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Information on Study
of

Mosaicism and Risk Prediction in Parents of Children with *de novo* Variants (MORNOVA)

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Dear probants,
Dear parents,

the following pages provide you with information on the MORNOVA research project.
This information sheet intents at itroducing you to the research and build an informational foundation upon with you can decide whether you would like to participate in the project.
Please take your time reading this information sheet and don‘t hesitate to ask any questions once they arise. Surely, speaking with your partner, familiy members, friends or seeking medical advice from a family doctor can be helpful before making a decision. In case of participation, we kindly ask you to fill out the declaration of consect you will find attached.

Why am I asked to participate in the study?

You have been asked to participate in the study because your child has been diagnosed with a genetic condition that, with the common diagnostic methods, could not be detected in blood samples of you as parents. For this reason, the detected genetic variant is classified as a spontaneous, newly occurring (*de novo*) variant. By this time, the variant has been identified by a diagnostic or scientific method independent of this study and a *de novo* classification could have already been verified by an analysis of blood samples of both parents.

What is the study about?

This study aims at achieving a better understanding of *de novo* genetic variants and intends to collect information on the background of the probability of reocurrence. Specifically, the genetic region that holds the variant will be analysed with the so called next generation sequencing, a very modern and precise method of sequencing that shows even the slightest anomalies (*mosaicism*). By analysing the genetic code with next generation sequencing, such anomalies can be identified even in clinically healthy parents which would give reason for allegedly *de novo* variants of the patient. Doing so, the risk of reoccurence in future children can be calculated.
To ensure a high informative value, analysis of the DNA is planned to be performed with samples from all three blastodermic layers (buccal swap → ectoderm; blood → mesoderm; urine → entoderm). On top of that, the study includes sperm samples, which analysis indicates direct results concerning the male germplasm. These processes exceed the common diagnostic measures (analysis of blood samples).

Who is doing the research?

The study is led by Prof. Dr. med. Rami Jamra and Dr. Sonja Neuser of the Institute of Human Genetics of Leipzig Medical Centre. We are experienced in international cooperations for studies concerning the topics of newly occurring mutations and rare genetic conditions. In collaboration with various diagnostic laboratories, we would like to access previous genetic reports and, if applicable, DNA samples of yours. In the inclosed declaration of consent you will be asked to give your permission.

Do I have to participate?

Participation in the study is not mandatory. Refraining from participation will not mean disadvantages for you concerning future medical support on genetic questions. The same applies if you decide to retract your consent at a later point of time, which is always an option. In this case an explanation is not needed. If you wish, the data and samples taken from you will be annihilated. The participation of a minor without the consent of their legal guardian is not possible. Participation in the study does not lead to any private or health insurance costs. Also, participation is not granted with a financial compensation. Any postal expenses are borne by us.

What is asked of me to participate in the study?

Requirements for the participation in this study are the absence of a pregnancy and that the child's parents are the biological parents. On top of that, full consent for the usage of preliminary reports from other diagnostic laboratories and, if applicable, also DNA-samples (from blood) is mandatory. These samples are, however, solely significant for quality assurance. Still, if samples run empty or appear missing, additional blood sampling by the family doctor will be necessary. On top of that, a urine sample of about 100 ml and two swaps of the oral mucosa are needed. Additionally, a semen sample is asked of the father. Instructions on sampling, transport containers and shipping materials will be provided by us. If no further blood samples are needed, an additional visit to the doctor will not be necessary. Even if, for prior diagnosis, you have already given your consent for the usage of your DNA-samples, a further declaration of consent is needed for our study since, on top of blood, we other tissue samples are used. We kindly ask you to give us permission to access genetic reports and former DNA-samples.

If, for any reason, sending all samples means too much of an effort for you, we kindly ask you to send at least the semen sample since it holds the greatest research value for us.

Which benefits does the study have for me?

If the analysis of your samples show normal results, there will be no further consequences for you. In the case of results pointing at mosaicism, you will have the opportunity to seek out advice concerning the overall effects such low-grade genetic variants have and the probability of recourrence in case of further pregnancies.

How will this study help other families in the future?

Looking into the future, the achievements made with this study can provide further diagnoses with a greater insight on the development of rare genetic conditions through *de novo* mutations. Furthermore, patients will receive more detailed information on a potential risk of recourrence in their families.

What could be the potential inconveniences?

For the study we asks to use DNA samples from urine, oral mucosa and blood from both parents and a semen sample of the father. At best, prior blood samples can be used. However, if these are not available, an additional blood sampling will be necessary. Here, blood will be drawn from the vein by using a small cannula. Doing so, small hematomas or local vein inflammation can occur. These do not mean any further health risks and normally heal within a few days without treatment. In rare cases clotting of the blood, so called thromboses, and damaging of the nerves are possible. If you decide to participate in the study, we ask you to use the material sent to you as instructed and send all samples, at least the semen sample, back to us. The samples are easily taken at home and sending them via the regular postal way is no problem. Here, no costs arise for you.

Please do not forget to add the signed declaration of consent to the package!

Which effects do abnomal findings have?

If the analysis of your samples show abnormal finding, we will reach out to you with a detailed report of the results as agreed upon by you in the declaration consent. Any wishes to not consent to receiving such reports will naturally be respected. The analysis of your DNA is limited to the area prior defined in the diagnosis of your child's genetic condition. On top of that, we will exvlusively focus on the finding of low-grade mosaicism.

How is my data stored and accessed?

In a scientific study, personal data and medical reports are collected. In this study, the data is anonymized and saved on servers of the University Hospital Leipzig. The data is subject to the european data protection law which means that clinical data must have a reference number of which only staff of the study itself know the corresponding patients. Your name will not occur in any publications whatsoever and during the study all rules and laws concerning data protection will be respected

Who can I reach out to concerning questions?

If anything is unclear to you or in case of further questions you can always reach out to the responsible doctors and members of the study group mentioned above.

Thank you for your participation and please do not hesitate to reach out to us.
Sincerely, Institute of Human Genetics Leipzig