



# TRIGR Family News

Dear TRIGR Study families,

TRIGR study will be end soon. Our study has been going on smoothly and we are happy that all of you have been in this study for such a long time. You may already have had your last visit to the TRIGR center, but some of you will still be coming to the final visit. This visit is extremely important to have as many endpoints as possible for the final study results.

The microbiome ancillary study is going on and warm thanks to all the participating families! A balanced microbiota is extremely important for the health of all of us. In this study, we study the significance of the microbiome in the disease process leading to type 1 diabetes. It is still possible to take part in this study.

We have analyzed a fifth diabetes-associated autoantibody, zinc transporter antibodies (ZnT8A). You will receive these results in the next autoantibody report. In TRIGR, we have also started a new ancillary study named DIVIA, which sets out to assess among other things the role of circulating vitamin D and fatty acid concentrations in the development of type 1 diabetes. The asthma allergy questionnaire is still open on the TRIGR website. Please respond to that, if you have not already done so.

We will report the TRIGR results to each participating family by personal contact or by letter during 2017 when all the analyses have been completed. At the same time, we will report to which study formula group your child was randomized. The TRIGR study will continue as a web-based follow-up study and we wish to ask you to inform us if your child is diagnosed with type 1 diabetes through the TRIGR website (access restricted for TRIGR study members only)

*Mila Hyytinen, behalf on TRIGR team*

## Science News

### Zinc transporter 8 autoantibodies in TRIGR subjects

The TRIGR laboratory has analyzed zinc transporter autoantibodies (ZnT8A), and the results are now available for TRIGR families. The analysis of

ZnT8A gives us additional information on the development of beta-cell autoimmunity.

ZnT8A have been analyzed in TRIGR serum samples obtained at the ages of 2, 3, 4, 6, 8, 10, and 12 years. If the participant tested positive in one of these samples, any preceding samples have been analyzed to define the age at seroconversion.

In the TRIGR study, 8.2 % of the subjects (170 out of 2070) were positive for ZnT8A. Only 1.4 % (15 out of 1115) initially autoantibody-negative children turned autoantibody positive after the analysis of ZnT8A. In addition, only two children initially positive for a single autoantibody turned positive for two autoantibodies after the ZnT8A analyses, when ICA were included among the autoantibodies.

The mean age at seroconversion to ZnT8A positivity was 4.3 years, but these autoantibodies may appear already at the age of 12 months. In relation to the family history ZnT8A were the most frequent in those with two or more affected family members and more frequent in offspring of affected fathers than in offspring of affected mothers. Certain genotypes (genotypes including HLA DQA1\*05-DQB1\*02-positive haplotypes without the presence of haplotypes positive for HLA DQB1\*0302) were also associated with a decreased frequency of ZnT8A.

In conclusion, the frequency of ZnT8A increases with increasing age at least up to the age of 8 years. There seems to be no major regional differences in the frequency of ZnT8A in children with at least one affected family member. Positivity for single ZnT8A is rare (< 2%) and these autoantibodies relatively seldom appear as the first autoantibody specificity. The contribution of ZnT8A to multiple ( $\geq 2$ ) autoantibody positivity is modest.



*Mikael Knip, Professor, TRIGR PI*

## TRIGR Asthma and Allergy study

Asthma and other allergic diseases comprise the most prevalent chronic disease group in children, and it would be important to find ways how to prevent these diseases. TRIGR Asthma and Allergy study is set to find out whether extensively hydrolyzed infant formula during infancy would protect from asthma and allergies during childhood. The TRIGR cohort is an unselected group as far as genetic asthma-/allergy risk is concerned and therefore offers a great setting for this research question.

So far 49% of all TRIGR children have completed the questionnaire. We do hope that all the rest of you will also participate in this study! Your input is important whether or not your child has ever had asthma or allergy.

You are able to answer the questionnaire at the final TRIGR visit or at the TRIGR website until the end of February 2017.

<https://www.trigr.org/asthma/views/welcome>.

*Tuuli Korhonen, Nutrition researcher*

## TRIGR DIVIA Study (Effect of early diet and virus infections on immune regulation and the development islet autoimmunity)

We have started a new TRIGR ancillary study called DIVIA, which will be carried out during the years 2015-2018. The DIVIA study will generate important new information about the environmental candidate risk factors of type 1 diabetes. The aim is to evaluate associations between dietary fatty acids, vitamin D, cow's milk exposure and viral infections with the function of the immune system as well as the development of prediabetes. The DIVIA study will be based on blood samples collected in the TRIGR cohort at 3 to 12 months' intervals. From the blood samples we will measure fatty acids and vitamin D concentrations as dietary biomarkers; virus antibodies as markers of viral infections; antibodies to cow's milk and dietary bovine insulin as immunological markers; and cytokines and chemokines as inflammatory markers. The DIVIA study will clarify complex interactions and mechanisms of the process leading to type 1 diabetes.

*Sari Niinistö, DIVIA coordinator and Nutrition researcher*

*Suvi Virtanen, Professor*

## Do vaccines cause type 1 diabetes?

TRIGR of course is focused primarily on the possibility of cow's milk being a factor increasing the risk of diabetes, but there have been other proposed agents such as other foods, viral infections, trace toxins, etc. In addition, vaccinations have always been questioned as being possible stimulants to the immune system that can start the islet cell destruction that eventually causes type 1 diabetes.

