patient label

AL-PID
Contact person: Prof. Dr. med. S. Ehl,
PD Dr. med. C. Speckmann, Dr. med. A. Rensing-Ehl
Medical Center – University of Freiburg
Department of Pediatric Hematology and Oncology
Center for Chronic Immunodeficiency (CCI) and
Institute for Immunodeficiency
Breisacher Str. 115
79106 Freiburg
Germany

Information sheet for parents

Genetic and immunological variability in
Autoimmune-Lymphoproliferative Primary Immunodeficiencies (AL-PID)
Short title: AL-PID

Dear parents/legal representative(s),

Your child and you are being invited to take part in the study „**Genetic and immunological variability in Autoimmune-Lymphoproliferative Primary Immunodeficiencies "(AL-PID study)**. This is a research project of the Center for Chronic Immunodeficiency (CCI) at the Medical Center - University of Freiburg, Germany and involves the collection of clinical, laboratory and genetic data in a database and (long-term) storage of biological material (blood, tissue samples) of your child in a "biobank". Database as well as biobank (CCI-biobank) are located at the CCI. The AL-PID study has been approved by the Ethics Committee of the Medical Center - University of Freiburg.

Apart from this written information your physician will talk to you about all procedures of the study. Study participation of your child is voluntary. Before you decide about your child's participation it is important for you to understand why the research is being done and which rights and obligations it involves. Please take time to read the following information and do not hesitate to ask for additional time or explanations if necessary.

1. What is the purpose/aim of the study?

Your child suffers or is suspected to from a rare disease of the immune system, which is associated with lymphoproliferation (enlargement of spleen and/or lymphnodes) and autoimmunity (caused by antibodies against blood cells and/or immune reactions in the gut, lung, liver or other organs). We have termed diseases characterized by these symptoms "Autoimmune Lymphoproliferative Immunodeficiencies" (AL-PID). Causes and consequences of many of these diseases are so far poorly understood and therapy is often not satisfactory. Further research is therefore urgently required to improve diagnostic and therapeutic options.

2. What are the study procedures?

The medical history and all findings of your child will be collected with the help of a standardized questionnaire and then kept in a database. It will only be asked for parameters that your physician is collecting anyway during your child's routine visits.

In addition, blood will be taken for medical investigations, which are required for establishing a diagnosis and/or for therapeutic monitoring. Residual material, which is not required any more for these investigations and would otherwise be destroyed, will be stored in the CCI-biobank, provided you have given consent. No additional venous puncture of your child is required but in some cases we may need to draw additional blood tubes. However, the additional amount of blood is so small, that your child will not have any symptoms from it. If tissue samples are taken for diagnostic purposes, remaining tissue will be stored in the CCI-biobank.
In approximately yearly intervals your physician will send us further information on your child's history and findings with the help of a standardized questionnaire as well as blood for storage in the CCI-biobank. Your

child will not have additional hospital or doctor visits. Participation in the study is not time restricted and may last over many years.

3. How will data and biomaterial be used?

Data:

The clinical data collected from the questionnaires will be transferred to two databases, which are separately stored on different data drives/devices at the CCI. Identifying data (name, date of birth) of your child are transferred to the "identification database". Only a small number of the CCI staff, who are obliged to discretion have access to this database. Identifying data will never be handed out. The "identification database" will be saved for 10 years after study termination and will subsequently be destroyed.

Clinical data of your child will be captured in pseudonymised form in the "research database". Pseudonymisation means that identifying data of your child are replaced by a pseudonym, i.e. a combination of numbers, and are thus encrypted. Data can only be related to your child by persons who have access to the „identification data base“. The research database will be saved for unlimited time.

If data are transferred to cooperating institutions (scientists, pharmaceutical industry), this will occur after repeated encryption, thus double pseudonymised. Publication of scientific research only takes place in anonymous form, i.e. in a form that precludes identification of your child.

With the described measures everything with the currently available technology will be done to protect your child´s privacy. Medical confidentiality and legal regulations for data privacy protection will be met (see also topics 5 and 7).

Biomaterial:

Biomaterial is stored for an unlimited period of time in the freezers of the CCI. In addition some associated data are stored for unlimited time in the CCI-biobank-database. Investigations are carried out by scientists of the CCI or scientists from institutions that collaborate with the CCI. These investigations include characterization of hereditary material (genetic material, genome) through genome sequencing with current sequencing methods and methods that will be developed for this purpose in the future. Transfer of samples and data to scientific partners of the CCI takes place exclusively in encrypted form and according to relevant data protection regulations. Transfer of samples and data to unauthorized third parties is ruled out. If you do not agree to the use and storage duration of the samples described above you should mark the corresponding points in the consent form with “no”. In this case, no biomaterial of your child will be stored in the CCI-biobank.

