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Identifying features contributing to the development and progression of primary sclerosing cholangitis

Submission date 20/09/2024	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 24/09/2024	**Overall study status** Ongoing	
Last Edited 16/10/2024	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
The study aims to understand more about the risk factors for developing Primary Sclerosing Cholangitis (PSC) and the processes that lead to its progression. While understanding of PSC has improved over time, there is still much that remains unknown about the condition. This study aims to collect blood, stool, and, if possible, samples from the large bowel and bile ducts, and analyze these samples. The outcome of this analysis is expected to enhance understanding of the disease process and guide potential treatment targets

Who can participate?
Individuals with one of the following conditions will be invited to participate: primary sclerosing cholangitis, primary biliary cholangitis, metabolic-associated steatotic liver disease, and inflammatory bowel disease. Additionally, 'healthy volunteers' with no evidence of liver or bowel disease will be asked to contribute to the study.

What does the study involve?
Participants will be invited to attend a screening visit at the Queen Elizabeth Hospital in Birmingham, lasting up to 30 minutes. During this visit, participants will be asked to:
1. Initial, date, and sign the Informed Consent Form to confirm their agreement to participate.
2. Provide a maximum of 35 ml of blood sample, equivalent to 7 teaspoons.
3. Provide a stool sample using the provided stool collection kit, which can be returned at a later date. If not returned within a week, follow-up will be conducted.
4. If participants are undergoing a colonoscopy to assess their large bowel as part of routine clinical care at a later date, the endoscopist will be asked to take extra biopsies from the colon. Participants will not be required to have a colonoscopy specifically for this study.

Alternatively, if participants are undergoing an endoscopic retrograde cholangiopancreatography (ERCP) to assess their bile ducts as part of routine clinical care at a later date, the endoscopist will be asked to take samples from the bile ducts during the procedure (one or more of: bile duct brushings, bile fluid, and/or bile duct biopsies). Participants will not be required to have an ERCP specifically for this study.

Ideally, most of these samples will be collected from the same participant, but participants are not obligated to provide any samples they do not wish to provide.

What are the possible benefits and risks of participating?
There is no direct benefit in terms of the care participants currently receive for their liver disease. However, the results from this study may help understand liver disease better and could lead to improved treatments for managing the condition in the future.

The main disadvantage is the extra time required to collect samples, including blood and stool samples.

If participants are undergoing a colonoscopy or ERCP, they will be consented by the endoscopist performing the test. This involves explaining the procedure and its risks and benefits.

Potential side effects from the tests or procedures include:
Blood test: Discomfort and bruising at the needle insertion site, fainting, and in rare cases, infection.
Endoscopy – colonoscopy: Additional biopsies may carry a small risk of bleeding (about 1-6 per 1000 procedures). Severe cases might require a blood transfusion.
Endoscopy - ERCP: Additional biopsies may carry a small risk of bleeding (about 1 per 5000 procedures). Severe cases might require a blood transfusion.

Where is the study run from?
The study is sponsored by the University of Birmingham (UK) and will be coordinated by the University of Birmingham Centre for Liver and Gastrointestinal Research and the University of Birmingham Liver Unit.

When is the study starting and how long is it expected to run for?
July 2023 to October 2026

Who is funding the study?
Regeneron Pharmaceuticals, Inc. (USA)

Who is the main contact?
Dr Palak Trivedi (Chief Investigator), p.j.trivedi@bham.ac.uk

Contact information

Type(s)
Public, Principal investigator

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Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
334983

Study information

Scientific Title
Cellular and molecular profiling of human primary sclerosing cholangitis (PSC)

Acronym
PSC Omics

Study objectives
In order to identify the key drivers of disease development and progression, it is important to integrate findings from microbiome studies with genomic data, cell-specific gene and protein expression patterns (from principal sites of tissue injury: liver, bile ducts and bowel), and the phenotypic profiles that patients present.

