Marinesco Sjogren Syndrome

NEWS

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About the Newsletter

In this edition of the MSS newsletter, Dr. Hendershot writes a very interesting article about protein folding disease, the SIL1 gene, and what it means for MSS. We also look at ways for improving mobility in people affected by MSS and provide growth data from some of our children.

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Marinesco-Sjögren syndrome: a protein folding disease

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It has been one year since two papers were published that mapped the genetic defect in individuals with Marinesco-Sjögren syndrome (MSS) to the *SIL1/BAP* gene [1,3]. At nearly the same time, a mouse strain was described in which the *SIL1* genes were disrupted. The "*woozy*" mouse showed many of the same symptoms that are associated with MSS including ataxia, cerebellar Purkinje cell loss, and electron dense structures in the cells, which are indicative of aggregated (or clumped) proteins [5]. This strongly suggested that indeed mutations in *SIL1* could cause MSS and argued that MSS should be classified as a protein folding disease.

What is a protein folding disease? In the past several years a number of diseases have been identified that result from the improper folding of a protein. The basic instructions for making a protein are encoded in DNA or gene. This information is copied into RNA, which serves as the template (or instruction manual) for making the protein. Each protein is initially produced as a linear sequence or long string of amino acids, but it is not functional in this form. The string of amino acids must fold into a particular three-

dimensional structure or shape in order to perform its given function. The folding pathways are guided by the physical properties of the individual amino acids that make up the protein. However, a change or deletion of a single amino acid can dramatically affect the final shape of the protein, often resulting in either an inactive protein or one that will aggregate or form large protein tangles. Most protein folding diseases are caused by mutations in a single protein that result in its inability to fold properly. These include cystic fibrosis, Huntington's disease, Alzheimer's disease, and Parkinson's disease to name just a few. MSS is unique in that the mutation is in a component of the cellular machinery that aids protein folding and therefore is likely to affect the maturation of many different kinds of proteins.

Why do mutations in SIL1 affect protein folding? The information to fold a protein is largely dictated by the composition of the protein itself. However, protein folding is a type of biochemical origami in which the newly formed chain of amino acids can fold in a number of different ways, only one of which is correct. We know now that all cells produce a group of proteins that are called molecular chaperones, which help guide the folding process. They were so named because they serve to "prevent inappropriate interactions" and remain bound to a young protein only until the time that "appropriate interactions" should be allowed to occur; only in this case young amino acids not young couples are being chaperoned! In mammalian cells, many proteins are produced in the endoplasmic reticulum and rely on the molecular chaperone, BiP, to fold properly. BiP is regulated by co-factors that help it to lock onto unfolded proteins, so they are protected until the time is right for them to fold, as well as exchange factors that help to remove BiP at the right time, which allows the newly made protein to fold. The Sil1 protein is an exchange factor [2], and therefore in the absence of functional Sil1 many different proteins will be "locked" onto BiP and therefore blocked at an unfolded or non-functional state. Thus, the cell, and therefore the individual, will lose many different functions that are normally performed by these proteins.

What types of mutations exist in Sil1? Should these make a difference to the disease? To date several different mutations have been identified that cause a premature stop in the coding instructions for Sil1 and therefore result in the synthesis of only a small portion of the BAP protein, as well as mutations that allow whole internal regions of the BAP protein to be deleted. One mutation was identified that results in the deletion of only the final five amino acids of Sil1 [1,3]. The last four amino acids are responsible for retaining Sil1 in the cell, and therefore although this mutant Sil1 protein is likely to still be fully functional as an exchange factor, it is believed that this protein does not stay in the endoplasmic reticulum where it is needed. Thus, mutations that block Sil1 synthesis, cellular levels or targeting to the correct cellular location as well as mutations that adversely affect its ability to bind to BiP or stimulate the release of BiP from unfolded proteins are all likely to have the same functional consequences (*i.e.*, the accumulation of unfolded, nonfunctional proteins in cells), even though each of them causes a very different change in the Sil1 protein.

Why do some organs seem to be more affected by mutations in Sil1? Sil1 was previously shown to be expressed in cells from many different types of tissues and organs, although the level of Sil1 expression varies greatly between them [2]. This suggests that not all cells need the same amount of Sil1 to function properly. In addition, recent studies have suggested that another chaperone, GRP170, can also function as an exchange factor for BiP [4]. Thus, it is possible that in some cell types (*i.e.*, those most affected in MSS) Sil1 is more important for removing BiP from proteins, while in other cell types GRP170 serves this function. Further research is required to understand how BiP and these two exchange factors function together in different tissues.

