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"InsightRP2: a global patient registry for *RP2*-associated retinitis pigmentosa"

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Study type: Register study, monocentric

Date and version of the study protocol: 24.10.2024, version 1.2

Signature study leaders: Prof. Dr. med. Bernd Wollnik Dr. med. Nina Bögershausen

Written consent of the department leader:
I consent to the conduct of the study at our institute.

Göttingen, 24.10.2024
City, date

Prof. Dr. med. Bernd Wollnik

Summary

Retinitis pigmentosa (RP) is a group of inherited retinal disorders characterized by progressive peripheral vision loss and night blindness, leading to central vision loss and eventual blindness. Among the various genetic mutations associated with RP, mutations in the *RP2* gene are responsible for a significant subset of X-linked retinitis pigmentosa (XLRP), an especially severe form of the disease.

There is currently no specific patient registry for *RP2*-associated retinitis pigmentosa. Due to the rarity of the disease, only a few patients with this disease are seen at various care sites, making clinical care and diagnosis very challenging. In addition, there are numerous knowledge gaps regarding the course of the disease, the disease mechanisms and therapeutic approaches, which poses additional challenges for patient care. Understanding and future treatment of *RP2*-associated RP is crucial due to its early onset and rapid progression. There is an urgent need for targeted research to develop effective therapies.

At the Institute of Human Genetics, we have set ourselves the goal of investigating the disease mechanisms of *RP2*-associated RP and contributing to the long-term development of a therapy for this rare disease. For this purpose, we would like to set up a patient registry specifically for *RP2*-associated RP, which is outlined in this protocol. The registry will use a secure REDCap-based database hosted by the Working Group for Biometrics, Data Management and Informatics in Clinical Trials at the University Medical Center Göttingen. The medical data collected will enable us to conduct studies on the natural history, mutation distribution and possible genotype-phenotype correlations of this disease. In addition, the collection of medical image data should enable evaluation for the purpose of improving diagnostic processes. Last but not least, we aim to form a patient collective who can be offered participation in possible therapy studies at a later date. The InsightRP2 registry therefore aims to support basic, preclinical and clinical research for this early-onset, rare disease and to improve long-term clinical care and the quality of life of those affected.

Zusammenfassung

Retinitis pigmentosa (RP) ist eine Gruppe erblicher Netzhauterkrankungen, die durch fortschreitenden zunächst peripheren, und später auch zentralen, Sehverlust und Nachtblindheit gekennzeichnet ist. In den meisten Fällen führt die Erkrankung schließlich zur Erblindung. Mutationen im *RP2*-Gen sind für einen erheblichen Teil der X-chromosomalen Retinitis pigmentosa (XLRP) verantwortlich, einer besonders schweren Form der Krankheit.

Bisher existiert noch kein spezifisches Patient*innenregister für die *RP2*-assoziierte Retinitis pigmentosa. Aufgrund der Seltenheit der Erkrankung werden nur vereinzelte Patienten mit dieser Erkrankung an verschiedenen Versorgungsstandpunkten gesehen, sodass die klinische Versorgung und die Diagnosestellung sehr herausfordernd sind. Darüber hinaus bestehen zahlreiche Wissenslücken in Bezug auf den Krankheitsverlauf, die Krankheitsmechanismen und über therapeutische Ansätze, was die Patientenversorgung zusätzlich vor erhebliche Herausforderungen stellt. Das Verständnis und die zukünftige Behandlung der *RP2*-assoziierten RP sind aufgrund des frühen Beginns und des rapiden Verlaufs von entscheidender Bedeutung. Es besteht ein dringender Bedarf an gezielter Forschung, um wirksame Therapien zu entwickeln.

