

Families of Spinal Muscular Atrophy  
 Transcript of Chat Live with an Expert  
 December 1, 2004

Topic: Genetics and SMA

Our expert is Louise Simard, PhD, and SMA researcher at Montreal's Saint Justine Hospital.

This transcript has been somewhat edited and revised to match questions with answers, to correct typos, and to remove extra remarks. Please note there may still be errors and omissions.

Admin	Dr Simard, Welcome!
Dr Simard	Welcome everyone, I am happy to be here today, please have patience with me it is my FIRST chat!
Administrator	Dr Simard, we have a couple of questions from people who were not available during the chat. If you don't mind I'm going to post those now.
Dr Simard	OK
Administrator	From R: Hi, I just want to know if it is possible that siblings can be of different types. That is, can one child be a type 1 or 2 and another child be a type 2 or 3? I did not think this could be possible, but I've been hearing of families with this. If this is true, how is it possible? Thank you so much and I hope that you have an answer for me.
Dr Simard	Absolutely. It does not necessarily happen often but there are many families that present with different types of SMA. There have even been families with type 1 SMA and type III SMA siblings. We do not understand exactly why this happens but suspect that there are other genes that MODIFY how the loss of SMN presents itself. Because these other genes are not at the same place as the SMN gene, they are not necessarily identical between siblings with SMA.
Administrator	Thanks from R!
Administrator	From C: I have a son who is four years old with SMA II. I was wondering for my siblings, their spouses and my husband - what do they need to do in order to be tested to see if they carry the SMA gene? I'm talking right now to a Genetic Counselor and he wants me to go through counseling and I don't think that it is necessary. What do you think about that?
Dr Simard	I am biased being a geneticist, but I believe that genetic counselling is an excellent idea. This will allow you a face to face consultation where you can ask all of your questions and have them explained to your satisfaction. Because you have a son that has SMA, you and your husband are most likely carriers. Your children are at risk of being carriers as well and the best way to determine this is to do what is called a QUANTITATIVE SMN test that will determine if they have one or two SMN1 genes. In most places, this test will only be done when an individual is an adult or of child bearing age.
Administrator	Thanks from C!
Administrator	From N: I'm a 25 year old female, married, have a 6 year old normal son, and I have SMA Type III. What I would like to know is, if I

	have another baby (daughter), will she have SMA too or is it likely that she would be a carrier considering my husband is normal?
Dr Simard	Because you have SMA, you have a mutation on both your SMN1 genes. This means that you will pass on one of these mutations to one of your children. However, what is important here is whether your husband is a carrier or not. It would be best if he undergoes the QUANTITATIVE SMN1 test I mentioned above. If he is not a carrier, all of your children will be NON SYMPTOMATIC (not affected) carriers. If he is a carrier then you have a 50% risk of having a child with SMA.
Administrator	Thanks from N!
V	Dr Simard, What can you say about the application results of Herpes Simplex Virus that included nerve neurotrophic growth factor NGF (34th conference in San Diego) and LentiVector technology (UK)? At what stage is the practical cellular therapy research? Thank you.
Dr Simard	I am somewhat at a disadvantage here as I was unable to attend the San Diego meeting and am not familiar with all of the details of the study you are talking about. Needless to say, all of the “gene” therapy and cell therapy approaches are still in their very early stages and much work must be done before we even come near to human trials. As I think that we would benefit from multiple “therapeutic” approaches. I think that it is great that many different strategies are being investigated, SMA patients can only benefit from this!
V	Thank you. How is the SMN protein being used by the body? When the SMN protein level reaches normal level, how quickly can it be used by the body and for what purposes?
Dr Simard	This is not an easy question to answer. I will try to break it up a little. SMN is a multi-functional protein that is being used for many purposes. It is a vital protein required for everyday functioning of a cell. We also now believe that it carries out a very precise function in motor neuron cells and the loss of this function is what is most felt by SMA patients. I believe that your question relates again to therapy so I will finish off by saying that most therapeutic strategies being studied are looking at introducing a constant supply of SMN, not by giving SMN protein itself but by attacking the SMN2 gene. So far, it is our understanding that increasing SMN protein levels a small amount will go a long way.
W	Dr. Simard, how strongly should I advise my sisters to have my nieces and nephews tested? (SMA 2, age 46 and counting)
Dr Simard	Again here is my genetics bias. Are you a carrier? If so your sisters AND brothers are at risk of being carriers. I like to do a step by step screening. If one of your siblings tests positive as carriers, then their spouses and their children (once of child bearing age) can also be tested. If they turn out to not be carriers, then you don’t have to proceed any further.
L	I have SMA III. I am 28 years old and up until about a year ago I was pretty strong. In the past year the condition has deteriorated quite a bit. I have hired a personal trainer to try and maintain the remaining muscle. Do you know if weight training makes a difference in stalling the progression? Is it worth intense physical