Why do some individuals with MSS not show evidence of mutations in Sil1? Greater than 50% of individuals with a diagnosis of MSS that have been tested have mutations in the *Sil1*gene, although there are people with MSS that do not appear to have mutations in this gene. The reason for this is presently unclear, but it is possible that either another component of the BiP cycle is affected in these individuals that also results in a failure of proteins to release from BiP and to fold properly or that there are specific proteins that rely on the BiP-Sil1 chaperones that are themselves affected by mutations. Further studies are needed to understand the underlying cause of disease in these individuals.

Does identification of the gene that is defective in MSS suggest a treatment or can protein folding diseases be treated? The ability to manipulate protein folding in a cell is currently a very active area of research. Chemical or biological agents that can generally act to help proteins fold are being investigated. In addition, research is being conducted to understand the basic mechanisms that control the release of proteins from molecular chaperones with the hope that a clearer understanding of the chaperone cycle will provide points to intervene. The availability of a mouse model for MSS provides an excellent resource to obtain a better understanding the disease at a molecular level as well as an opportunity to examine the effects of various agents that might assist protein folding and diminish the symptoms of the disease. Although the recent identification of mutations in Sil1 as a cause of MSS have provided real insights into the disease and a means of screening, there is still a great deal to be done. In addition to clinical research, much of this will rely on very basic research of a type similar to the studies that first identified molecular chaperones and their regulators and determined how they work. Most funding for biomedical research, both clinical and basic, comes from the National Institutes of Health, which receives this money from Congress. Thus, it is important to urge your representative officials in Washington to continue to support research in this country.

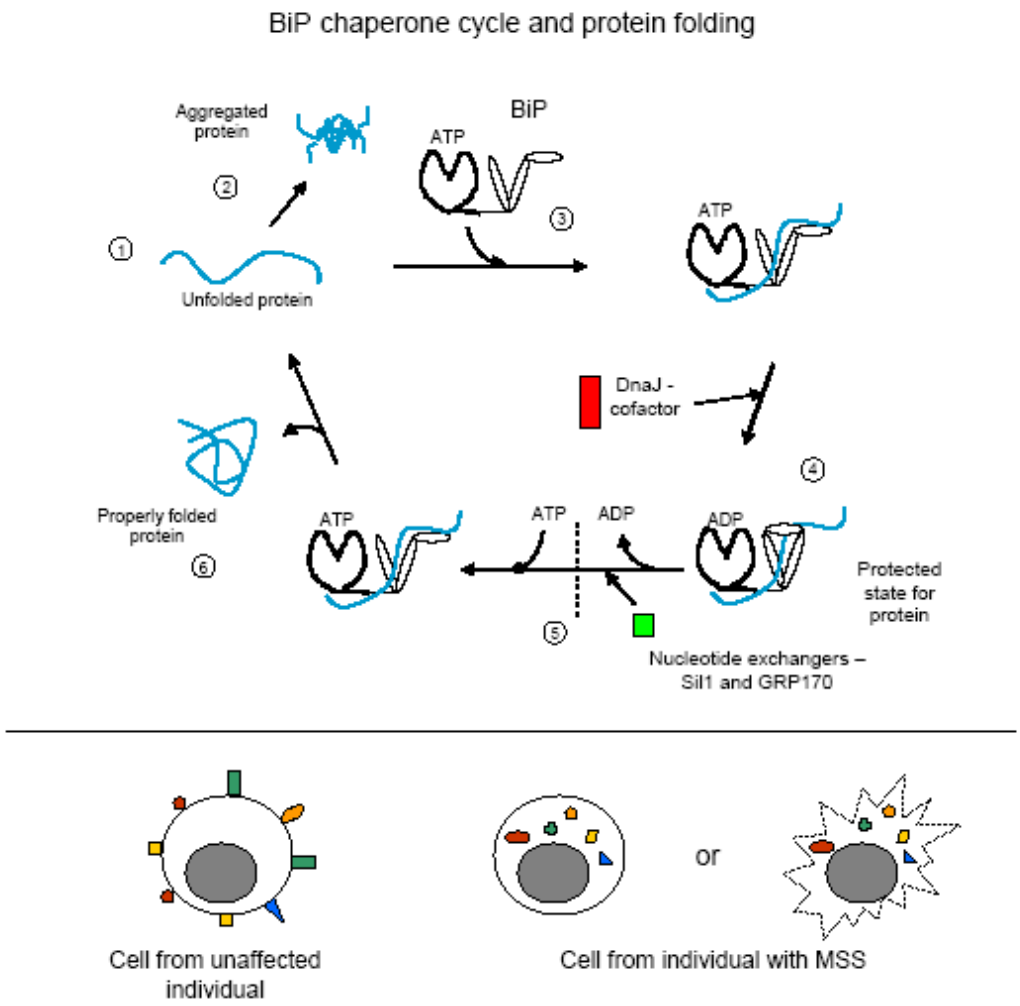
[1] A. K. Anttonen, *et al.*, "The gene disrupted in Marinesco-Sjogren syndrome encodes SIL1, an HSPA5 cochaperone," Nat. Genet. **37**, 1309 (2005).