4. What personal benefits or risks are incurred from participation in the AL-PID study?

Study participation will presumably not be of immediate benefit to your child. However, study results could contribute to better diagnostic and therapeutic options for future patients. Since your child has a chronic disease, he/she may also benefit him/herself from the insights and experience gained from the research project.

Both study participation and donation of biomaterial do not entail any additional health hazard for your child nor does it lead to additional costs and doctor visits. The only biomaterial used for the CCI-biobank are samples collected for anticipated diagnostic or therapeutic measures, which would otherwise be disposed of.

We cannot provide compensation for donated samples. You will not be involved in research endeavors with a commercial aim. Your consent involves waiver of commercial rights (particularly patents) to the samples donated, the data resulting from their investigation and the copyrights of research results. The samples deposited at the CCI-biobank are considered property of the CCI-biobank. With your consent you grant the CCI-biobank authority to process and use the data of your child.

Collection, storage and transmission of data from your child’s biomaterial in research projects carry confidentiality risks (e.g. identification) particularly regarding information on the hereditary material. These risks cannot be fully excluded and increase when multiple data can be linked to each other. The risk of confidentiality breach is even greater if you yourself publish your genetic data on the internet (as in an-

cestry research). The CCI-biobank assures you that all technically feasible measures to protect your child´s privacy will be undertaken, and that your child's samples and data will be transferred only to projects that can demonstrate application of adequate data protection procedures (topic 5).

5. Who has access to your child‘s data and biomaterial and how are they protected?

Your child‘s biomaterial and data will be saved for an unlimited period of time in the CCI-biobank under standardized quality and safety conditions. Upon request they will be handed out for medical research. According to the best available technology they will be protected from access by unauthorized persons. The CCI-biobank will provide biomaterial and data only to medical research projects that have been evaluated under ethical and judicial aspects and approved by an independent ethics committee.

a) Samples are encrypted – pseudonymised - before they are stored or/and transferred. Each patient and participant receives a biobank identification number, which is used to identify samples and test results. Then the dataset will get a new code and will be saved. The biobank identification number will be connected to identifying data of your child in the above described „identification data base“(topic 3). Transmission of biomaterial to cooperating researchers takes place exclusively with the biobank identification number precluding exposure of personal information. Tracing of data to your person by a third party is ruled out. All persons who can access these data are obliged to maintain confidentiality and are under obligation of medical discretion (possible risks are described under topic 4).

b) Twice encrypted biomaterial and medical data can be transferred on demand and after fulfillment of predetermined criteria to other universities, research institutions or industry, including abroad, for the purpose of medical research. Data as well as medical records can be linked to other databases under given circumstances as long as legal requirements are fulfilled.

c) Biomaterial and data transferred to a third party can only be used for the determined research purpose. Recipients are not allowed to transfer biomaterial and data further. Biomaterial that is not used is returned to the CCI-biobank or is disposed of.

6. Can study participation be withdrawn at any time?

Study participation of your child is voluntary and requires your written consent. Your child will not be at a disadvantage by refusing to take part. You may also withdraw your consent at any point in time without justification. In case of withdrawal of consent you are free to choose whether your child's biomaterial and associated data should be destroyed or further anonymously used for research purposes. However, completed research and publications cannot be reversed or withdrawn (topic 7). An association of genetic material with your child through other sources cannot be completely ruled out despite withdrawal of consent. Please inform your treating physician if you want to withdraw your consent.
If your child has completed the 18th year of life, your treating physician will contact you and give your adult child the opportunity to decide him/herself about further storage of data and biomaterial.

7. What other rights do you have in relation to your child´s data?

The EU General Data Protection Regulation (EU-GDPR) ensures your and your child`s personal rights and privacy; it enables more transparency and your active involvement. Of course, this also applies to the AL-PID study, whose internal processes follow the requirements of the GDPR and ensure the security of data processing. The GDPR demands extended information obligations: according to art.13 and 14 GDPR, we are obliged to provide you with basic information on the property rights of the GDPR and the implementation of data protection at the Medical Center - University of Freiburg at the time of data collection. This information is provided (in German) on our website (www.uniklinik-freiburg.de) under the link "Datenschutz " and as written information at the following places: patient registration and waiting room of the outpatient clinics and other central locations within the Medical Center - University of Freiburg. Upon request you will receive information about the specific personal data that has been processed on the person of your child as a free copy (right to information on processed data, art. 15 GDPR). If necessary, you can correct or complete it (right to correct incorrect data, art. 16 GDPR). The right to deletion (art. 17 GDPR), to restriction of processing (art. 18 GDPR) and the right to object to the processing (art. 21 GDPR) have already been explained to you in topic 6: In the case of data processing based on a consent you have the right to withdraw

the consent at any time with effect for the future! The legitimacy of the processing until the time of withdrawal remains unaffected. Please direct your inquiries as well as any objections to the processing of your child's data or a withdrawal of your consent to your child's participation in the AL-PID study to the persons responsible for data privacy in the study (see topic 8).

