feel free to email us with any questions about the listserv.

To subscribe, send us an email (mss@marinesco-sjogren.org) requesting to be added to the listserv, **or** simply click on the link below and enter the requested information (email, name, and password):
http://www.galists.org/read/all_forums/subscribe?name=mss

After subscribing, you can post messages to the discussion group by sending email to:
mss@listserv.galists.org

If you already subscribe to the listserv, please post a message introducing your family or other connection to MSS. Most small, rare disease support groups find listservs to be a great way for connecting families worldwide.

New Brochures Available

New MSS brochures are available. The updated version includes an overview of MSS symptoms, info on the Sil1 gene, and describes our support group services. Email us with your name, address, and number desired. You can also preview the brochure at:
www.marinesco-sjogren.org/brochure.pdf

Genetics Resource

What is the difference between a missense mutation and a nonsense mutation? What is an amino acid? What did the Human Genome Project accomplish? Visit the on-line Genetics Home Reference for a great source of genetics-related information written for the lay-person.
http://ghr.nlm.nih.gov/ghr/glossary

Upcoming Conferences

Genetic Alliance Conference, Bethesda, Maryland, July 28-30, 2006,
http://www.geneticalliance.org/ws_display.asp?filter=conference06

International Congress of Human Genetics, Brisbane, Australia, August 6-10, 2006,
www.ichg2006.com

American Society of Human Genetics (ASHG) Annual Meeting, New Orleans, Louisiana, October 9-13, 2006,
http://www.ashg.org/genetics/ashg/menu-annmeet.shtml

Child Neurology Society, Pittsburgh, PA, October 18-21, 2006.
www.childneurologysociety.org

Website on Protein Folding

A family-friendly website created by Stanford University is a fun source of information about protein folding and protein folding disorders. Learn how to build a simple protein using styrofoam balls or play the protein folding trivia game. (No endorsement of the protein folding distributed computing project is implied.)
http://folding.stanford.edu/education/diseases.html

Genomics in Perspective Lecture Series

Genomics in Perspective is a lecture series sponsored by the National Library of Medicine's History of Medicine Division. The presentations concern historical and social science perspectives on genomics for scientists, physicians, policy makers, and the general public. The session "Standing on the Biological Horizon" discusses genetic health advocacy, with participation by Sharon Terry, CEO of the Genetic Alliance.
http://collab.nlm.nih.gov/webcastsandvideos/genomics/genomics.html

Molly's Story

Despite the challenges we encounter finding appropriate education, therapy services, and job opportunities for our children, the quality of life for the physically and developmentally disabled has dramatically improved over the past 40 years. Here is a touching story recently featured in Readers Digest about a man who renews his relationship with his mentally retarded sister, Molly, years after she was institutionalized as a young child. www.rd.com/molly

Write Your Own Family Story

If you wish to submit a family story to the MSS website (or wish to update your current one), let us know. When families first visit our website, the family stories page is usually the part they enjoy the most because it makes them feel most connected to us. Please help make this page even better by sharing your experiences! Family stories for the newsletters are also welcome.

DNA Day Winning Essays

Enjoy some wonderful DNA Day essays written by high school students. Several of the winning authors are affected by genetic disorders. Congratulations to these promising young people!
http://www.ashg.org/genetics/ashg/dnaday06winners.shtml

National Disability Rights Network

The National Disability Rights Network provides protection and advocacy for individuals with disabilities. Their website includes links to services for each state (see "Consumers: get help in your state").
http://www.napas.org/

Access to Federal Research

The Cornyn-Lieberman Bill has been introduced into Congress requiring federal agencies that fund over $100 million in annual external research to make electronic manuscripts of peer-reviewed journal articles stemming from their research publicly available via the Internet. Supporters of the bill believe that public access to research will accelerate multi-disciplinary breakthroughs in research.
http://www.taxpayeraccess.org/frpaa/index.html