



**REGISTER FOR
AUTOINFLAMMATORY DISEASES (AID)**

Information letter for parents

Dear parents,

Hereditary periodic fever syndromes (HPF) belong to a rare subgroup of autoinflammatory diseases (**autoinflammatory diseases = AIDs**) in childhood. These are characterised by recurring self-limiting episodes of fever and increasingly relieved by molecular-genetic research methods. HPFs include

e.g. familial Mediterranean fever, hyper-IgD syndrome (HIDS),
tumour necrosis factor receptor 1-associated periodic syndrome (TRAPS),
Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and
chronic infantile neurological, cutaneous and articular (CINCA) syndrome.

Current data on HPF shows that there were approx. 50 to 130 newly diagnosed children aged up to 16 years per year in Germany between 2003 and 2006.

The systemic onset juvenile idiopathic arthritis (SOJIA) is an AID without a genetic background. SoJIA is characterised by joint inflammation, fever and at least one criterion of specially defined criteria. There are also other autoinflammatory diseases such as the PFAPA syndrome, which is accompanied by fever, mouth/throat inflammation and lymphadenitis, and diseases not yet characterised in greater detail, which are systematically recorded in the AID register.

Studying this unknown group of diseases is an important task for improving patient support and the possibilities of treatment in the long term and for ensuring medical quality. Unfortunately, little is known about the frequency, diagnosis confirmation and therapy of AIDs in Germany. As recent data shows, familial Mediterranean fever is the most frequent HPF across Germany and worldwide.

Our **goal** is to increase our knowledge about AIDs: How frequently do HPFs arise in childhood? Which complaints are there when disease begins? Which gene mutation leads to which symptoms? Which treatment is helpful? Which therapy side effects and complications arise? Can newer medication also be used in childhood without hesitation? We urgently need long-term experience concerning the treatment. Awareness of AIDs is also to be increased among the population with one goal being to recognise the beginnings of disease sooner and to give those affected adequate treatment sooner.

Who are we? We are two research assistants of the children's hospital of the university in Essen (Dr. E. Lainka, Dr. U. Neudorf, Uniklinikum Essen, Pädiatrische Rheumatologie (paediatric rheumatology), Hufelandstraße 55, 45122 Essen, Tel: +49 (0) 201/723 3350) and the head physician of the children's hospital in Krefeld (Prof. Dr. T. Niehues, HELIOS Klinikum Krefeld, Lutherplatz 40, 47805 Krefeld, Tel: +49 (0) 2151/322301).

The genetic tests are carried out in the institute for clinical chemistry of the LMU in Munich (Prof. Dr. P. Lohse, Marchioninistraße 15, 81377 Munich, Tel: +49 (0) 89/7095 3233).

Our HPF working group, which belongs to the GKJR (German Society for Paediatric and Adolescent Rheumatology) deals with various questions regarding HPF in childhood.



What do we do? To start with, all children with AID are documented across the country via an online AID register at the time of diagnosis. The family history is important for evaluating the anamnesis, since the diseases concerned can be passed down in the family. For this purpose a genealogical tree (parents, siblings and patient) is stored in the diagnosis form, where positive molecular-genetic findings and relatives with diseases can be entered without personal data. All German paediatric clinics as well as all specialised outpatient clinics and laboratories are taking part in this research project.

Next, the known cases are documented online following an outpatient or inpatient follow-up performed by the paediatrician in the course of the disease (at least four times a year). Monitoring the course of the disease makes it possible to determine therapeutic success and failure and to draw conclusions from this for treatment. The data is processed further in a statistic program. Thanks to the fast statistic processing, results from the respective patient report are immediately available and conclusions can be drawn quickly.

What is documented? The forms (master data, diagnosis, follow-up and therapy) can be downloaded via the homepage of the AID register. The data currently requested in the register can be seen in these forms:

Master data: Month/year of birth, sex, encrypted patient code (PID)

Diagnosis: Diagnosis and genetic findings, family history, consanguinity, ethnicity, symptoms and laboratory parameters before diagnosis confirmation

Follow-up: Kind of follow-up, size and weight, symptoms, laboratory parameters, therapy plus side effects

Therapy: Selection and dosages of medication

Cooperation: There is a cooperation established with the DRFZ (German Rheumatism Research Center) in Berlin, which also collects data (core documentation in childhood) on patient history once a year. So that your attending physician does not have to document twice (inputs in AID register and core documentation) and so that there are no duplications or mix-ups, we are asking you to consent to the core documentation data of your child being passed on from the online register to the DRFZ with its own identification number. The identification number of the core documentation can be recorded on the master data form in the AID register by the attending physician. Data collected by the DRFZ can be seen in the HPF core documentation form on the AID register homepage (year of birth, sex, beginning of disease, body size, weight, parents' country of origin, advice, diagnosis, symptoms, disease activity, episodes of fever, laboratory parameters, family history, therapy).

This is dependent on your written agreement. We are hereby asking you to participate in the AID register. Participation is voluntary and can be cancelled at any time without giving reasons and without any disadvantages for the medical care of your child. In the case of cancellation, the data of your child that has already been collected will be deleted.