[2] K. T. Chung, Y. Shen, and L. M. Hendershot, "BAP, a mammalian BiP associated protein, is a nucleotide exchange factor that regulates the ATPase activity of BiP," J. Biol. Chem. **277**, 47557 (2002).

[3] J. Senderek, *et al.*, "Mutations in SIL1 cause Marinesco-Sjogren syndrome, a cerebellar ataxia with cataract and myopathy," Nat. Genet. **37**, 1312 (2005).

[4] A. Weitzmann, J. Volkmer, and R. Zimmermann, "The nucleotide exchange factor activity of Grp170 may explain the non-lethal phenotype of loss of Sil1 function in man and mouse," FEBS Lett. **580**, 5237 (2006).

[5] L. Zhao, *et al.*, "Protein accumulation and neurodegeneration in the woozy mutant mouse is caused by disruption of SIL1, a cochaperone of BiP," Nat. Genet. **37**, 974 (2005).



Top panel shows the BiP chaperone cycle of binding to unfolded proteins. 1. Represents the unfolded protein (blue line) that is mostly an extended chain of amino acids. 2. If left alone it will form aggregated or form large clumps. 3. When BiP has ATP-bound, it is in the "open" form and can bind to the unfolded protein. 4. Entry of the DnaJ cofactor (red square) causes ATP to be hydrolyzed to ADP, which now "closes" BiP onto the unfolded protein and prevents it from forming aggregates. The binding of nucleotide exchange factors like Sil1 or GRP170 releases ADP from BiP so that ATP can bind and "reopen" BiP. 6. This allows the unfolded protein to be released and to fold. Individuals with MSS that have mutations in Sil1 are blocked at stage 5 in this cycle, which means their proteins cannot be released from BiP and allowed to fold.

Bottom panel shows how this affects a cell. In unaffected individuals (left cell), the newly synthesized proteins are released from BiP, fold normally, and are then transferred to the surface of the cell. Each color and shape indicates a different kind of protein. In people with a deficiency in Sil1, the different proteins remain bound to BiP and therefore do not finish folding properly and stay inside the cell where they are unable to perform their proper function (middle cell). Alternatively the accumulation of so many proteins in the cell can cause the cell to die (right cell). In both cases individuals would have a shortage of the proteins these cells should make and thus the functions these proteins would normally perform.

Oregon Newspaper Features Woman Diagnosed with MSS

A Bend, Oregon newspaper had a feature article on a 31-year old woman diagnosed with MSS. We were contacted by the reporter for information about MSS and our support group. Follow the link below to read the article online.
http://www.bendbulletin.com/apps/pbcs.dll/article?AID=/20061105/NEWS0107/61105001&SearchID=73262172895977

Improving Mobility in MSS Children

How can I get my child to walk better? How can I get him to use his walker? How can I motivate my child to become more mobile? To help answer these questions, we asked some of our families with older children for ideas. Here is what we learned. Be sure to try ideas that are appropriate for your child's age and development.

- Practice standing when watching TV or playing with a toy or game on a table.
- Put a favorite toy at the end of hallway and encourage him to walk to it.
- Go to the park and encourage her to walk between the slides and jungle gyms. The distances are just about right for early walkers and the ground surfaces are soft in case of falling.
- Hold onto the back of the child's shirt as he walks to give him the minimum amount of support he needs.
- Try walking in new places – the shopping mall or the toy store. The excitement and fun things to watch help them forget that they are working hard.
- Work with the school, particularly the physical education teacher, to look for opportunities for increasingly independent walking during the school day.
- Consider slow walking on a treadmill.
- For children with better mobility, practice walking on slopes or uneven surfaces to improve strength and balance.

