



# The Genetics of Childhood and Adolescent Epilepsies

Research Project of the Pediatric Epilepsy Genetics Research Group,  
Department of Neuropediatrics,  
University Medical Center Schleswig-Holstein, Campus Kiel

Group Leader:  
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Enclosed are

- Information sheet for genetic research
- Declaration of Consent (2 pages) for the participation in scientific research
- Declaration of Consent for the release of confidential medical information



## **Information Sheet for Genetic Research**

### **Project: The Genetics of Childhood and Adolescent Epilepsies**

**Investigators:** PD Dr. med. Andreas van Baalen, PD Dr. med. Hiltrud Muhle (group leader), Prof. Dr. med. Ulrich Stephani (Dean, Faculty of Medicine), PD Dr. med. Sarah von Spiczak, Dipl.-Biochem. Manuela Pendziwiat, Annika Rademacher – Pediatric Epilepsy Genetics Research Group, Department of Neuropediatrics, UKSH, Campus Kiel.

**Thank you for taking the time to read this information sheet.**

This information sheet contains eight pages. Please ensure that you read all eight pages.

The following pages contain information about a research project, in which we invite you and/or your child to participate. The purpose of this information sheet is to detail all of the steps and procedures of this research project. This information should help you decide if you would like to take part in this project.

Please read this information sheet carefully. At any time you may ask questions regarding any aspect of this research project. You may discuss this project further with your partner, family members, or friends or with a healthcare professional whom you trust (nurse, pediatrician, family physician). If you understand the intentions and goals of our research project and would like to consent to your (or your child's) participation in this project, we ask that you please sign the Declaration of Consent, which you will find at the end of this information sheet. You will receive a copy of the Declaration of Consent with the signature of an investigator to keep.

If you are treated at another hospital or in another department and were asked to participate in this research project, a co-operative agreement exists between your hospital and the Department of Neuropediatrics in Kiel.

**For individuals, whose first language is not German or English**

This information sheet and the attached consent forms have been translated from the original German version, which has been approved by the Ethics Committee at the University of Kiel, Germany. If German is your preferred language, please ask for the German information sheet and consent forms.

If you speak a language other than German or English and are interested in participating in our research but have difficulties understanding, please have a person whom you trust explain this project and/or translate this information sheet. We ask that you only consent to participate in our research if you understand this information sheet.

**You are asked to participate in a research project, which will be explained on the following pages.**

**We would first like to explain to you some terms, which will be used repeatedly in the following pages:**

- Genetics: Science of Inheritance and Heredity, aiming to understand the factors that are responsible for variation in living organisms
- Chromosome: Structures in the cell nucleus, which contain genes and hereditary information. Humans have 22 chromosomes, which are present in pairs, as well as sex chromosomes. The same number of chromosomes is inherited from the father as from the mother.
- DNA: Deoxyribonucleic Acid, contains hereditary material. This is extracted from blood cells and used for further research.
- Gene: Section of DNA, which contains instructions for a specific protein. Humans have approximately 30,000 genes.
- Exome: All protein-coding parts of the DNA.
- Genome: All genetic material, including genes and parts between genes (which still might include relevant information).



### **What is this research project about?**

The term “epilepsy” covers a wide and heterogeneous spectrum of different seizure types, which may have a wide range of causes. If seizures occur more than once without a provoking factor, the diagnosis of epilepsy is made. About 1% of the population worldwide has some form of epilepsy, and about 3-4% of the population will have an epileptic seizure at some point during their lives. Therefore the epilepsies are among the most common neurological disorders.

There are two main forms of epilepsies: idiopathic and symptomatic epilepsies. In symptomatic epilepsies, the cause is known: for example, the epilepsy develops after an accident or brain injury. However, idiopathic means that the cause is unknown. It is assumed that in these forms of epilepsy, genetic changes, i.e. changes in the hereditary material, predispose to the development of epileptic seizures. In addition to these genetic factors, additional factors are likely necessary for the development of epilepsy, such as certain environmental factors. The knowledge of these basic principles would help us better understand what conditions and alterations are necessary for the development of epileptic seizures. This knowledge could improve diagnostic techniques and therapies for seizure disorders. Further research could lead to the development of medications that specifically affect the genetic alteration, and therefore better treatment results with fewer side effects could be made possible. This is already essentially possible in Severe Myoclonic Epilepsy of Infancy, in which, due to the underlying genetic alteration, certain medications are avoided and special newer antiepileptic drugs are used instead. Similarly, commercially available genetic tests allow for a definitive diagnosis of Severe Myoclonic Epilepsy of Infancy. During the last few years, more examples of treatment approaches specific to certain genetic defects were described.

