Patient information[1] and informed consent for participation in the register study

Functional testing of variants of unclear significance in the *ALPL* gene as a cause of hypophosphatasia.

Dear participant!

We invite you to participate in the above-mentioned clinical study. You will be informed about this in a detailed medical consultation.

Your participation in this register study is voluntary. You may withdraw from the study at any time without giving any reason. Refusal to participate or early withdrawal from this study will not adversely affect your medical care.

Clinical studies are necessary to obtain reliable new medical research results. However, an indispensable prerequisite for conducting a clinical study is that you give your written consent to participate in this clinical study. Please read the following text carefully as a supplement to the information discussion with your physician and do not hesitate to ask questions.

Please sign the informed consent form only

- if you fully understand the nature and procedure of the clinical trial,
- if you are willing to consent to participate, and
- if you are aware of your rights as a participant in this clinical trial.

The responsible ethics committee issued a favorable opinion on this clinical study, as well as on the patient information and consent form.

1. What is the purpose of the clinical study?

The rare, inherited disease hypophosphatasia (HPP) is caused by disease-causing mutations in the *ALPL* gene. You have been found to have a genetic variant of unclear significance (VUS) in the *ALPL* gene, meaning it is not clear whether or not this gene variant is disease-causing. This study is investigating such VUS to find out whether they are disease-causing or not. The presence of VUS is one of the reasons why HPP, like many other genetic diseases, is often diagnosed years late. Early diagnosis through genetic testing allows for early referral to, and intervention by, the, specialist. The results of this study will contribute to improved diagnosis and ultimately improved clinical management of the disease, and reduce the burden on the health care system.

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[1] For the sake of better readability, the simultaneous use of feminine and masculine personal terms has been partially dispensed with in the remainder of the text. Both genders are always meant and addressed - if applicable.

2. How does the clinical study proceed?

The study center is the research laboratory of the Department of Pediatrics and Adolescent Medicine at the Johannes Kepler University (JKU) Linz, which will perform the testing of the genetic variants that will make it possible to determine whether a VUS is disease-causing or not. The genetic code of your VUS will also be sent to this laboratory, along with anonymized information about your condition. This will include your following data: ethnicity, geographic origin, age, gender, height, weight, family history, serum ALP, serum phosphate, age at onset, symptoms at onset, a history of early cranial suture closure, early tooth loss, failure to thrive, bone fractures, deformities, rickets, pain, epileptic seizures, and renal calcification (nephrocalcinosis).

These clinical data are transmitted together with the genetic VUS code in the *ALPL* gene in pseudonymized form to the study center. The data transfer to the study center takes place in a password-protected online portal of the JKU research group. Here, it is checked whether the inclusion criteria are fulfilled, and if confirmed, the VUS is tested in the laboratory. The result of the variant testing is entered into a publicly accessible HPP gene variant database. This will ultimately inform yourself and your physician or geneticist of the outcome of the testing. Very little clinical information (your age at the first symptoms of HPP) is published on a database (website) that serves as a reference for physicians and geneticists. The data collection is purely descriptive in nature.

No additional visits to the clinic are necessary.

3. What are the benefits of participating in the Clinical Study?

It is possible that you will derive direct health benefits from your participation in this clinical study. The knowledge gained may have an impact on establishing an HPP diagnosis in yourself. The publication of the variant in the public database will then also help other people who carry "your" variant.

4. Are there risks, complaints and side effects?

This study is a registry study. No patient is identifiable in the study. This means the study participants have no additional risk by participating in this study.

5. When is the clinical study terminated prematurely?

You can revoke your willingness to participate and withdraw from the clinical study at any time, even without giving reasons, without any disadvantages for your further medical care.

Your supervising physician will inform you immediately about any new findings that become known with regard to this clinical study (e.g. when "your" variant is updated in the database) and could become essential for you

6. Data protection

In the course of this clinical study, data about you will be collected and processed. A basic distinction must be made between

1) those personal data by which a person is directly identifiable (e.g. name, date of birth, address, social security number, image recordings...),
2) pseudonymized personal data, i.e., data in which all information that allows direct conclusions to be drawn about the specific person is either removed, replaced by a code (e.g., a number) or (e.g., in the case of image recordings) made unrecognizable. However, despite compliance with these measures, it cannot be completely ruled out that unauthorized re-identification may occur.
3) anonymized data for which a traceability to the specific person can be ruled out.