8. Who can be contacted in case of remaining questions?

If you have further questions, please contact:

- your treating physician: Telephone:

_____ _____

- the investigators responsible for the AL-PID study and the data privacy:

Medical Center – University of Freiburg
Department of Pediatric Hematology and Oncology
Center for Chronic Immunodeficiency (CCI) and
Institute for Immunodeficiency
Breisacher Str. 115
79106 Freiburg

PD Dr. med. C. Speckmann
Tel. 0049 (0)761/270 45500
carsten.speckmann@uniklinik-freiburg.de

Dr. med. A. Rensing-Ehl
Tel. 0049 (0)761/270 71080
anne.rensing-ehl@uniklinik-freiburg.de

- the data protection officer of Medical Center – University of Freiburg:

Medical Center – University of Freiburg
Data protection officer
Agnesenstraße 6-8
79106 Freiburg
E-Mail: datenschutz@uniklinik-freiburg.de

If you believe that the processing of your personal data is not legitimate, you have the right to complain to a regulatory authority (art. 77 GDPR). An overview of the German regulatory authorities is provided here: https://www.bfdi.bund.de/DE/Infothek/Anschriften_Links/anschriften_links-node.htmlIm

patient label

AL-PID
Contact person: Prof. Dr. med. S. Ehl,
PD Dr. med. C. Speckmann, Dr. med. A. Rensing-Ehl
Medical Center – University of Freiburg
Department of Pediatric Hematology and Oncology
Center for Chronic Immunodeficiency (CCI) and
Institute for Immunodeficiency
Breisacher Str. 115
79106 Freiburg
Germany

Consent for Parents

Genetic and immunological variability in
Autoimmune-Lymphoproliferative Primary Immunodeficiencies (AL-PID)

Short title: AL-PID

I confirm that I have been informed sufficiently in oral and written form about the aims of the AL-PID study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. I understand that the participation of my child is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care or legal rights of my child being affected. I am aware that my consent as a parent/legal representative must reflect the assumed will of my child and I confirm this with my signature.

I confirm that I was informed:

- that personal data, especially medical reports of my child, are captured on questionnaires and saved in databases after pseudonymisation, which preclude tracing the patient's identity.
- that the treating physician of my child

  ……*(Name and city, physician)* is released from medical confidentiality to pass on medical data to the Medical Center – University of Freiburg in the context of the AL-PID study.
- that biomaterial of my child is stored in the CCI-biobank of the Medical Center – University of Freiburg for unlimited time if agreed upon by crossing „yes".
- that stored biomaterial can be used for future medical research projects.
- that my child's treating physician will be contact us in yearly intervals with a follow-up questionnaire.
- that there is no financial reimbursement for participation or for any product that might result from this study.
- that participation is voluntary and I am free to withdraw at any time, without giving any reasons and without any disadvantage for my child.

Information and consent to data protection: I was informed and agree, that biomaterial is stored and personal and clinical data of my child is saved in pseudonymised form at the CCI, Medical Center – University of Freiburg and are subsequently analysed. When data is used for research purposes and/or is published in scientific journals it is impossible to trace the child's identity. Biomaterial can be used for unlimited time for research projects. If confirmed by crossing „yes", biomaterial and data may be used and passed on to other research institutes or research industry, including abroad, for medical research purposes after double pseudonymisation. This may include commercial purposes (pharmaceutical industry, patent development at the Medical Center – University of Freiburg).
I understand that I can withdraw my consent at any time without justification. In case of study withdrawal I can ask for destruction of remaining biomaterial and deletion or anonymisation of collected data. Data of completed analyses cannot be withdrawn.