	therapy? Also, is there anything else I can do to fight the progression?
Dr Simard	I would very much like to be able to answer your question but I am more familiar with DNA and genes than I am with physical training etc. and I would definitely not want to guide you in the wrong direction. I think we had a chat previously with a physiotherapist, and may well again. Otherwise, send your question directly to the Families of SMA web site and they will find someone to answer your question adequately.
Administrator	H would like to ask: Do you think that patients, carrying SMN1 point mutations should have interest in other research than patients who miss this gene? Thank you.
Dr Simard	Absolutely, any mutation in the SMN gene can lead to SMA. We are lucky that most of the mutations are deletions or specifically affecting exon 7 because that makes mutation screening much simpler. But treatment of SMA does not depend on the type of mutation and thus should target all patients. I hope that this is what you wanted to know.
Admin	Thank you from H!
K	I'm the father of a 3½ year old boy with SMAII. Does there exist a known correlation between the SMN concentration in cells and the number (%) of motor neurons, which is active/working?
Dr Simard	We cannot really study motor neurons that closely and besides it would be very invasive in children that are already compromised. Therefore we really do not know what the correlation between SMN concentration and the number of motor neurons. This being said, in the animal models, there has been some work done and indeed animals with more SMN protein (in the SMA models) have more motor neurons. Thus it would be reasonable to assume that if we can increase SMN protein in motor neurons, they should function better. However, increasing SMN protein will not create new motor neurons. Unfortunately, motor neurons do not regenerate.
D	Can you tell us anything about the Indoprofin research news that went out yesterday?
Dr Simard	I took a little time this morning to read the article on Indoprofin. As you know, there are a number of groups that are screening known drugs for their ability to increase SMN expression from the SMN2 gene. Those that we know about include sodium butyrate, valproic acid and aclarubicin. There are positive and negative points on all of these drugs. This recent study identifies another drug that also has a small affect on increasing the amount of SMN made from the SMN2 gene. What is important in all of these studies is that they identify molecules that will allow chemists to now do research to try and improve them. By improving I mean, make them more potent, more safe etcetera.
T	Dr. Simard, I had a gene specialist tell me that if I go to a reproductive genetics institute and have them do testing on the sperm and the egg and have it implanted after the bad genes are taken out, that would make my chances of having another child with SMA at 0%. Would you recommend this?

Dr Simard	<p>What you say is correct. One can use reproductive technologies to make sure that you do not implant an embryo at risk of having SMA. What is done is they only implant the fertilized eggs that are not homozygous for SMN1 mutations. It really is not my place to recommend or not this approach. This is a decision that you will have to make on your own depending on how you feel about the success rates of this technology (and I am not talking about SMA risk here but of implantation) versus getting pregnant and then undergoing prenatal diagnosis and all that is attached with this. There is no perfect approach! Is this a sufficient answer?</p>
K	<p>Are the motor neurons, which are not "active" due to the low SMN protein level, dead, or are they just "sleeping" waiting for better times. I have learned from research that treating a paralysed rat with human stem cells presumably helps some of the existing ineffective motor neurons to work better.</p>
Dr Simard	<p>This is an excellent question and again difficult to answer because of our inability to do such invasive studies in the human. As best as I know, it is necessary for a motor neuron to make an effective contact with the muscle in order for a mature neuromuscular junction to be formed. If this does not happen (which is most likely the case in SMA) then the motor neuron retracts from the muscle, the muscle atrophies (thus the muscle weakness in SMA) and the axon slowly becomes smaller and smaller because it is not getting the proper contact with the muscle. The cell body of the motor neuron is in the spinal cord. When the cell body dies, I really do not know and I am not sure we have this information. This is why it may be important to replace motor neuron cells in SMA patients. And yes, having normal motor neuron cells will protect sick motor neuron cells.</p>
S	<p>Let me see if I understand all this - so if you have SMA III or SMA II then you should have an active SMN2 - since this one makes function of the motor neuron better than none? or am I completely wrong here?</p>
Dr Simard	<p>This is a great question - I was hoping that someone would get to this. Ok, we have two SMN genes that we call SMN1 and SMN2. SMA is caused by mutations in the SMN1 gene. Therefore, we can ask, but why is it that SMN2 does not take over for SMN1? This is because, SMN2, during evolution, underwent a very small change in exon 7 and now the SMN2 gene makes SMN that is missing the information provided by exon 7. This protein is unstable and cannot do the job sufficiently in motor neuron cells. BUT, SMN2 can make a little normal SMN protein, this is the hope. So the therapies are trying to trick SMN2 into making more normal SMN protein. Does this help?</p>
S	<p>Slowly ... getting there .. thanks.</p>
K	<p>Has it been confirmed that physical training of SMA patients leads to increased sprouting from axon end point (synapses?) of working motor neurons to muscle cells original connected to non-working neurons, and if yes what is the upper limit of this mechanism measured in strength increase if any?</p>
S	<p>I will join K and ask - how come you can see physical improvement</p>

