# THROMKIDplus Patient Registry and Biomaterial Banking for Children with Inherited Platelet Disorders

Matthias Ballmaier[1,*] Manuela Germeshausen[1,*] Harald Schulze[2,3] Oliver Andres[3,4] on behalf of the THROMKIDplus Study Group

[1] Central Research Facility Cell Sorting, Hannover Medical School, Hannover, Germany
[2] Institute for Experimental Biomedicine, University Hospital Würzburg, Würzburg, Germany
[3] Center of Inherited Blood Cell Disorders, University Hospital Würzburg, Würzburg, Germany
[4] Department of Pediatrics, University Hospital Würzburg, Würzburg, Germany

Address for correspondence PD Dr. med. Oliver Andres, Universitätsklinikum Würzburg, Kinderklinik und Poliklinik, Josef-Schneider-Straße 2, 97080 Würzburg, Deutschland, Germany (e-mail: andres_o@ukw.de).

Dr. rer. nat. Matthias Ballmaier, Medizinische Hochschule Hannover, OE9411, Carl-Neuberg-Straße 1, 30625 Hannover, Deutschland, Germany (e-mail: ballmaier.matthias@mh-hannover.de).

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## Abstract

Inherited platelet disorders (IPDs) represent a heterogeneous group of disorders that include both quantitative (thrombocytopenia or thrombocytosis) and qualitative (thrombocytopathy) defects. To gain better knowledge about the prevalence, pathogenesis, and clinical consequences of specific diseases, to improve diagnosis and treatment of patients with IPD, and to support translational research on a genetic, molecular, and physiological basis, the THROMKIDplus study group currently comprising 24 sites in Germany, Austria, and Switzerland decided to establish a patient registry with associated biomaterial banking for children. This registry is designed as a retrospective-prospective, multicenter observational study and supposed to launch in the second half of 2023. Blood smears, plasma, platelet pellets, and DNA of patients will be stored in certified biomaterial banks for future translational research projects. The main inclusion criteria are (1) diagnosis of or highly suspected IPD after assessment of a THROMKIDplus competence center and (2) patients aged 0 to 17 years. Initial and follow-up data on patient history, laboratory parameters, standardized documentation of bleeding tendency, and congenital defects are collected according to good clinical practice and current data protection acts by using the MARVIN platform, a broadly used data management system supported by the German Society for Pediatric Oncology Hematology (GPOH). The THROMKIDplus study group intends to enroll ~200 patients retrospectively and an annual amount of ~50 patients prospectively.

**Keywords**
- inherited platelet disorder
- patient registry
- biomaterial banking

## Zusammenfassung

Angeborene Erkrankungen der Thrombozyten (IPD) stellen eine heterogene Gruppe von Erkrankungen dar, die sowohl quantitative (Thrombozytopenie oder Thrombozytose) als auch qualitative (Thrombozytopathie) Defekte umfassen. Die THROMKIDplus-Studiengruppe mit momentan 24 Standorten in Deutschland, Österreich und der Schweiz hat beschlossen, ein Patientenregister mit angeschlossenem Biomaterialbanking für Kinder und Jugendliche einzurichten, um mehr über die Prävalenz, die Entwicklung und die Folgen

**Schlüsselwörter**
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- Thrombozytopathie
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* *These authors contributed equally to the manuscript.*

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spezifischer Erkrankungen zu erfahren, die Diagnose und Behandlung von Patienten mit IPD zu verbessern und die translationale Forschung auf genetischer, molekularer und physiologischer Ebene zu unterstützen. Das Patientenregister ist als retrospektiv-prospektive, multizentrische Beobachtungsstudie konzipiert und soll Ende 2023 starten. Blutausstriche, Plasma, Thrombozytenpellets und DNA von Patienten werden in zertifizierten Biomaterialbanken für zukünftige translationale Forschungsprojekte gelagert. Die wichtigsten Einschlusskriterien sind (1) die Diagnose oder der dringende Verdacht auf eine IPD nach Beurteilung durch ein THROMKIDplus-Kompetenzzentrum und (2) das Alter von 0–17 Jahren. Erst- und Folgedaten zur Anamnese, zu Laborparametern, zur standardisierten Dokumentation der Blutungsneigung und zu angeborenen Defekten werden nach guter klinischer Praxis und den aktuellen Datenschutzgesetzen unter Verwendung der MARVIN-Plattform, einem elektronischen Datenerfassungssystem der Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH), erhoben. Die THROMKIDplus-Studiengruppe beabsichtigt, etwa 200 Patienten/-innen retrospektiv und jährlich etwa 50 Patienten/-innen prospektiv einzuschließen.