Thus, the overarching goal of this study is to further understanding of PSC risk and pathogenesis through coordinated sample collection, and subsequent integrated analysis of genetic, cellular, molecular and microbiome profiling of patients' biospecimens. Similar analysis will be conducted in comparator cohorts, which will constitute non-PSC chronic liver diseases (primary biliary cholangitis [PBC] and metabolic dysfunction associated steatotic liver disease [MASLD], individuals with extra-hepatic cancers with liver metastases, IBD without PSC, and healthy controls without liver disease or IBD. Individuals attending specialist liver and gastroenterology

outpatient clinics will be screened for eligibility. Healthy controls that are invited to participate will consist of patients attending these specialist clinics who have no known autoimmune, malignant, liver or inflammatory bowel disease following clinically appropriate investigation.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 16/09/2024, West of Scotland Research Ethics Service (Ward 11, Dykebar Hospital, Paisley, PA2 7DE, United Kingdom; +44 141 314 0213; WoSREC5@ggc.scot.nhs.uk), ref: 24/WS/0134

Study design
Single-centre cross-sectional observational cohort study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Primary sclerosing cholangitis

Interventions
This is a single-centre cross-sectional observational cohort study with sample and data collection taking place in line with the routine standard of clinical care visits.

Participants eligible for the study will be identified through specialist liver and gastroenterology clinics, including endoscopy lists, at University Hospitals Birmingham. Participants will be approached during their routine clinic visit and once consented will be sent a patient information sheet and invitation letter to participate in this study. After signing an informed consent form, investigators will complete a case record form together with the participant, detailing the minimum required dataset pertaining to medical background, disease activity and severity, treatment regimens and routinely collected clinical, laboratory and radiological information.

Routine samples will be obtained at the same time as routine standard-of-care hospital visits. Samples will include peripheral blood, stool, colonic biopsies and biliary biopsies or aspirates. All samples will be processed in line with sample-specific protocols. The minimum sample set per patient is blood and stool samples, in addition to colonic samples for those with primary sclerosing cholangitis and concomitant inflammatory bowel disease. No long-term follow-up data will be collected from any of the study participants.

The total number of participants across all aetiologies will be approximately 350; however, it is intended that a single patient is eligible to donate more than one sample type. The total number of participants will be dictated by the number required to meet the target sample size for each sample subgroup as per the following breakdown:

Peripheral Blood:
• PSC=100

• IBD alone=100
• Healthy controls=50
• Primary biliary cholangitis (PBC)=20
• Metabolic dysfunction associated steatotic liver disease (MASLD)=20

Stool Samples:
• PSC=100
• IBD alone=100
• Healthy controls=50
• PBC=20
• MASLD=20

Colonic Biopsies:
• PSC with IBD=50
• IBD alone=20
•. People who are undergoing colonoscopies, without evidence of IBD or cancer (Non-PSC, non-IBD controls)=20

Biliary Biopsies/Brushings:
• PSC=10

The samples collected will be analysed as per the breakdown below:
The following samples will be collected from participants who fulfil the eligibility criteria. A breakdown of the planned analysis per sample type is outlined below:

Peripheral blood for:
• Genetic association studies using whole-exome sequencing and/or array genotyping to identify single variants and/or gene-based burden tests.
• Transcriptional profiling through single-cell RNA sequencing of peripheral blood mononuclear cells.
• Cellular profiling by multi-parameter flow cytometry on peripheral blood mononuclear cells.
• T-cell receptor (TCR) sequencing of blood to identify TCR sequences differentially expressed.
• Proteomic profiling of peripheral blood to identify proteins that are differentially expressed.

Colonic biopsies:
• Transcriptional profiling through single-cell RNA sequencing of colonic biopsies.
• Cellular profiling by multi-parameter flow cytometry on immune cells isolated from colon biopsies.
• T-cell receptor (TCR) sequencing of colonic biopsies to identify TCR sequences differentially expressed.
• In situ hybridization/immunohistochemistry measures on colonic biopsies that are differentially expressed.

Stool samples:
• 16S rRNA and targeted metagenomic profiling of microbial species in stool.

Biliary aspirates or biopsies:
• Transcriptional profiling through single-cell RNA sequencing of biliary samples.
• Cellular profiling by multi-parameter flow cytometry on immune cells isolated from biliary aspirates/biopsies.
• T-cell receptor (TCR) sequencing of biliary aspirates/biopsies to identify TCR sequences differentially expressed.

• In situ hybridization/immunohistochemistry measures on biliary biopsies that are differentially expressed.
• 16S rRNA and targeted metagenomic profiling of microbial species in bile, and stool.