Am Institut für Humangenetik haben wir es uns zum Ziel gesetzt, die Krankheitsmechanismen der *RP2*-assoziierten RP zu erforschen und langfristig zur Entwicklung einer Therapie dieser seltenen Erkrankung beizutragen. Zu diesem Zweck möchten wir ein Patient*innenregister speziell für die *RP2*-assoziierte RP aufbauen. Das Register wird eine sichere REDCap-basierte Datenbank nutzen, die von der Arbeitsgruppe für Biometrie, Datenmanagement und Informatik in klinischen Studien der Universitätsmedizin Göttingen gehostet wird. Die erhobenen medizinischen Daten sollen uns ermöglichen, Studien zum natürlichen Krankheitsverlauf, der Mutationsverteilung und möglichen Genotyp-Phänotyp-Korrelationen durchzuführen. Darüberhinaus soll durch die Erhebung von medizinischen Bilddaten eine Auswertung zum Zweck der Verbesserung diagnostischer Prozesse ermöglicht werden. Nicht zuletzt wollen wir ein Patientenkollektiv bilden, welchem zu einem späteren Zeitpunkt die Teilnahme an möglichen Therapiestudien angeboten werden kann. Das InsightRP2 Register verfolgt somit das Ziel, die Grundlagen-, präklinische und klinische Forschung für diese frühmanifestierende, seltene Erkrankung zu unterstützen und langfristig, die klinische Versorgung und die Lebensqualität der Betroffenen zu verbessern.

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1. Introduction

Retinitis pigmentosa (RP) represents a diverse group of inherited retinal dystrophies (IRD) characterized by progressive photoreceptor degeneration leading to visual impairment and eventual blindness. Affecting approximately 1 in 4,000 individuals worldwide, RP exhibits significant genetic heterogeneity, with mutations identified in over 100 different genes (Hartong et al. 2006). Among these, mutations in the *RP2* gene account for approximately 20% of X-linked retinitis pigmentosa (XLRP), a particularly severe and early-onset form of the disease (Georgiou et al. 2023; Cheloni et al. 2022; Fahim et al. 1993).

In Germany, roughly four million people are living with one of approximately 8,000 rare diseases, including roughly two million children and adolescents (*National Action League for People with Rare Diseases (NAMSE): National Plan of Action for People with Rare Diseases*, 2013). Rare diseases present a remarkable challenge by affecting a relatively small number of individuals who are broadly distributed across Germany and the world. Retinitis pigmentosa collectively qualifies as a rare disorder, which, by definition, affects less than 5 in 10,000 people (*Regulation (EG) No. 141/2000 of the European Parliament and Council, Preamble Para. 5*, 1999). However, *RP2*-associated RP is even rarer and thus, only few patients are seen at individual ophthalmological and human genetics facilities (personal communication). This aspect hinders participation in rare disease studies and access to evolving treatment modalities that are reasonably projected to go beyond currently used devices (glasses or special visual aids) to include gene therapies for visual impairment (Birch et al. 2023). However, since *RP2*-associated RP accounts only for a minor fraction of XLRP as compared to *RPGR*-associated RP, current therapeutic efforts have focused on the latter, which is the more prevalent disease. Small patient numbers may be the main reason hindering efforts to finding a cure, in spite of promising pre-clinical study results (Mookherjee et al. 2015; Lane et al. 2020). We aim to help end this inequity by creating a collaborative patient registry, linking patients from Germany and around the world with physicians and researchers trying to better understand and eventually treat this rare condition.

Patient registries serve as a mechanism to engage patients who may otherwise face hurdles in connecting with rare disease studies. Registries support research into pathogenesis, therapy, and longitudinal natural history studies and can serve as a tool to recruit participants into clinical trials. Unlike the situation in countries such as France with the National Database of Rare Disease (BNDMR), a national coordinated registry, Germany currently lacks a central coordinated registration of patients with rare diseases and it appears there are neither plans for forming, maintaining nor financing registries for these purposes. The Council of the European Union has recommended that each member country prepare its own respective national plan and establish national centers for

research and treatment (*National Action League for People with Rare Diseases (NAMSE): National Plan of Action for People with Rare Diseases*, 2013). It is therefore the duty of the expert center itself to form such registries. The establishment of centers for individuals with rare diseases and the inclusion of research activities are of central importance to strengthening research on rare diseases in Germany.