## Inherited Platelet Disorders

Inherited platelet disorders (IPDs) represent a heterogeneous group of rare disorders with various impacts on platelet physiology that result in quantitative (thrombocytopenia or thrombocytosis), qualitative (thrombocytopathy), or combined defects. Alterations in genes that regulate formation, structure, and function of platelets can lead to platelet dysfunction, thrombocytopenia, or thrombocytosis. If these genes are not only involved in platelet formation or function, but are also essential for other organ systems, the platelet disorder may also be a component of complex syndromic diseases.[1–4] In addition, some genetic defects result in relatively mild and clinically benign thrombocytopenia, but predispose to malignancies and may be considered as cancer predisposition syndromes.[5]

The exact prevalence of IPD is widely unknown. Reliable estimates are available only for some disorders with a well-defined pheno- and genotype (e.g., Glanzmann thrombasthenia, TAR syndrome). Other disorders are likely to be significantly underdiagnosed due to milder symptoms, difficulties in diagnosis, or misdiagnoses as acquired platelet disorders (most commonly immune thrombocytopenia).

The group of IPDs can be subdivided into:

- Inherited thrombocytopenias,[2] in which the low platelet count and resulting clinical features are the leading symptoms.
- Inherited thrombocytopathies, which are mainly characterized by functional defects of the platelets (platelet function disorders): defects of receptors, granules, transcription factors, components of signal transduction cascades, the cytoskeleton, or the membrane.[6]
- Platelet defects that combine features of thrombocytopenia and impaired platelet function.
- Hereditary thrombocytoses (familial thrombocythemia), usually caused by germ-line mutations in the *THPO*, *MPL*, *CALR*, or *JAK2* genes, which result in abnormal increases in megakaryopoiesis and thrombopoiesis.[7,8]

## The THROMKIDplus Study Group

THROMKID was initiated in 2004 as a project of the Standing Committee Pediatrics of the Society for Thrombosis and Hemostasis Research (Ständige Kommission Pädiatrie der Gesellschaft für Thrombose und Hämostaseforschung, GTH) to improve the diagnosis and treatment of patients with inherited thrombopathies.[9] These efforts resulted in two guidelines for Germany, Austria, and Switzerland aiming standardized diagnostic procedures[10] and consented recommendations for treatment.[11]

In the follow-up project THROMKIDplus, objectives were expanded to include patients with quantitative platelet defects (thrombocytopenias and thrombocytoses). THROMKIDplus was commissioned in 2015 as the first joint study project of the GTH and the Society for Pediatric Oncology and Hematology (Gesellschaft für Pädiatrische Hämatologie und Onkologie, GPOH). Currently, members of the following 24 centers are part of the study group (in alphabetical order for each country): Charité – University Medicine Berlin, Hannover Medical School, University Hospitals or University Medicine Dresden, Freiburg, Greifswald, Mainz, Mannheim, München, Münster, Tübingen, Ulm, and Würzburg, Helios Hospital Berlin-Buch and DKD Hospital Wiesbaden, Children's Hospitals Braunschweig and Garmisch-Partenkirchen, Medical Care Centers amedes wagnerstibbe, Hannover, and Labor Leipzig, Leipzig, Gerinnungszentrum Rhein-Ruhr, Duisburg, German Red Cross Blood Donation Service, Springe, all Germany; Medical Universities of Graz, Innsbruck, and Vienna, all Austria; University Children's Hospital Zürich, Switzerland.

To further improve diagnosis and therapy and thus the quality of life of the young patients, the main objectives of the THROMKIDplus group were the amendment of current guidelines, the development of criteria for a quality control of specialized coagulation laboratories,[12] and the designation

 

of competence centers or even reference centers for the diagnosis and therapy of IPD that give advice for other participating or nonparticipating centers. The establishment of a patient registry for IPD as an important tool has been an essential goal from the beginning of the THROMKIDplus project. This has been developed over the last years and is expected to start enrolling patients in the second half of 2023.