Data protection! In order to register patients, the attending physician of your child will assign a code number (PID) using a random number generator on a server. Only the physician can match the PID number to a person. This is why this letter has been kindly passed on to you by your paediatric clinic or laboratory. No personal data will be entered into the online register apart from the date of birth (month/year) and the sex of your child, and the data will be carefully kept under the PID number and protected against unauthorised access. The name and address etc. of your child will not be stored. As already described, the data is collected in pseudonymous form and processed in anonymous form for research purposes. All information is treated confidentially in all cases. The results of the test are represented exclusively in the form of anonymous summary statistics, which do not allow any conclusions



to made as to specific individuals. Each centre physician can view his own entered data. The Essen employees have access to the data of all centres (laboratory and paediatric clinic) in the PC centre and evaluate these.

Anonymous partial data on patient history is only passed on to a participating centre (see homepage) by the direction of studies of the AID register on request and with an explicit study question. In this case you will be provided with a separate consent form. As soon as the AID direction of studies determines, in co-operation with the participating centres, that certain questions for improving therapy need clarifying scientifically, a research project is arranged. The responsible project manager can apply for the right to view the data from the AID register in order to solve his particular issue and to initiate the necessary measures for completing his task, as long as the directors of studies of the AID network evaluate the project positively.

Since data records are not always complete, we are asking for your permission to make further enquiries to the attending physician of your child in our capacity of directors of studies (see above), in order to complete missing data and if necessary put across suggestions for improvement on therapy concepts following literature or register results.

If you have any further questions, do not hesitate to contact us directly (address above). You will find further information on the Internet at www.AID-register.uk-essen.de. You can keep this information text with your personal documents.

Thank you in advance for your cooperation.

Kind regards,

Dr. med. E. Lainka
Coordinating investigator



BIO BANKS FOR AUTOINFLAMMATORY DISEASES (AID)

Information letter for parents

Dear parents,

First we would like to thank you again for your willingness to take part in the register for autoinflammatory diseases. At present it is hard to gear the therapy to the disease activity. Apart from visible signs of disease, there may also be measured values in laboratory tests that indicate inflammation activity. We are not yet aware of any sure risk factors that make a complicated course of disease likely. However, more recent studies have shown that inflammations can be detected by measuring inflammation proteins MRP8/14 and S100A12. In the last years we have learned much about changes in genetic makeup that can lead to autoinflammatory disease. Nevertheless, in every second patient until now, none of the known genetic causes have been detected. It is therefore important to look for genetic changes that are thus far unknown. This can help to better predict the course of certain diseases and develop new therapies.

What do we do?

It is therefore planned in the network for autoinflammatory diseases (AID-Net) to also perform laboratory tests. In addition to the documentation already produced and the laboratory tests performed as standard, new biomarkers are also to be investigated. For this purpose, serum (2 ml) and a one-off EDTA sample (5 ml for obtaining the DNA - information carriers of the hereditary substance) are to be taken as part of a medically indicated blood sample in order to analyse the inflammation markers MRP8/14, S100A12 and new genes associated with the disease. For each blood test, serum is to be sent to a central sample bank at the Münster university clinic. The EDTA sample for the DNA is only taken once and stored in the central genetic biobank at the German Society for Paediatric and Adolescent Rheumatology.

The blood samples of your child will be used exclusively for research purposes.

Who are we?

Prof. Dr. med. Dirk Föll works at the children's hospital of the university in Münster and is spokesperson of the "clinical studies" commission of the German Society for Paediatric and Adolescent Rheumatology. He already supervises the central sample bank for children and adolescents with rheumatism and has been working on the investigation of laboratory tests for inflammatory diseases for a long time. Dr. med. Helmut Wittkowski works at the children's hospital of the university in Münster and will supervise the sample bank for the register for autoinflammatory diseases. He has been working on the investigation of laboratory tests for inflammatory diseases for a long time, especially for autoinflammatory diseases. Address: UKM Kinderklinik, Albert-Schweitzer-Str. 33, 48149 Münster, telephone: 0251-83 56578, fax: 0251-83 56549, email: h_wittkowski@yahoo.de.

PD Dr. med. Johannes-Peter Haas works at the clinic for paediatric and adolescent rheumatology in Garmisch-Partenkirchen. He has been supervising the Genetic Biobank of the Society for Paediatric and Adolescent Rheumatology for several years and has already led several genetic studies. Address: Deutsches Zentrum für Kinder- und



Jugendrheumatologie, Gehfeldstr. 24, 82467 Garmisch-Partenkirchen, tel.: 08821-701117,
fax: 08821-701201, email: haas.johannes-peter@rummelsberger.net

This is dependent on your written agreement!

We are hereby asking you to agree to the laboratory tests in addition your participation in the AID register. The samples will be stored for scientific purposes with the intention of performing promising laboratory tests on these blood samples in the future. Your participation is voluntary and can be cancelled at any time without giving reasons and without any disadvantages for the medical care of your child. In the case of cancellation, the data of your child that has already been collected will be deleted and the samples discarded.

Data protection

No data will be passed on which can be traced back to a specific person. This is why this letter has been kindly passed on to you by your paediatric clinic or laboratory. All data is carefully kept and protected against unauthorised access. The data is collected in pseudonymous form and processed exclusively for research purposes in anonymous form. All information will be treated confidentially in all cases and used only for the purpose of this study. The results of the test will be represented in the form of summary statistics, which do not allow any conclusions to be made as to specific individuals.

If you have any further questions, do not hesitate to contact us directly (see address above). You will also find further information on the Internet on the homepage of the HPF therapy register (www.AID-register.uk-essen.de). You can keep this information text with your personal documents.

Thank you in advance for your cooperation.
Kind regards,

Prof. Dr. D. Föll

Dr. H. Wittkowski

PD Dr. J.P. Haas

- Coordinating investigators -