The only German patient register for IRD, hosted by the German patient organization ProRetina (https://www.pro-retina.de/forschung/patientenregister) registers patients with retinal disease, irrespective of the genetic cause, which is tremendously important work for the IRD community. In contrast to ProRetina, this study aims to develop a REDCap-based registry specifically for individuals with an established diagnosis of *RP2*-associated RP. The "InsightRP2" registry is tailored to document the clinical and genetic diagnostic data that are specific to *RP2*-associated RP, thus enabling more focused clinical and basic as well as pre-clinical research. We believe our registry will work to address many unmet needs for *RP2* patients while complementing the extensive efforts and expertise at the Göttingen Campus. The key stakeholders of our registry are the patients, their physicians, and research teams with long-established expertise.

Literature

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National Action League for People with Rare Diseases (NAMSE): National Plan of Action for People with Rare Diseases, 2013. NAMSE Coordinating Office.

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2. Study Aims

The study goal is to establish a patient registry, in both German and English languages, for patients with hereditary retinal disease due to variants in *RP2.* We wish to engage patients by guiding them to our center for coordinated longitudinal natural history studies, opening possibilities of functional studies of *RP2* variants, and to provide consent to be informed about possible longer-term future studies that match our expertise profile, following respective (forthcoming) study approvals.

Main objective criterion:

To create a collaborative registry for patients with a molecular genetic diagnosis of *RP2*-associated RP to increase understanding of natural history and types of genetic variants in patients from Germany and around the world and to facilitate clinical and basic research on *RP2*-associated RP.

Secondary objective criterion:

Knowledge of *RP2* variants with possible permitted contacts to patients may lead to improved access to therapies and knowledge that will better characterize this patient group in the long term and create prerequisites for improved, patient-tailored therapy and care.

3. Study Design

3.1. Patient count

We intend to include approximately 200 patients in the study. There is no major limitation to participant numbers through the REDCap-based database tool.

4. Study Implementation

4.1. Recruitment

The registry will be stored as a secure online database, making it potentially accessible to a broad participant base. Participants will include parents/guardians of minors and adult patients from multiple potential sources. Potential participants of this study can be offered a specialized consultation led by Dr. Nina Bögershausen at the Institute of Human Genetics and Center for Rare

Diseases Göttingen, either in person or via video call (using e.g. “Sprechstunde online” as platform tool). Furthermore, we anticipate recruiting participants who were diagnosed through other molecular genetic diagnostic laboratories in Germany and around the world. Access to the study information and consent forms will be linked on the Institute of Human Genetics and Department of Ophthalmology webpages at UMG, as well as a central “registry of registries” such as the European Rare Disease Registry Infrastructure Directory of Registries (https://eu-rd-platform.jrc.ec.europa.eu/erdri-description_de) and the Orphanet portal (https://www.orpha.net/consor4.01/www/cgi-bin/ResearchTrials_RegistriesMaterials.php?lng=EN) to provide visibility to participants. Visibility to the intended national/international audience will occur via four possible modalities: (1) through registration of the registry in multiple rare disease registries (such as those listed above), (2) through placement on a variety of UMG websites (such as those mentioned above), (3) through contacting the ProRetina patient organization and (4) through potential contacts via social media (e.g. Facebook: Retinitis Pigmentosa patient groups). We anticipate that these procedures will offer broad dissemination of this registry on national and international scales and, if successful, it will solely be due to the motivation and engagement of families who seek more information.

Only patients who have completed the consent procedure with a signature will be allowed to access the registry questionnaire, which is stored separately from personal data. Consent will be obtained again for underage subjects when they reach the age of majority. No fees or honorariums will be paid.