Unfortunately, despite intensive research from many groups around the world, still little is known about the genetics of the epilepsies. One of the reasons for this is that for common forms of epilepsy, for example Childhood Absence Epilepsy, many different genetic alterations are necessary, each of which contributes a very small effect to the development of epilepsy. Furthermore, the clinical characteristics of the epilepsies are often different, which can make the diagnosis and classification of disorders difficult. Therefore, research into the genetic basis of the epilepsies requires very large patient numbers, which are typically only attainable through collaborations between many international groups.

### **Who carries out this research?**

The research project for the Genetic Basis of Childhood and Adolescent Epilepsies is carried out by the Pediatric Epilepsy Genetics Research Group in the Department of Neuropediatrics at the University Medical Center Schleswig-Holstein. The research group is led by PD Dr. Hiltrud Muhle (group leader, consultant), PD Dr. Andreas van Baalen (Acting Director, Department of Neuropediatrics, UKSH), and consists further of Prof. Dr. med. Ulrich Stephani (Dean, Faculty of Medicine), PD Dr. med. Sarah von Spiczak (consultant, Northern German Epilepsy Center for Children and Adolescents), Annika Rademacher (resident physician, Department of Neuropediatrics, UKSH) and Dipl.-Biochem. Manuela Pendziwiat (biochemist). Our research group is contactable on the internet at [www.epilepsygenetics.net](http://www.epilepsygenetics.net) and via e-mail at [info@epilepsygenetics.net](mailto:info@epilepsygenetics.net).

We carry out various projects investigating the genetics of childhood and adolescent epilepsies both ourselves and in collaboration with other research groups from Europe, the United States, and Australia. On our homepage, you can also find detailed descriptions of individual projects.

### **Why was I invited to participate in this study?**

You and/or your child were invited to participate in this study because you and/or your child or one of your family members have had an epileptic seizure or febrile seizures, a diagnosis of epilepsy, another neurological disorder (for example Restless Legs Syndrome), or a positive EEG recording.

### **What are the alternatives to participating in this project?**

If you or your child decides not to participate in this project, this decision will not affect your or your family members' medical treatment. You or your child will experience no disadvantages in your treatment. Furthermore, at any time you and/or your child are permitted without explanation to end your participation in this study, to not answer questions regarding this study, or withdraw from further investigations. In this case, genetic material, information about potential results, as well as clinical data collected for this study will be destroyed.



It is important to us that we clarify that medical treatment and participation in our research project are independent of one another. If you decline to participate in this study, we will make an appropriate note in your medical record in consultation with you, in order to save you from repeated questions about participation.

### **What must I do to participate in this study?**

For participation in our study, we require a blood sample or a sputum / urine spot (see below) as well as some information about your medical history relevant to our research.

**Medical history data:** We are primarily interested in the details of any epileptic seizures that either you or your child/family member have experienced. For unaffected family members, we utilize a questionnaire to determine whether the individual previously had seizures, which were possibly unrecognized. There are certain types of seizures that are very brief and do not have typical epileptic “convulsions”, which perhaps would not be recognized. We will ask you further questions about your birth, developmental milestones, and medical history to determine if there is anything noteworthy. This information will be handled with strict confidentiality.

**Further examinations:** In some families, it is scientifically reasonable to further investigate the disorders of affected individuals. Should this be the case, we would recontact you and possibly ask you or your family members to undergo clinical or neurological investigations. For such investigations, typically tests of reflexes, strength, or function of the eyes and muscles are undertaken. Occasionally we ask study participants to have an EEG. The EEG (electroencephalogram) records electricity in the brain. This is not painful.