I agree, that biomaterial(s) of my child is/are stored in the CCI-biobank:	yes ☐	no ☐
I agree to genetic investigations:	yes ☐	no ☐
I agree that I may be re-contacted at a later time point with possible information about results relevant for my child´s health.	yes ☐	no ☐
I agree, that after double pseudonymisation, data and biomaterial can be used or passed on to cooperating research partners in Germany or abroad (EU countries to which GDPR applies, non-EU countries for which an adequacy decision by the EU commission or appropriate/adequate guarantees exists, as well as countries for which no such adequacy decision or appropriate/adequate guarantees exist)	yes ☐	no☐
I agree, that after double pseudonymisation, data and biomaterial may also be used for **commercial** purpose, e.g. for the development of new medication for this disease in the pharmaceutical industry or for patent development at the Medical Center – University of Freiburg.	yes ☐	no ☐
I agree, that in case of study withdrawal data and biomaterial acquired until this timepoint can be used for the study.	yes ☐	no ☐

I would like to be informed about results generated in the context oft he AL-PID study and receive the AL-PID newsletter.

☐ Yes no ☐

E-Mail:_____

or

Address:_____

I have received a copy of this patient informed consent form. The original will be kept by the treating physician.

Consent of minors

Date		signature of the legal representative of the patient	
Date		if applicable signature of a second legal representative*	
Date		if applicable signature of the child	
	name of the physician taking consent		
Date		signature of the physician	

*In principle it is required that both legal representatives/parents sign. If the signature of only one legal representatives/parent is present, the signatory also affirms that he is acting in agreement with the other legal representatives/parent or that he has the sole custody of the child.

AL - PID Study

Autoimmune lymphoproliferative primary immunodeficiency

Information Sheet - Study Inclusion

Clinical contact person

Prof. Dr. Stephan Ehl
PD Dr. Carsten Speckmann
MEDICAL CENTER - UNIVERSITY OF FREIBURG
Center for Chronic Immunodeficiency
at Center for Translational Cell Research

Breisacher Str. 115 (1. OG)
D - 79106 Freiburg
Tel. + 49 (0) 761 270 - 77 300
Fax + 49 (0) 761 270 - 77 744
E-mail: stephan.ehl@uniklinik-freiburg.de
carsten.speckmann@uniklinik-freiburg.de

Lab contact

Ilka Fuchs
Dr. Anne Rensing-Ehl
MEDICAL CENTER - UNIVERSITY OF FREIBURG
Center for Chronic Immunodeficiency
at Center for Translational Cell Research
CCI - Advanced Diagnostic Unit

Breisacher Str. 115 (EG)
D - 79106 Freiburg
Tel. + 49 (0) 761 270 - 71 010 / - 71 070
Fax + 49 (0) 761 270 - 96 71 070
E-mail: ilka.fuchs@uniklinik-freiburg.de
anne.rensing-ehl@uniklinik-freiburg.de

Shipment of blood samples

- Please send 10 ml - if acceptable - 15 ml EDTA blood and 4 ml serum.
- **Please announce any material > 3 days before sending it.** (via e-mail or phone, see Lab Contact)
- Send via express **(delivery until 8 am).**
- For patients with German health insurance: please include transfer form (Überweisungs-schein) for genetic analysis.
- Please also send signed consent form and the initial clinical data sheet. (IMPORTANT!)

Thank you for your cooperation!

Clinical contact person

Name _____

Phone _____ Fax _____

E-mail _____

Patient label - if applicable

Name of patient

_____

Date of birth (day/month/year) ____ ____ ____

Shipment of

Date of blood sample
day / month / year

____ ml EDTA ____ ____ ____

____ ml serum ____ ____ ____

Center for Chronic Immunodeficiency

Sponsored by the Federal Ministry of Education and Research

AL-PID

Center for Chronic Immunodeficiency

SPONSORED BY THE Federal Ministry of Education and Research

PATIENT INFORMATION

Patient label - if applicable

Name of patient

Gender ○ female ○ male

Study consent signed ○ yes ○ no

Date of birth (day/month/year) ___

PATIENT'S HISTORY

Lymphoproliferation (**NOW** or **PREVIOUSLY**)

Lymphadenopathy → ○ yes ○ no ○ unknown
(> 6 months, > 2 locations)

Splenomegaly → ○ yes ○ no ○ unknown

If yes, current status
- ○ enlarged (ultrasound investigation) but not palpable
- ○ palpable: cm below ribcage ___ ○ distance unknown
- ○ current status unknown

Has the patient been **splenectomized**? → ○ yes ○ no ○ unknown

If yes, reason for splenectomy _____ (year of splenectomy) ____
- ○ reason unknown
- ○ year unknown

Hepatomegaly → ○ yes ○ no ○ unknown

If yes, current status
- ○ enlarged (ultrasound investigation) but not palpable
- ○ palpable: cm below ribcage ___ ○ distance unknown
- ○ current status unknown