## Aims and Design of the THROMKIDplus Patient Registry

The THROMKIDplus patient registry is designed as a retrospective-prospective, multicenter observational study. We expect to enroll patients from the currently 24 centers in Germany, Austria, and Switzerland that are part of the THROMKIDplus study group. The collection of patient data will be accompanied by storing of biomaterials from recruited patients. A substantial number of patients with IPD should be enrolled in the registry to achieve the following goals:

- Gaining better knowledge about the prevalence, pathogenesis, and clinical consequences of IPD:
  - Multinational, central registration of patients with IPD.
  - Recording disease- or defect-specific laboratory parameters.
  - Documentation of associated malformations and other phenotypic abnormalities based on the Human Phenotype Ontology (HPO) system.[13]
  - Collection of periodical follow-up information and severe events.
- Improving the diagnosis and treatment of patients with IPD:
  - Review of diagnoses by competence centers.
  - Quality management and standardization of special laboratory tests.
  - Documentation of therapeutic measures and outcome.
  - Establishing the basis for further development of diagnostic and therapeutic guidelines.
  - Advising participating and nonparticipating centers in patient care.
- Supporting basic research on genetic, molecular, and physiological basis of IPD:
  - Classification of the underlying defects of platelet disorders.
  - Linking the registry with the patient samples from the biomaterial banks making them available for biomedical research projects.
  - Providing the basis for cross-center research on patients with specific forms of IPD.
  - Defining patient groups with unknown causes of IPD for further analysis of genetic courses and pathophysiology.

## Inclusion and Exclusion Criteria

The THROMKIDplus study group has defined the following inclusion and exclusion criteria:

### Inclusion Criteria

- Diagnosis of an IPD (thrombocytopathy, thrombocytopenia, or thrombocytosis) or highly suspected IPD after assessment by a competence center.
- Age 0 to 17 years.
- Signed informed consent.

### Exclusion Criteria

- Acquired qualitative platelet disorders (e.g., due to drugs or uremia).
- Acquired quantitative platelet disorders (e.g., immune thrombocytopenia, infections, myeloproliferative diseases, secondary thrombocytosis, liver failure, hypersplenism, bone marrow infiltration by malignant disease, and somatically acquired myeloproliferative disorders).
- Thrombotic-thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS).
- Plasmatic coagulation disorders without involvement of platelets (e.g., hemophilia, von Willebrand disease).
- Following bone marrow failure syndromes: Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, reticular dysgenesis, or Pearson syndrome.

## Data Collection

A basic dataset is mandatory for all patients, with further data being requested only for specific disease groups, respectively. Furthermore, there is the option to archive additional results of specific tests for each patient. With this approach, we aim to address the seemingly conflicting requirements that (1) the heterogeneity of the diseases included in the patient registry necessitates the collection of very different parameters and (2) the complete documentation of these data for all patients would place a high burden on the reporting physicians and centers. The data to be collected are structured as follows (see also ►**Table 1**) and centrally revised by the coordinating sites for completeness and plausibility.

*Registration data*: Basic data include patient's name, date of birth, gender, and inclusion or exclusion criteria for the registry and are stored only within the treating center. During registration, an identifier (MARVIN ID) is generated to pseudonymize all patients' data and to which all further records are linked. The storage of the data collected within the registry and that of the personal data takes place on separate locations or servers.

*Basic examination*: When the individual is enrolled in the THROMKIDplus patient registry, we request data on (1) the (preliminary) diagnosis, (2) the age of onset of bleeding signs or symptoms of syndromic disease first occurred, and (3) the family history. Basic somatic data, information on physical and mental development, and previous inpatient stays are also recorded. Bleeding tendency is assessed in a standardized manner using the country-specific language version of the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT).[14] Associated anomalies and other symptoms that may be related to the underlying disease

 

**Table 1** Data recorded in the registry

| |
|---|
| • Registration/master data |
| - Name, date of birth, gender, met inclusion criteria |
| • Basic examination |
| - (Preliminary) diagnosis, first manifestation of symptoms |
| - Family history (pedigree), migrational background |
| - Somatic data (height, weight, physical and mental development) |
| - Bleeding tendency (ISTH-BAT score) |
| - Associated malformations (human phenotype ontology) |
| - In-patient stays |
| • Laboratory data: |
| - Complete blood count |
| - Microscopic evaluation of blood smears[a] |
| - Coagulation[a] |
| - Aggregometry[a] and other platelet function testing[a] |
| - Clinical chemistry (GPT, total protein, creatinine) |
| • Therapy data: |
| - Local measurements |
| - Medications (antifibrinolytics, desmopressin, recombinant factor VIIa, hormonal contraceptives, thrombopoietin receptor agonists) |
| - Transfusions (platelets, erythrocytes) |
| - Hematopoietic stem cell transplantation |
| - Splenectomy |
| • Follow-up data (if possible, annually): |
| - Somatic data |
| - Blood counts |
| - Bleeding tendency |
| - Therapeutic interventions |
| - Relevant laboratory data |
| - Special events (inpatient stays, development of additional symptoms/malignancies) |
| - Change or specification of diagnosis |