**Taking a blood sample:** To participate in this study, we require a blood sample (20 ml, approximately two tablespoons) to examine the genes that are related to the illnesses discussed above. We require a smaller sample from children. From the blood cells, we will extract the genetic material, which contains DNA, which will be used in further investigations. If you agree, we would additionally ask for your permission to use a portion of the blood cells to create a cell culture line, i.e. to grow up cells so that we have more hereditary material (DNA) available for our investigations. In these cases, we will ask separately for your permission, and this will only happen with your explicit consent. The required blood sample will normally be taken during routine blood draws, so that no further blood draws are necessary. If an additional blood sample was taken at a previous blood draw, we would ask for your permission to use this sample. It is also possible to obtain a blood sample at a future medically necessary blood draw (e.g. from your family physician).

Occasionally, we request additional saliva or urine specimens. DNA can be derived from blood and skin cells within these samples and might be used for further research. Saliva specimens are taken by swabbing the mouth with a small brush, urine is collected in special containers.

**Sample storage:** Your blood / saliva / urine sample, labeled with your name and date of birth, will be brought to our laboratory, where a number will be assigned to the sample. This sample, which no longer contains your name, will be used to extract the hereditary material (DNA) (eventually by an external laboratory, e.g. The Institute for Clinical Molecular Biology, Prof. Schreiber, Christian-Albrechts University Kiel and UK-SH, Campus Kiel). The employees of this laboratory are not able to obtain your name or personal information from the sample number.

The samples are stored for current and prospective research projects until they are used up, you withdraw from the study or the Epilepsy Genetics Research Group at the Department of Neuropediatrics dissolves.

**Sample analysis:** The genetic material is used exclusively in investigations of genes that play a role in the epilepsies, other neurological disorders (for example, Restless Legs Syndrome) and positive EEG patterns. Different genetic methods are used such as sequencing of single genes, investigation of larger anomalies such as gains or losses of genetic material. Newer methods make it possible to search for alterations in the entire genome (i.e. all the genes humans have). The analysis of these studies pertains exclusively to genes that appear to be relevant to the epilepsies.

**Inclusion of parents:** For many investigations, it is necessary that both parents are recruited in addition to the patient. Additional genetic information gained from the parents is used to assess the relevance of research findings. Large scale projects such as exome or genome sequencing are dependent on the recruitment of parental samples as these as essential for data analysis.

**Contact to family members:** To assess the relevance of research findings, it is often very helpful to use additional information from further family members. Affected as well as unaffected family members will



be contacted by telephone, if they indicate that they are willing to be contacted. We ask that you inform your family members about this study and ask if they are willing to participate. Any interested family members can gladly call us, or you can pass along their contact information so that we can explain the research project to them and send them an information sheet and consent form. If an individual declines participation in the study, we will not contact them.

Occasionally we also ask unaffected people to take part in these investigations because, for example, a positive EEG recording can also be seen in healthy individuals. We would also ask you in these cases to inform your family members about this procedure and ask if they are willing to participate.

It is important that you decide which information about your disorder/your child's disorder or information about your medical history in general you would like to pass on to other family members. If you prefer that family members not know about your diagnosis or your participation in this study, we will respect this wish, and no further contact will be pursued. This decision has no influence on your or your family members' medical treatment in our hospital. In consultation with you, we would make a note in your medical record, to prevent further questions about participation.

### **What is done to ensure that my information remains confidential?**

We are particularly interested in epilepsies of childhood and adolescence, which commonly change during the course of development or occur only in certain age groups. Often specific aspects of a disorder are important for research. For both reasons, it is important that we obtain information about the diagnosis, seizure types, the response to certain medications if applicable, and the occurrence of seizures, epilepsies, and other neurological disorders in the family.

Only a member of the Pediatric Epilepsy Genetics Research Group in the Department of Neuropediatrics, UK-SH, Kiel is able to correlate personally identifying data to a specific blood or DNA sample. All other colleagues receive only the sample number as identification. When samples are sent to a collaborative partner, the sample receives a new code. Personally identifying data will never be given to a collaborative partner.

**Samples dispatch, external data storage and data transfer:** Genetic studies are often performed in national or international research collaborations due to the complexity and high costs of these investigations. Accordingly, pseudonymized samples (labelled with numbers without any reference to personal data) might be sent to other research groups at universities, research institutes or companies performing research in Germany or abroad for specific research projects. It might happen that data are linked to other data and databases as far as legal regulations are respected. We cannot exclude that data protection laws are less strict in other countries compared to Germany. Samples that are sent to other research groups are used only for specific projects and will not be sent on from there. Genetic material that is left over from these projects will be sent back to us or destroyed.