The local investigator who sends your pseudonymized data to the study center or other persons involved in your local medical care have access to the data by which you are directly identifiable (see point 1). In addition, authorized representatives of the sponsor, JKU Linz, who are bound to secrecy, as well as representatives of domestic and/or foreign health authorities and ethics committees responsible in each case may inspect this data, insofar as this is necessary or prescribed for the verification of the proper conduct of the clinical study. All persons who have access to this data are subject to the applicable national data protection regulations and/or the EU General Data Protection Regulation (GDPR) when handling the data.

The code that allows the pseudonymized data to be assigned to you is kept only at your study center.

Data will only be passed on in pseudonymized or anonymized form.

Only the pseudonymized or anonymized data will be used for any publications.

In the context of this clinical study, no transfer of data to countries outside the EU (third country) is intended.

Your consent forms the legal basis for the processing of your personal data. You can revoke your consent to the collection and processing of your data at any time without giving reasons. After your revocation, no further data will be collected about you. However, the data collected up to the revocation may continue to be processed in the context of this clinical study.

According to the GDPR, you are generally entitled to the rights of access, rectification, deletion, restriction of processing, data portability and objection, provided that this does not render the objectives of the clinical study impossible or seriously impair and provided that this is not contradicted by other statutory provisions.

The expected duration of the clinical study is 4 years. The duration of storage of your data beyond the end or discontinuation of the clinical study is regulated by legal provisions.

If you have any questions about the handling of your data in this clinical study, please contact your investigator first. s/he may be able to forward your request to the persons responsible for data protection.

Contact details of the data protection officers of the institutions involved in this clinical study:
Data protection officer of JKU: datenschutz@jku.at

Data protection officer of Kepler University Hospital: datenschutz@ooeg.at

You have the right to lodge a complaint about the handling of your data with the Austrian data protection authority (www.dsb.gv.at; e-mail: dsb@dsb.gv.at).

7. are there any costs for the participants? Is there any reimbursement of costs or compensation?

There are no additional costs for you due to your participation in this clinical study.

8. opportunity to discuss further questions

If you have any further questions related to this clinical trial, your study doctor and his or her staff will be happy to answer them. They will also be happy to answer questions regarding your rights as a patient and participant in this clinical trial.

Name of contact person: Dr. Ahmed El-Gazzar Can be reached at any time at: +43 732 2468 8892

Name of contact person: Univ.-Prof. Dr Wolfgang Högler Can be reached at any time at: +43 57680 84-22001
- Contact details for Upper Austria:

- Upper Austrian Patient Representation
- Bahnhofplatz 1
- 4021 Linz
- Phone: (+43 732) 77 20 142 15
- Fax: (+43 732) 77 20 21 43 55
- E-mail: ppv.post@ooe.gv.at

9. Declaration of consent

Name of patient:

Date of birth:

I agree to participate in the clinical study "Functional testing of variants of unclear significance in the *ALPL* gene as a cause of hypophosphatasia". I have been informed that I may refuse to participate without adverse consequences, particularly to my medical care.

I have been informed by Mrs./Mr. (Dr.med.) ....

in a detailed and comprehensible manner about the clinical study, possible burdens and risks, as well as about the nature, significance and scope of the clinical study and the requirements resulting from it for me. In addition, I have read the text of this patient information and consent form, which comprises a total of 5 pages. Questions that arose were answered by the investigator in a comprehensible and satisfactory manner. I have had sufficient time to make up my mind. I have no further questions at this time.

I will comply with the physician's orders required for the conduct of the clinical trial, but reserve the right to withdraw my voluntary participation at any time without any disadvantages for me, in particular for my medical care.

I expressly consent to the processing of my data collected in the course of this clinical study as described in the "Data protection" section of this document.

I have received a copy of this patient information and consent form. The original will remain with the investigator.

....

(Date and signature of patient)

....

(Date, name and signature of the responsible investigator)

(The patient will receive a signed copy of the patient information and consent form, the original will remain in the investigator's study folder