	with training on SMAs?
Dr Simard	Again, this is one question that I simply am not qualified to answer. I think that it would be best to speak with a physical therapist because I really do not want to recommend something that could do more harm. However, it is true that one can encourage non-working neurons to sprout and make new contacts with muscle. This is why one of the therapeutic strategies that is being researched specifically targets ways at protecting the existing motor neurons to encourage this sprouting mechanism. And this ties in with S's comment. I am not familiar with the physical training data but one can encourage non-dead motor neurons to sprout (this means send out new axons) and make contact with muscle. As I mentioned before, as long as the cell body (this is where all the DNA, RNA and protein is being made) is intact, it can respond to stimuli.
V	Dr Simard, can the virus that is positioned on the gene break the replication program? Thank you.
Dr Simard	I am not sure what your question is but I guess your concern is the toxic effect of the viruses being used for gene therapy. A lot of work has been done to render these vectors non-toxic and they have been manipulated so that they function simply as vehicles to transport the gene of interest. So, this means that we remove as much of the DNA in the vector (e.g. herpes virus) as is possible so that it does not replicate itself. Then we insert, for example, the SMN gene with all the information it needs to produce SMN mRNA and thus SMN protein. So while these viruses sound scary because they have always been associated with disease, those being used for therapy have been modified. This being said, all studies must be carefully controlled to ensure that this is indeed the case and I believe that mechanisms are in place to ensure that these studies are tightly controlled.
V	I don't mean virus vector. May be another virus situated on gene and break normal splicing?
Dr Simard	I am not aware of anyone using viruses to alter splicing. But yes, one can put a different gene (not SMN) if that gene has a role in splicing. You are right in thinking that one of the targets is to change the splicing pattern of SMN2.
K	I had hoped that FES (functional electrical stimulation) might help keeping the motor units not working so good in a better shape, but from the research on this area it seems that this has no effect. Do you have any comment to this? Also, which stem cell strategy do you find the most promising - embryonic or adult (side population) stem cell approach?
Dr Simard	I know nothing about FES. As for stem cell therapy - it is still too early to say. Embryonic stem cell research has been severely hampered by government regulations and therefore there has been much energy placed in the research of adult stem cells. The data looks promising and we must continue to move forward. We must wait and see if adult stem cells will be as good as embryonic stem cells.
K	Would you advise parents to SMA children to get hold of stem cells

	from the umbilical cord during delivery of subsequent children?
Dr Simard	I have not really thought about this - it may be a good idea but it might be best to discuss this with your local hospital to see availability, safety and ethics of this strategy.
H	Back to genetics issues. Our adult son has SMA2. His brother has 2 kids apparently unaffected at ages 10 and 13. Sister has 4 "normal" kids ages 8-13. If I read you correctly, the children should consider genetic testing when they are of child-bearing age. Correct? Or are we hoping that by that era, the consequences of SMA2 will be trivial.
Dr Simard	I sincerely hope that your last comment is the right one! Unless we know the carrier status of your children it is hard to advise on their children. It would be advisable that all the brother and sisters be tested and if they are not carriers, then their children need not be.
H	Thank you.
F	I had a child recently pass away that had type1. I have a half-brother that I have not been in contact with in over 10 years who has three children of child bearing age. What is the chance that they would be affected by SMA?
Dr Simard	If the parent that was the SMA carrier is the parent in common to you both then he would be at risk. Do you know from whom you inherited the SMA mutation? This is not always the case because the grandparents are not always tested.
F	No I do not....so both of my parents would not have to be carriers?
Dr Simard	No, only one of your parents would most likely be the carrier because they never had an SMA child. I guess the best thing would be to simply suggest that he be tested if he is interested. If he is not a carrier, then his children again are not at risk. If that is not possible and they are concerned about being carriers, the best thing would be for them to talk with their doctor or a genetic counsellor and explain the situation and then the medical professional can guide them via their options.
F	Thanks!
Administrator	Our time is just about over. Thank you very much Dr Simard for coming and answering questions today!!
Dr Simard	It has been my pleasure!
V	Thank you Dr Simard - very interesting answers!