4.2. Inclusion and exclusion criteria

Inclusion criteria:

A molecular genetic diagnosis involving a heterozygous or hemizygous variant in *RP2* and a written informed consent to participate are required for access to the registry questionnaire. The *RP2* variants and clinical data will be re-reviewed by the study leaders mentioned on the first page of the Patient Information document (Prof. Bernd Wollnik and Dr. Nina Bögershausen) and associated team members (scientists at the Göttingen Campus, who will only see pseudonymized data). Patients of all ages meeting the above criteria will be allowed to participate. As documentation will be in English and German, those who can navigate these pages will be included.

Exclusion criteria:

Patients with evidence of non-*RP2* molecular genetic diagnoses will be excluded. Collection of data and further analysis will not be possible without the consent of the patient or legal guardian. Patients who cannot navigate registry documentation in English or German will be excluded.

4.3. Planned study procedure

Interventions

This study will collect already existing genetic and clinical data and will not require additional specimen sampling. Double pseudonymized medical data may be used for a review of mutational landscapes and natural history, double pseudonymized image data may be used for bioinformatic image analysis aiming to improve clinical diagnostic procedures, laboratory results may inform clinicians about possible biomarkers that might be investigated in future studies (Fig. 1). Thus, the collected data are intended to enable future studies aiming to better understand the pathophysiology of *RP2*-associated RP, to optimize clinical management, and to develop novel therapeutic strategies.

