Participant information for adults, parents and/or caregivers

DECADE- Deciphering the CACNA1E- Developmental and epileptic encephalopathy - a natural history study

This participant information has been given and explained to you because you/your child or care recipient has a genetic alteration in the *CACNA1E* gene that is classified as pathogenic or likely pathogenic, resulting in a neurodevelopmental disorder with epilepsy and/or a movement disorder.

Scientific Background:

The *CACNA1E*-associated encephalopathy was scientifically described for the first time in 2018 in a larger cohort. The disease, which is caused by changes in the DNA often leads to severe impairments in mental development as well as epilepsy and other movement disorders. Patients often present with low muscle tone after birth and contractures already present at birth. There is also descriptions of patients in literature who only presented with mental disability but not epilepsy. A total of 40 patients are currently described in the literature. Thus, *CACNA1E* encephalopathy is considered a very rare disorder.

The gene *CACNA1E* encodes for $Ca_V2.3$, a protein that belongs to the family of voltage-gated calcium channels. These proteins are located in the cell membrane of nerve cells, where they perform important functions such as making nerve cells electrically excitable and converting electrical signals into chemical signals by making the cell membrane permeable to charged particles, so-called calcium ions.

Most of the genetic alterations described so far lead to a gain of function of this protein. This results in more calcium ions passing the cell membrane which most likely results in an increased excitability of these cells. In addition, the study will also investigate the extent to which individual genetic findings influence the disease and whether there are certain subgroups of patients who, for example, show certain symptoms or respond to certain therapies. However, the detailed mechanism of disease is not yet understood. There is currently no specific therapy for the disease, although singular positive effects for the antiseizure drug topiramate have been described.

Aim of the Study:

This study seeks to better understand the natural course of disease of the *CACNA1E*-encephalopathy. In addition, the study will also investigate the extent to which individual genetic findings influence the disease and whether there are certain subgroups of patients who, for example, show certain symptoms or respond to certain therapies. Another goal of the study is to identify effective treatment options that already exist. Furthermore, the results of the study will help to plan studies to develop specific drugs to treat the disease.

What are the benefits to me/my child/my care recipient from the study?

There is no direct individual benefit resulting from the study in the first place. However, understanding the disease may lead to the identification of effective therapies for the disease.

Inclusion in the cohort creates an indirect link to the coordinating study center in Tübingen, from where further treatment studies are planned in the future.

What are the risks?

Sensitive health data is processed in this study. Processing is generally pseudonymized and subject to a data protection concept approved by the responsible data protection officer. Nevertheless, there are residual risks with regard to the confidentiality of this data, which are minimized as far as possible by the study team.

If you agree to the voluntary recording of video recordings (see next paragraph for details), there is a residual risk that you/your child/recipient of care may be recognized by the study team.

The individual study visit does not pose a higher risk than a normal visit to your doctor.

Necessary data & examination materials/effort of the study:

The study consists of annual questionnaires, which you fill out together with the including doctor, and optional video recordings of you/your child/your care recipient to monitor the course of the movement disorder known in this disease, which will only be made with your explicit consent. Video recordings are planned because the complex movement disorders can change during the course of normal motor development and standard questionnaires cannot adequately record details over the wide age range. These videos will be evaluated centrally by a central neuropediatrician after quality assessment by the study team in Tübingen and can only be included in scientific publications with your explicit consent. As the movement disorder can also affect the face, it is not intended to alienate the face as part of the study-internal examinations, so that recognition by the study team cannot be ruled out. The unalienated video files will not be published. If you have explicitly consented to the publication of the videos as part of a scientific publication, the videos will be anonymized for this purpose. The time required for the individual study visits is between 30 minutes and 1 hour once a year. The follow-up period is currently planned for 5 years. For inclusion in the study, the enrolling physician will ask you for a copy of your genetic test results to check the inclusion criteria. The questions refer to the entire medical (previous) history, the mental and motor development in the course of the disease, the epilepsy including the seizure types with frequency, the development of the movement disorder, as well as the exact drug and non-drug treatment of the disease including effects and side effects. In addition, open-ended questions allow the disclosure of important aspects of the disease that were previously unknown.

In order to supplement missing information, it may be necessary for us to obtain information from other treating physicians (general practitioners, specialists). For this purpose, it is necessary for you to release these doctors from their duty of confidentiality as part of your consent.

Voluntary participation:

Participation in the study is voluntary. You have the possibility to withdraw your consent at any time and to request deletion of your data. Refusal to participate in the study or withdrawal of consent will not result in any disadvantage to the participant or the future medical treatment.

Study Funding:

The study is initially supported by third-party funds from the BMBF-funded research network "Treat-Ion" (funding code 01GM2210A). The study is also financed by donations made through the patient organisation CACNA1E international. In the future funding by Lario Therapeutics Ltd. Is planned. Lario

Therapeutics is an emerging pharmaceutical company developing a specific therapy for CACNA1E encephalopathy.

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Copy for the patient/proband
(to be completed and signed by the subject or his7her legal representative)

I hereby confirm…

1. ... that I have been informed about the aims, the duration, the procedure, the benefits and the risks of the participation in the study,

2. ....that I have been informed that participation in the study is completely voluntary and that the participation in the study is completely voluntary and that consent can be revoked at any time without the need for providing reasons and without disadvantages. Further medical treatment will not be disadvantaged.

3. ...that additional questions were answered to my satisfaction.

4. ...that I agree to participate in the study and to the use of the data obtained in the data obtained in the study.

_____
Participant First and Surname

_____	_____	_____
Place, date	Signature legal representative For persons not capable of providing consent	Signature patient

_____
Name of legal representative
For persons not capable of providing consent

_____	_____	_____
Place, date	Name of informing physician	Signature informing physician