[a]Only conspicuous findings are documented in detail.

are documented using the HPO system, which has become a standard for the recording of phenotypic anomalies and allows exchange with international research projects.[13] Genetic data are not deposited in the registry, except for information on whether a diagnosis has been genetically confirmed. The registry also asks whether data from next-generation sequencing analyses (panel sequencing, whole exome sequencing, whole genome sequencing) are available to enable exchange between research groups and avoid duplication of testing.

*Laboratory data*: Some laboratory analyses are mandatory for enrollment and follow-up. These include complete blood cell counts and few basic clinical chemistry parameters. Additional laboratory data relevant to certain diseases may be collected. These include information on microscopic evaluation of blood or bone marrow smears, coagulation factor activities, or platelet function tests, especially aggregometry.[15] Detailed documentation of findings is usually performed in case of borderline or pathological findings. In addition, the upload of image files of microscopic images of smears or scans of aggregation curves for comparative analysis in downstream research projects and the entry of laboratory data retrospectively for any time point is also possible.

*Therapy data*: Therapeutic interventions should also be recorded at enrollment and follow-up. These include local measures to stop bleeding, medications, transfusions, and other measures such as splenectomy. Children who have undergone hematopoietic allogeneic stem cell transplantation should also be registered in the Pediatric Registry for Stem Cell Transplantation (PRST).

 

*Follow-up data*: Follow-up data are supposed to be collected once a year. Some records are mandatory: basic somatic data, complete blood cell counts, grade of bleeding tendency, and data on therapeutic interventions since the last visit. Furthermore, severe adverse events such as life-threatening bleeding episodes, hospitalizations, or the development of additional symptoms or malignancies are recorded. Changes in a preliminary diagnosis or the diagnostic strength should also be documented. Relevant laboratory test results may be revised as part of the follow-up report.

## Biomaterial Banking

As a basis for translational research projects using registry data, biological material will be preserved in a decentralized biomaterial bank ensuring high-quality requirements for certified biomaterial banking (e.g., the Hannover Unified Biobank [HUB], Germany, or the Interdisciplinary Bank for Biomaterials and Data Würzburg [ibdw], Germany). Unstained and May-Grünwald-Giemsa–stained blood smears will be archived and an age-dependent target amount of blood remaining after completion of initiated diagnostics or additionally collected for biomaterial banking will be stored. Platelet pellets and plasma as well as DNA will be isolated from the blood samples. In individual cases, other materials collected for diagnostic purposes, such as umbilical cord blood, serum, bone marrow smears, or punch cylinders, can be preserved according to quality standards.

## Data Management and Protection

Data collection and management are performed by pseudonymized electronic case report forms (eCRF) using the MARVIN platform, which is maintained by the central data management system of the GPOH (GPOH ZDM gGmbH) at the Hannover Medical School. MARVIN is well established in many pediatric hematology oncology centers in Germany, Austria, and Switzerland and allows decentralized electronic capture of patient data including images (e.g., microscopic images of blood smears or platelet aggregation curves). The platform provides general support to create plausible eCRF, to train users (e.g., investigators or study coordinators) at local sites, implement specific database operations, to program reports, and to export data for further statistical analysis. Treating physicians who do not have direct access to a MARVIN system will have the option of submitting paper-based CRF to a competence center. Basis for data protection is the General Data Protection Regulation 2016/679 of the European Parliament and of the European Council of April 27, 2016 (EU-DSGVO) and the Federal Data Protection Act (BDGS) of July 5, 2017, of the Federal Republic of Germany as the seat of the central database in its latest version. The data protection compliant operation and maintenance of the database, the secure archiving of the collected data, the authenticated input and encrypted data transmission, and the training of the users are ensured by the MARVIN platform.