In this context, the generated genetic data may be stored in external research centers. In addition, we might transfer limited clinical information to external research centers such as gender, type of epilepsy, age of onset. Personal and identifying clinical data will never be transferred to other research centers.

In addition, some collaborative research projects require that genetic and limited clinical data be transferred to third-party research groups for future projects, without obtaining the approval of the study participants or the Pediatric Epilepsy Research Group, Kiel for each future project. One example may be the storage of genetic information within the *European Genome Phenome Archive* ([www.ebi.ac.uk/ega/page.php](http://www.ebi.ac.uk/ega/page.php)) or other depositories. This requirement aims to maximize the scientific output of the generated genetic data. Third-party research groups may also use the genetic data for additional scientific purposes other than looking for epilepsy genes.

If you withdraw from the study, clinical and genetic data will be deleted in the associated external research centers as far as possible. However, in principle, we cannot exclude that copies of the dataset still exist due to prior transfer to third party research groups.

### **What happens if a positive result is found in my genes?**

Finding genes that contribute to the epilepsies is a lengthy process and is not always successful. It may take several years before we can provide significant information.

If we do obtain a result that pertains to you or your child, we will only communicate this information if you have expressly indicated that you wish this (see Declaration of Consent). This is indicated by an appropriate tick in the box "I would like to be informed about any results from this research project concerning me/my child." If you would not like to be informed about potential results, we will naturally respect this wish.



Within the framework of genetic research projects different forms of results might come up depending on the methods used:

**Risk factors:** In many cases, the results from genetic investigations pertain only to a group of probands or patients but not to individual people. In these cases, a risk factor is identified. This is comparable to statements such as, “Smoking increases the risk for heart disease” (a prediction for an individual smoker cannot be made). In this case, we cannot give you a prediction about your personal result.

**Results with definite clinical relevance with respect to the epilepsy:** In other cases, in which we search for specific alterations in individual genes, we will receive a personal result. Possibly, the identified gene is a definitive cause of a known disorder. For example, such results are obtained from (diagnostic) tests for alterations in the gene *SCN1A* in Severe Myoclonic Epilepsy of Infancy. Because this result would be obtained in the context of a scientific investigation and not for diagnostic purposes, we would only communicate this result if you expressly indicated that you wish this. Please consider this for the appropriate point in the Declaration of Consent. An appropriate tick in the box “I would like to be informed about any results from this research project concerning me/my child” indicates that you would like us to communicate this information to you.

**Results with unknown relevance to the epilepsy:** There are also known alterations that are found more often in patients with a specific disorder. However, the exact meaning of such an alteration in such disorders is still unclear. This pertains to alterations in which parts of the chromosomes are lost or gained. Should we find such a result in you/your child, we would share this information – if you wish to be informed of it – in the context of a genetic counseling session.

**Incidental findings:** The term “incidental findings” describes results of scientific or diagnostic genetic investigations, that are not linked to the disease of question (i.e. epilepsy). However, these findings may be relevant to individual participants in the context of diagnosing, preventing or treating disorders other than epilepsy. One example may be the identification of genetic alterations that predispose to cancer or to cardiovascular disorders that might result in early detection and possibly treatment of these disorders.

**During this project, we are not purposefully looking for these alterations.** However, should we identify relevant results incidentally, we will discuss within an expert panel whether and in which context these results will be returned to you. This information will only be returned to you if you indicate that you would like to be informed about incidental findings. Incidental findings regarding future diseases without any possibility of prevention or treatment (e.g. Huntington’s Disease) will never be reported.

#### **Will this study benefit me?**

Most probably, participation in this study will not directly benefit you/your child, regarding treatment or disease prognosis.

#### **Will this study benefit others in the future?**

The knowledge that we obtain through your participation in this study may lead to a better understanding of the epilepsies in the future. These findings may possibly also lead to the development of newer medications or other treatment options.

#### **What are the potential discomforts of participating in this study?**

A blood draw may be associated with brief pain or discomfort for you or your child and may lead to a bruise. Hence, it is possible that you combine the blood draw for this study with a routine blood draw by your family physician or pediatrician. Rare risks associated with blood draws are infection or nerve damage at the injection side.