Recent Publications on MSS

R Raininko, O Eeg-Olofsson, "Abnormal MR Signals in the Cerebellar Cortex in Marinesco-Sjogren Syndrome", Neuropediatrics, June 2006.
http://www.thieme-connect.com/ejournals/abstract/neuropediatrics/doi/10.1055/s-2006-945816

Fatma Mujgan Sonmez, et. al., "Marinesco-Sjogren Syndrome and olivopontocerebellar hypoplasia with BAP/SIL mutations: report of a family with three siblings", G-P-2.04, Neuromuscular Disorders 16 (2006).
http://www.icnmd2006istanbul.org/nmd_abstracts.pdf

Zimmermann, R., et. al., "Protein transport into the endoplasmic reticulum: mechanisms and pathologies", Trends in Molecular Medicine, October 27, 2006.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17071140&query_hl=4&itool=pubmed_docsum

MSS Summary on GeneTests Website

The GeneTests Website, a source of information on genetic testing and its use in diagnosis, management, and genetic counseling, now has a GeneReview on MSS. The article summarizes MSS symptoms, clinical and molecular diagnosis, intervention, and availability and applicability of genetic testing. The authors of the article are from Finland and are one of two European teams that identified mutations in the Sil1 gene as a cause of MSS over a year ago.
http://www.geneclinics.org/query?dz=mss

Family Story Updates

Jake Miller now has his own family story with lot of pictures. Kimberly's story has been updated with new pictures, too.
www.marinesco-sjogren.org/family.html

The Conway family recently updated their family story on Shaun and his development over the last few years. Phil Conway was a strong supporter of the creation of the MSS website and support group. We are excited to hear that Phil will be taking a two-year leave of absence from his regular job to serve as an advisor to the "Contact a Family" charity that provides support to families of all disabled children in the United Kingdom. www.cafamily.org.uk

If you would like to update your on-line story, or add your family story to our collection, just send an email containing your story (Word or plain text) along with any pictures or short videos you would like to include. Family stories are very popular with new visitors to our MSS website.

MSS Articles on Wikipedia

Wikipedia, the free, on-line encyclopedia now has articles about MSS in both English and French.

English:
http://en.wikipedia.org/wiki/Marinesco-Sjogren

French:
http://fr.wikipedia.org/wiki/Syndrome_de_Marinesco-Sj%C3%B6gren

What is Sjogren's Syndrome?

We are often contacted by people looking for information about Sjogren's Syndrome. Sjogren's is an autoimmune disorder that causes severely dry eyes and mouth, as well as other medical problems. In the past, syndromes were often named after physicians who reported the earliest cases (e.g., Dr. Marinesco, a neurologist from Romania, and Dr. Sjogren, an ophthalmologist from Sweden, who wrote about MSS in the 1930s and 1940s). Sjogren's syndrome has no similarity to MSS, except for the fact that Dr. Sjogren wrote about both diseases. Syndromes are now more likely to given a name (often a very long name) that describes the underlying physiology of the disease.

The Genetic Support Council of Australia wrote an article "What's in a Name?" in their recent newsletter (page 6) contrasting MSS and Sjogren's Syndrome.
http://geneticsupportcouncil.org.au/uploads/pdfs/Gene%20Advocate%20Ed%2045%20AugSep06_680.pdf

We also added a link to the home page of our MSS website to help people with Sjogren's Syndrome find the right website.
www.sjogrens.org

2nd Annual DNA Day Essay Contest

The American Society of Human Genetics (ASHG) is sponsoring the Second Annual National DNA Day High School Essay Contest. The contest challenges students to examine, question, and reflect on the importance and social implications of genetic research. Essays must be submitted by March 16, 2007.
http://www.genednet.org/pages/k12_dnaday.shtml

Students can choose from either of two topics:

1. If you could be a human genetics researcher, what would you study and why?

2. In what ways will knowledge of genetics and genomics make changes to health and health care in the US possible?

How Tall are MSS Children?

Some of the most common questions we get from new families are "How tall is our child?", "How tall was she when she was my child's age?", or "Can a child with typical height have MSS?" The following charts show heights of several girls and boys from our support group and how they compare to the 50th percentile (average) child and the 5th percentile child (95% of other children are taller).

The charts show heights for a very small sample of MSS children, so they may differ from the larger MSS population. However, all of the children for whom we have information are 5th percentile or shorter. Small size is evident from early childhood. In contrast, some people described in the MSS medical literature (even those with Sil1 mutations) are within the normal height range.

If you would like to provide us with more height data on your child, or you would like to add your child to the data, please send us the information in an email. No names will be associated with the data. Height charts can also be found on the website at www.marinesco-sjogren.org/Height.html.