Age at first episode of lymphadenopathy or splenomegaly or hepatomegaly ___ years ○ unknown

Malignancy → ○ yes ○ no ○ unknown

If yes, type of malignancy (e.g. lymphoma) _____ (year of diagnosis) ____
- ○ type unknown
- ○ year unknown

Autoimmunity and infections (**NOW** or **PREVIOUSLY**)

Anemia (Hb < 10 g/dl) → ○ yes ○ no ○ unknown

If yes, coomb's positive ○ yes ○ no ○ not done ○ unknown

requiring immunosuppression / IVIG ○ yes ○ no ○ unknown

Thrombocytopenia (Plt < 100.000/µl) → ○ yes ○ no ○ unknown

If yes, anti-platelet antibodies ○ yes ○ no ○ not done ○ unknown

requiring immunosuppression / IVIG ○ yes ○ no ○ unknown

Neutropenia (ANC < 1000/µl) → ○ yes ○ no ○ unknown

If yes, anti-neutrophil antibodies ○ yes ○ no ○ not done ○ unknown

requiring immunosuppression / IVIG ○ yes ○ no ○ unknown

Age at the first episode of any cytopenia ___ years ○ unknown

Please see next page.

FINAL Version 9.0, 22.06.2017

AL - PID Study

Initial Clinical Data Sheet

Patient label - if applicable

Name of patient

Date of birth (day/month/year) |_|_| |_|_| |_|_|_|_|

Autoimmunity and infections (**NOW** or **PREVIOUSLY**)

Inflammatory gut disease (frequent diarrhoea without infectious trigger OR histologic evidence) ○ yes ○ no ○ unknown

Interstitial lung disease (assessed by CO_2 diffusion capacity OR HRCT) ○ yes ○ no ○ unknown

Bronchiectasis ○ yes ○ no ○ unknown

Inflammatory brain disease (indicated by MRI AND/OR CSF investigation) ○ yes ○ no ○ unknown

Inflammatory skin disease ○ yes ○ no ○ unknown

Other **autoimmunity /immunodysregulation** (eg. liver, kidney, thyroid, joints) ○ yes ○ no ○ unknown

If yes, please specify: _____

○ autoimmunity / immunodysregulation unknown

Is the patient prone to **infections**? ○ yes ○ no ○ unknown

If yes, bronchopulmonary infections ○ yes ○ no ○ unknown

candidiasis ○ yes ○ no ○ unknown

warts ○ yes ○ no ○ unknown

systemic or chronic viral infections (eg. EBV, CMV, Noro, Adeno) ○ yes ○ no ○ unknown

If yes, please specify: _____

○ systemic or chronic viral infections unknown

Hypogammaglobulinemia ○ yes ○ no ○ unknown

If yes, minimal **IgG** value (prior to substitution) |_|_|_|_|,|_|_| ○ g/l ○ mg/dl ○ unknown

Hyper-IgM ○ yes ○ no ○ unknown

If yes, maximal **IgM** value (in the past or current) |_|_|_|_|,|_|_| ○ g/l ○ mg/dl ○ unknown

Syndromal features

Developmental delay ○ yes ○ no ○ unknown

Short stature ○ yes ○ no ○ unknown

Facial dysplasia ○ yes ○ no ○ unknown

Please see next page.

FINAL Version 9.0, 22.06.2017

AL - PID Study

Initial Clinical Data Sheet

Patient label - if applicable

Name of patient

Date of birth (day/month/year)

Family History (indicate kind of relative)

Similar disease ○ yes ○ no ○ unknown
↳ ○ kind of relative unknown

Lymphoma ○ yes ○ no ○ unknown
↳ ○ kind of relative unknown

Autoimmunity ○ yes ○ no ○ unknown
↳ ○ kind of relative unknown

Consanguinity ○ yes ○ no ○ unknown

CURRENT SITUATION

Full blood count (determined on the day blood is drawn for diagnostic testing)

Leucocytes / µl ○ unknown

Lymphocytes % ○ unknown

Monocytes % ○ unknown

Is the patient CURRENTLY treated with:

Steroids ○ yes ○ no ○ unknown

Other Immunosuppression ○ yes ○ no ○ unknown
↳ please specify:
○ other immunosuppression unknown

Rituximab (last six months) ○ yes ○ no ○ unknown
↳ Date of the last dose ○ Date unknown
(day/month/year)

IVIG/SCIG ○ yes ○ no ○ unknown

Other specific therapy:

Date Signature of Physician