Taking a saliva specimen might be associated with mild discomfort for the moment of sampling. In very rare cases superficial trauma of the buccal mucous membranes might be caused which normally heals very quickly.

#### **What are the potential risks or side effects of participating in this study?**

There is the theoretical possibility that in the future, genetic information that is communicated to the family could influence your health insurance (especially private health insurance) or professional opportunities. In Germany, this is legally forbidden for diagnostic genetic tests (except for very high insured amounts, e.g. Life-, Long Term Disability- or Disability- Insurance, with benefits exceeding 300,000€ in total or 30,000€ per year; Gene Diagnostics Law). Similar legal frameworks prohibiting patients from discrimination based on genetic findings are in place in the United States of America. In Germany, an ap-



appropriate law now does not exist for genetic data obtained through the participation in a research project. Although an effect of potential results of genetic research on insurance, etc. is very unlikely, it cannot be excluded now due to inadequate laws.

Theoretically, it is possible to identify individual study participants based upon their genetic data. Any attempts to use research data to re-identify study participants is unethical. All research projects using your DNA samples or sequence data agree not to identify research participants by contract. Accordingly, any attempt to identify research participants is illegal.

In rare cases, genetic investigations uncover unexpected results, e.g. the fact that parents are not the biological parents. This information will **NOT** be communicated.

There is the possibility that you may feel guilty about the knowledge of your genetic risk factors. It may be that genetic alterations that appear to be responsible for a child's illness are also found in an unaffected parent. This may also make you feel guilty. Passing on genetic material to a child occurs by chance and is not intentional. It is very important that we stress that nobody is responsible for the child's illness.

### **May I decide on the participation of my minor child?**

If you as a parent are asked to agree to your child's participation in our research project, the special situation exists that you must decide for your child what information is to be disclosed. We ask you to consider that the knowledge of genetic risk factors or genetic alterations at a later time point may cause guilt for your child, such as during puberty or when your child starts a family of his/her own. We will not directly pass on information about genetic findings to minors.

Should your child for him/herself decline participation in the study, we will respect this decision. The participation of a minor aged child against the will of a parent/legal guardian is not possible.

### **What happens if my child turns age 18?**

We will contact all probands who were recruited for our research project as children when they reach the age of 18, to obtain renewed consent for the use of their DNA samples for research purposes. At that time, we would also discuss again issues surrounding the disclosure of results. Should the individual decline further participation, we would destroy the DNA sample as well as all clinical information. In the case that the individual is still treated in our hospital, under no circumstances would there be any disadvantages for medical care.

If, despite appropriate efforts, contact is unable to be made with an adult age proband, we will make this individual's DNA sample anonymous. This means that all personally identifying information will be destroyed, so that a correlation between sample and individual is no longer possible, even for us.



**You can freely decide if you would like to participate in this research project. You can at any time end your participation in this project without explanation. In this case, genetic material, information about potential results, as well as study related clinical data will be destroyed.**

**It is possible that you would like to discuss participation in this research project with your family or your (family) physician. If you would like, you can obtain further information from us.**

**If you would like further information about this study, please contact one of the following individuals:**

PD Dr. med. Hiltrud Muhle, Consultant, Dpt. of Neuropediatrics, Tel.: +49 (0)431-500 24140 / 23982, E-Mail: [hiltrud.muhle@uksh.de](mailto:hiltrud.muhle@uksh.de)

PD Dr. med. Sarah von Spiczak, Consultant, Dpt. of Neuropediatrics and Northern German Epilepsy Center for Children and Adolescents, Schwentinal-Raisdorf, Tel.: +49 (0)4307-909 201, E-Mail: [s.spiczak@drk-sutz.de](mailto:s.spiczak@drk-sutz.de)



## Declaration of Consent for participation in a scientific study

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Telephone

### Project: The Genetics of Childhood and Adolescent Epilepsies

**Investigators:** PD Dr. med. Andreas van Baalen, PD Dr. med. Hiltrud Muhle (group leader), Prof. Dr. med. Ulrich Stephani, PD Dr. med. Sarah von Spiczak, Dipl.-Biochem. Manuela Pendziwiat, Annika Rademacher – Pediatric Epilepsy Genetics Research Group, Department of Neuropediatrics, UKSH, Campus Kiel.