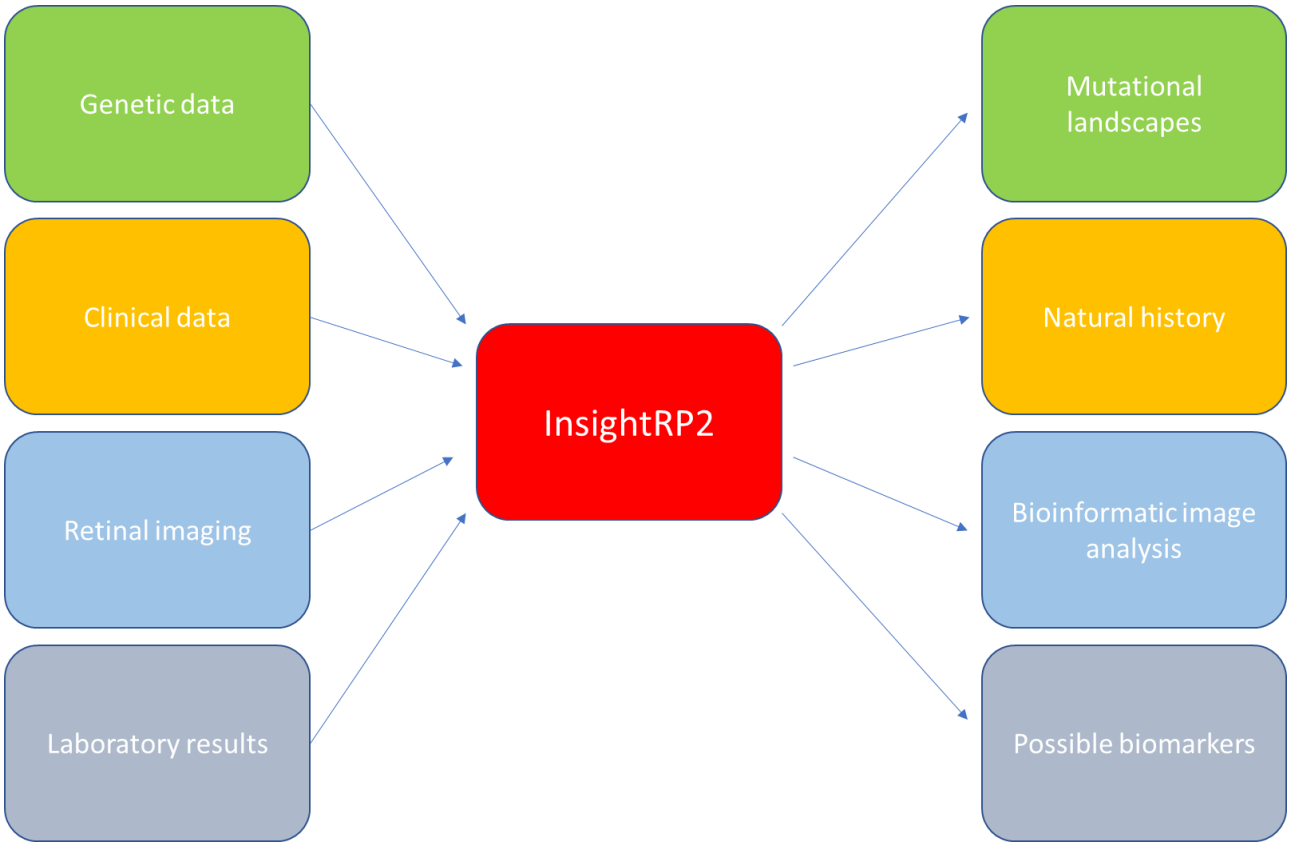

Figure 1. Data collection and possible use for future studies aiming to better understand *RP2*-RP.

4.4. Possible risks for the study participants

Since biosampling is not required, there is no health risk to the participant. This is a low-risk study.

4.5. Discontinuation criteria

Individual discontinuation criteria

Consent for participation can be withdrawn at any time, without any need to provide reasoning. Study participants have the right not to know of any results of the study, such as results from the natural history or functional/experimental studies. They have the right to stop the study procedure at any time until the results have been published or communicated.

Discontinuation criteria of the overall study

The study will be discontinued prematurely if voluntary personnel no longer have the capacity to execute the study.

4.6. Time and costs

The study is planned for a maximum period of 25 years. The data will be anonymized after 25 years unless the participants consent to use of email address to receive continued information about treatment options for a longer period of time. Following this, the study leaders will no longer be able to match personal data with medical data and the email address will be kept separate from the medical data. All patient personal information with exception of participant email address will be deleted, if given permission to contact the patient by email, otherwise, this will also be deleted. This appears as a mandatory field that the patient must select either “yes” or “no” in the study consent form. We would like to maintain the option to contact participants via email to possibly circulate information in the form of potential newsletters about new therapies. The patient can opt out at any time. Access to REDCap software is maintained free of charge by the working group for Biometrics, Data Management and Informatics in Clinical Studies at the University Medical Center Göttingen. Personnel will be funded through various in-house and third-party sources.

5. Legal and ethical aspects

Informed consent and voluntary participation

Study participation is voluntary. Prior to the study, patients will receive study information that has been written for children between 10 and 13 years of age, adolescents between 14 and 17 years of age and adults. Prospective participants are encouraged to direct questions to a study leader who volunteered to be the point of contact (Dr. Nina Bögershausen), whose email is at the top left corner

of all information sheets and, for convenience, disclosed directly in the information materials. We will also emphasize contact details on the institutional websites (that will be designed following ethical approval) to ensure this is clear to all participants. The participants will be informed about the nature and scope of the planned study and the manner and way their data will be used for the study. They will also be informed about any possible risks and benefits that may derive from the study. Consent will be obtained through signature via use of a computer mouse/mouse pad. Participants also have the right not to know about new findings that may be of relevance and/or to be re-contacted to learn about new therapy developments (right not to know). Consent to study participation can be withdrawn at any time without stating reasons and without disadvantages to further medical care. In case of withdrawal of consent, the collected data will be deleted. In instances when the patient is a minor, consent from both parents or legal guardian(s) will be required for participation.

Handling of patient data

Data are digitally recorded using an electronic case report form (eCRF) in the REDCap® database, a web-based database solution which meets all technical GCP requirements. Plausibility checks and checks for missing values are carried out continuously over the course of the study in order to promote data quality. The REDCap® instance is installed on servers of the Gesellschaft für wissenschaftliche Datenverarbeitung Göttingen (GWDG) and is managed according to the SOPs of the clinical trials unit UMG. Daily backups are created and kept for up to 90 days.