### Ethical and Legal Aspects

The patient registry and the biomaterial bank are managed in accordance with the ethical principles of the 1964 Declaration of Helsinki and its current revision, and in accordance with the recommendations of the Ethics Committee of the Medical Faculty of the University of Würzburg. Furthermore, the legal provisions of the country concerned and the recommendations of the local ethics committee apply to the institutions participating in the project. The study protocol and informed consent forms have been approved by the Ethics Committee of the Medical Faculty of the University of Würzburg (reference no. 128/17).

### Data Availability

Inquiries for detailed information on data collection or requested biomaterials can be directed to the corresponding authors.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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## References

1 Palma-Barqueros V, Revilla N, Sánchez A, et al. Inherited platelet disorders: an updated overview. Int J Mol Sci 2021;22(09):4521
2 Warren JT, Di Paola J. Genetics of inherited thrombocytopenias. Blood 2022;139(22):3264–3277
3 Boeckelmann D, Glonnegger H, Sandrock-Lang K, Zieger B. Pathogenic aspects of inherited platelet disorders. Hamostaseologie 2021;41(06):460–468
4 Kim B. Diagnostic workup of inherited platelet disorders. Blood Res 2022;57(S1):11–19
5 Homan CC, Scott HS, Brown AL. Hereditary platelet disorders associated with germ line variants in RUNX1, ETV6, and ANKRD26. Blood 2023;141(13):1533–1543
6 Wagner M, Uzun G, Bakchoul T, Althaus K. Diagnosis of platelet function disorders: a challenge for laboratories. Hamostaseologie 2022;42(01):36–45
7 Stockklausner C, Duffert CM, Cario H, Knöfler R, Streif W Kulozik AE, THROMKID-Plus Studiengruppe der Gesellschaft für Thrombose- und Hämostaseforschung (GTH) and of Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH). Thrombocytosis in children and adolescents-classification, diagnostic approach, and clinical management. Ann Hematol 2021;100(07): 1647–1665
8 Teofili L, Larocca LM. Advances in understanding the pathogenesis of familial thrombocythaemia. Br J Haematol 2011;152(06): 701–712
9 Knöfler R, Olivieri M, Weickardt S, Eberl W, Streif W, THROMKID Studiengruppe der Gesellschaft für Thrombose- und Hämostaseforschung e.V. Erste Ergebnisse der THROMKID-Studie: Qualitätsprojekt zur Erfassung von Kindern und Jugendlichen mit

 

angeborenen Thrombozytenfunktionsstörungen in Deutschland, Osterreich und der Schweiz. [First results of the THROMKID study: a quality project for the registration of children and adolescents with hereditary platelet function defects in Germany, Austria, and Switzerland] Hamostaseologie 2007;27 (01):48–53

10 Gesellschaft für Thrombose- und Hämostaseforschung. Diagnose von Thrombozytenfunktionsstörungen - Thrombozytopathien. S2k-Leitlinie, AWMF-Register Nr. 086–003. 2018. https://register.awmf.org/assets/guidelines/086-003l_S2k_Diagnostik_Thrombozytenfunktionsstoerungen_Thrombozytopathien_2018-09.pdf

11 Gesellschaft für Thrombose- und Hämostaseforschung. Therapie angeborener thrombozytärer Erkrankungen. S2k-Leitlinie, AWMF-Register Nr. 086–004. 2020. Accessed July 31, 2023 at: https://register.awmf.org/assets/guidelines/086-004l_S2k_Therapie-angeborener-thrombozytaerer-Erkrankungen_2020-05.pdf

12 Althaus K, Zieger B, Bakchoul T, Jurk K, THROMKID-Plus Studiengruppe der Gesellschaft für Thrombose- und Hämostaseforschung (GTH) und der Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH). Standardization of light transmission aggregometry for diagnosis of platelet disorders: an inter-laboratory external quality assessment. Thromb Haemost 2019;119 (07):1154–1161

13 Köhler S, Gargano M, Matentzoglu N, et al. The human phenotype ontology in 2021. Nucleic Acids Res 2021;49(D1):D1207–D1217

14 Bidlingmaier C, Grote V, Budde U, Olivieri M, Kurnik K. Prospective evaluation of a pediatric bleeding questionnaire and the ISTH bleeding assessment tool in children and parents in routine clinical practice. J Thromb Haemost 2012;10(07):1335–1341

15 Zaninetti C, Leinøe E, Lozano ML, et al. Validation of immunofluorescence analysis of blood smears in patients with inherited platelet disorders. J Thromb Haemost 2023;21(04):1010–1019



 