I \_\_\_\_\_ consent to participate in the above-named study, which was explained to me by Dr. \_\_\_\_\_.

- I received a copy of the Information Sheet, and I understand the purpose of this project. I understand the explanations of each point of the Information Sheet and know what is required of me in the context of this research project.
- I understand that results from this research will only be passed on to me if I wish this.
- I understand that I have a right not to know.
- I understand that genetic counseling will be offered to me upon communication of research results.
- I understand that research results can have personal consequences for me/my child.
- I had the opportunity to ask questions and am satisfied with the provided answers.
- I understand that the researchers are obligated to handle all my personal information with strict confidentiality. This is required in the context of this research project by the vote of the Ethics Committee of the Christian-Albrechts-University Kiel.
- I know that within collaborative research projects pseudonymized samples (i.e. without any identifying data) might be send to partners within Germany and abroad.
- I understand that my identity cannot be determined if the results of this research project are published in any form.
- I understand that, in the case of declining participation or withdrawal from this research project, I/my child will receive the best possible treatment at the Children's Hospital of UKSH and that this will not affect my medical care.
- I know that in this case, genetic material, information about potential results, as well as clinical data will be destroyed.



I, \_\_\_\_\_, agree to the following  
(Please place a tick in the appropriate box).

- The taking of a blood/tissue sample exclusively for this research project:

**OR**

- The taking of a blood/ tissue sample for this research project and future research projects, which have been reviewed by the Ethics Committee. I have been informed that I will **BY ALL MEANS** be asked before my blood/tissue sample is used in a future research project on the topic of “The Genetics of Childhood and Adolescent Epilepsies.”

**OR**

- The taking of a blood / tissue sample for this research project and future research projects, which have been reviewed by the Ethics Committee. I have been informed that I will **NOT** be asked before my blood/tissue sample is used in such a future research project on the topic of “The Genetics of Childhood and Adolescent Epilepsies.”

After discussing this consent form with the explaining physician, I have been sufficiently informed about:

- Specific consent for high-throughput sequencing**
- Returning information to participants**
- Dealing with incidental findings**
- External data storage, data management and data transfer**
- Withdrawing from the study**
- Inclusion of parents in the study**
- I would like to be informed about results of this research project of **clear and unambiguous clinical relevance** that concern **me/my child**. I know that in this context, genetic counseling will be provided.
- I would like to be informed about **incidental findings** of this research project that concern **me/my child**. I know that in this context, genetic counseling will be provided.

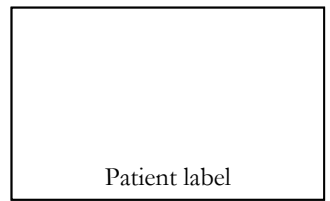
Signature of participants (> age 18 y) OR both parents / legal guardian (< age 18 y)

Signature of Participant: \_\_\_\_\_ Date \_\_\_\_\_  
Signature of Mother: \_\_\_\_\_ Date \_\_\_\_\_  
Signature of Father: \_\_\_\_\_ Date \_\_\_\_\_

**I have explained the research project to the above named participant and insure that, in my opinion, the participant understands the purpose, scope, and possible side effects of the research project.**

Signature of explaining physician \_\_\_\_\_ Date \_\_\_\_\_

Note: All signing individuals must fill in the date themselves



**Declaration of Consent for  
the release of confidential medical information**

I, \_\_\_\_\_, agree to the use and release of medical records  
from the following physicians:

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regarding: \_\_\_\_\_

for the research project “The Genetics of Childhood and Adolescent Epilepsies”, carried out by  
PD Dr. med. Andreas von Baalen, PD Dr. med. Hiltrud Muhle, Prof. Dr. med. Ulrich Stephani,  
PD Dr. med. Sarah von Spiczak, Dipl.-Biochem. Manuela Pendziwiat, Annika Rademacher. Use  
of data for other purposes is prohibited.

I know that this agreement can be revoked at any time without disadvantages for myself and my  
medical and personal treatment.

Signature of Participant \_\_\_\_\_ Date \_\_\_\_\_

|               |
|---------------|
| Patient label |
|---------------|

## Pedigree

Please indicate the proband and further family member for whom blood samples are available / who are affected by epilepsy, febrile seizures, other relevant disorders. In addition, please indicate the ethnicity of these persons.