Patient names and all other confidential information are subject to medical confidentiality and provisions of the General Data Protection Regulation (GDPR/DSGVO), as well as the State of Federal Data Protection Act (LDSG/BDSG). A detailed data security and data protection concept is described in **Appendix 2**. Briefly, the registry is divided into two separate databases to allow separation of patient identifying data from clinical and genetic data: the consent and patient information database (personal data), and the InsightRP2 registry database (medical data). This structure guarantees the strict separation of person identifying data and medical information. Registration and participation in this study will happen in a two-step process, which also includes a two-step pseudonymization procedure:

1.) Registration requires the completion two online consent forms (study consent and a declaration of consent for data protection), both available via the REDCap-based online “Consent Forms” portal. Following review of the study information, the patient or legal guardian(s) will complete a patient information sheet, as well as the two consent forms online. The data entered at this step will automatically be pseudonymized with a record ID and stored in REDCap under this pseudonym. Only the study leaders have access to the data submitted to the consent and patient information database. The study leaders will be notified of the data entry by the REDCap interface. The study

leaders will then ascribe a separate case ID within the InsightRP2 registry database, which will be used for the processing of medical data, assuring pseudonymization of medical data. At this point, only the study leaders mentioned on the first page of the patient information document (Prof. Bernd Wollnik and Dr. Nina Bögershausen) will have access to a password secured reference list, linking record ID and case ID, which is stored on a secure server of the GWDG with restricted access.

2.) For participation, the patient or legal guardian(s) will be provided a link and a case-specific log-in via an encrypted email (Cryptshare), for completion of the registry questionnaire. The participant can complete the questionnaire to whatever extent desired and / or include his / her physician in this task by sharing the link that has been provided. Participants will also receive pdf copies of the Study Information, Information on the Processing of Personal Data and signed consent forms via Cryptshare for their personal records. In the study information and again in the relevant registry fields, individuals are requested to remove (e.g. by pen or marker) personal information, such as name or date of birth, on all uploaded documents. To ensure that all personal data have been properly redacted before allowing access to members of the study group, a study leader will review all patient data upon submission.

All other members of the study group will have restricted access to pseudonymized data only. Genetic and clinical data will be shared with the study team to accelerate understanding of *RP2*-associated RP for eventual publication, most likely as a natural history study, following double pseudonymization. Internal data sharing can include selected genetic and clinical data or analysis results, which, in all cases, will be pseudonymized. Selected results from this study will be used in a double pseudonymized form for teaching, research or presentations at scientific conferences and will be available in this form for a longer time. This means that the original case ID will undergo a second round of pseudonymization with a number generated by a random number generator and take the form “Individual” (or appropriate synonym) then random “number,” as is customary in human genetics publications (e.g. individual 10). The new list (password protected excel) is stored on a secured server separately from the REDCap pseudonymized list and protected from unauthorized access. The assignment of persons after pseudonymization and double pseudonymization can only be done by the study leaders and not by third parties. More details concerning data security are described in **Appendix 2**.

The study will be conducted in accordance with the current version of the Declaration of Helsinki.

The study protocol and database structure will be submitted to the Ethics Committee of the University Medical Center Göttingen for approval prior to the start of the study.

6. Relevance of the study results to the study participants

The benefit for the study participants consists of a possible better understanding of *RP2*-associated RP and by serving as a close stakeholder to the multidisciplinary efforts to cure inherited retinal diseases on the Göttingen Campus. Participants will have the option to be informed with updates of gene therapy options as they are expected to materialize at the University Medical Center Göttingen.

Göttingen, 24.10.2024 _____

City, date Dr. Nina Bögershausen

(Study coordinator)

Attachments:

- Appendix 2