Measles, rubella, hemophilus, pertussis, hepatitis B and influenza have all at one time been implicated, but as yet no credible evidence exists that suggests that any one, or any combination of vaccines, increases the risk of T1D. In fact, the most recent research strongly finds no effect of vaccinations on T1D incidence.

The TRIGR trial, because of its large worldwide collection of children at high risk for diabetes, is in a unique position to help determine whether there is an association between diabetes and vaccinations, or to confirm that there is not. By using the vaccine information received from all participating families, we will be able to "look backwards" and see if any particular vaccines or combinations of vaccines increase the incidence of type 1 diabetes in our study cohort.

But we cannot do this without the data! Please be sure to make sure that you report all vaccines to your TRIGR coordinator, so that we have the most accurate information possible. Thank you!



*Barney Softness, M.D.  
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## Kid's stories

Hi!



I had the pleasure to interview 12-year-old Liisa Aaltonen. I have met Liisa for the first time as a small baby. Liisa's family consists of the mother, father, 15-year-old sister Kirsikka and the dogs Arttu and Bruno. Arttu is 11-year-old mix of border collie and kelpie, and Bruno is 3-year-old border

collie. Liisa walks dogs every week close her home, which is in eastern Helsinki.

On Thursdays Liisa travels by metro cello lessons in Western Helsinki. Liisa belongs to pet club and scouting. The name of her scout group is Kontu Girls. Other hobbies are dance-gymnastics and rock climbing. Liisa dates also her friends and plays with her new computer. Game night is Thursday. Liisa plays usually SSO (Star Stable Online). She also listens to pop music on Youtube and socialize with her friends on Skype. On Thursday of this week there is a my school trips different program: she is going with her godfather to an ice hockey match and after the match they will go to a good restaurant for dinner. This is a birthday gift from her godfather. At weekends Liisa has also time to chill out.



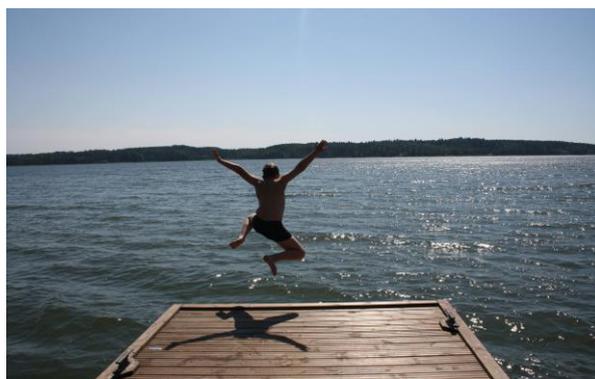
Liisa's mother heard of TRIGR when she was expecting Liisa. Liisa's father has type 1 diabetes. They wanted to register Liisa already before her birth. Liisa thinks that it has been nice to come for the TRIGR visit, even she has been nervous before the blood sampling similar to her feelings before vaccinations. However, EMLA anesthetic patch has helped, although sometimes Liisa has wondered whether it is working. She has anyway survived blood sampling just fine. Visits to playroom of Children's Hospital have also been fun.

*Päivi Kleemola, TRIGR-coordinator*

Hi!

I am 13-year-old Saku Ahde from Finland. I have been in TRIGR since I was born, and I had now my last study visit in the Children's Hospital in Helsinki. The mother has diabetes in our family.

We live in Helsinki, which is the capital of Finland. I go to Arabia elementary school. The school has 600 pupils and there are 24 students in my class, more girls than boys. I travel my school trips by bus or cycle. It depends on how busy I am that morning. I like English, math, physical education and arts.



My hobbies are swimming and architecture. I have practiced swimming 5 years, and at the moment I practice five times a week. We carry out a variety of guided exercises, refine our technology and we are developing our resistance. The best thing in swimming is training camps with friends. Sometimes it's boring in swimming competition, because you have to wait for your own execution for several hours. I have got one of my best friends through my swimming hobby. I see him also otherwise than in the swimming hall.

My second hobby is architecture. I go to Children's and Youth School of Architecture "Ark". I have been there for 7 years, and we meet once a week. We design and implement our ideas using unusual materials. It's possible to implement even crazy ideas, if they are designed properly. We are learning how to use design programs and scales, shape clay and participate in various design competitions. Sometimes we participate also in exhibitions. At the moment we are scaling models of the future houses, in which we would like to live.

I play outdoors Pokémon go with my friends. Best Pokémons can be found in Sea Fortress Suomenlinna, which is an island of Helsinki. We travel to Suomenlinna by ferry. I spend time with my family at our cottage, we cycle, cook together, surf with sup board and we are interested in other water sports. I was able to explore underwater

world, enjoy warm water and a big natural aquarium last winter, when we were on vacation in Mauritius. The fish were just amazing!

My autumn holiday is beginning. It takes one week. I and my mother are travelling to my grandmother's place Tihusniemi. I'm going to help my grandfather with building a cottage, fish and grill sausages by the campfire. Not forgetting sauna and gourmet food! We also celebrate my birthday with a larger group. My grandmother is a very good cook. In the summer I go fishing with my grandparents to River Teno, which is located in Lapland, Northern Finland. Two summers ago I got the first salmon in my life. It weighed 3.7 kg.

*With autumn wishes, Saku*