Intervention Type
Other

Primary outcome(s)
1. Cellular and molecular signatures in immune, stromal, and epithelial cell populations in bile, colon and peripheral blood will be measured using the following methods at a single time point:
1.1. Transcriptional profiling through single-cell RNA sequencing of colonic biopsies, and biliary samples (biliary aspirates and/or brushings and/or biopsies)
1.2. Transcriptional profiling through bulk RNA sequencing of peripheral blood mononuclear cells, colonic biopsies, and biliary samples (biliary aspirates and/or brushings and/or biopsies)
1.3. Cellular profiling by multi-parameter flow cytometry on peripheral blood mononuclear cells
1.4. Cellular profiling by multi-parameter flow cytometry on immune cells isolated from biliary and colon samples

2. Human genetic variants that are associated with PSC, its disease severity, and progressive (high-risk) disease phenotypes will be measured genetic association studies using whole-exome sequencing and/or array genotyping to identify single variant and/or gene-based burden associations to disease risk, severity, progression, and related clinical traits using the following methods at a single time point

Key secondary outcome(s))
1. Plasma proteome associated with PSC measured using proteomic profiling of peripheral blood plasma using Olink and/or complementary technologies to identify proteins that are differentially expressed at a single time point
2. Associations between the plasma proteome in PSC and disease severity measured using protein and/or RNA profiling using in situ hybridization/immunohistochemistry measures on colon and biliary biopsies at a single time point
3. T-cell receptor (TCR) repertoire in PSC versus disease controls and healthy controls measured using TCR sequencing of blood, biliary brushings/biopsies, and colonic biopsies for TCR repertoire analysis at a single time point

Completion date
15/10/2026

Eligibility

Key inclusion criteria
Eligible participants must fulfil the criteria set out below, as related to the sample type in question.

Peripheral blood:
1. Adults (age 18 – 75 years).
2. Be able to provide written (signed) informed consent.
3. Be willing and able to comply with routine clinic visits and study-related procedures.
4. Be able to understand and complete study-related questionnaires.
5. Liver disease populations - participants must have an established diagnosis of any of the following conditions:

5.1. PSC
5.2. PBC
5.3. MASLD
6. IBD alone populations - participants must have an established diagnosis of one of the following, without a concurrent diagnosis of PSC:
6.1. Ulcerative colitis (UC)
6.2. Crohn's disease with colonic involvement
6.3. IBD unclassified with colonic involvement
7. Healthy controls -defined as participants who do not have present or previous gastrointestinal or liver disease. Participants with functional gastrointestinal disorder (FGID) can be included. This will be clinician defined.

Stool:
1. Adults (age 18 – 75 years).
2. Be able to provide written (signed) informed consent.
3. Be willing and able to comply with routine clinic visits and study-related procedures.
4. Be able to understand and complete study-related questionnaires.
5. Liver disease populations: participants must have an established diagnosis of any of the following conditions:
5.1. PSC
5.2. PBC
5.3. MASLD
6. IBD populations: participants must have an established diagnosis of one of the following, without a concurrent diagnosis of PSC:
6.1. Ulcerative colitis (UC)
6.2. Crohn's disease with colonic involvement
6.3. IBD unclassified with colonic involvement
7. Healthy control populations: defined as participants who do not have present or previous gastrointestinal or liver disease. Participants with functional gastrointestinal disorder (FGID) can be included. This will be clinician defined.

Colonic biopsies:
1. Adults (age 18 – 75 years).
2. Be able to provide written (signed) informed consent.
3. Be willing and able to comply with routine clinic visits and study-related procedures.
4. Be able to understand and complete study-related questionnaires.
5. Liver disease populations: participants must have an established diagnosis of PSC.
6. IBD population: participants must have an established diagnosis of one of the following, without a concurrent diagnosis of PSC:
6.1. Ulcerative colitis (UC)
6.2. Crohn's disease with colonic involvement
6.3. IBD unclassified with colonic involvement
7. Healthy control populations:
7.1. Participants without a diagnosis of PSC or IBD, attending for a colonoscopy who do not meet the exclusion criteria.

Biliary aspirates/biopsies:
1. Adults (age 18 – 75 years).
2. Be able to provide written (signed) informed consent.
3. Be willing and able to comply with routine clinic visits and study-related procedures.
4. Be able to understand and complete study-related questionnaires.
5. Established diagnosis of PSC.

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Key exclusion criteria
Here is the revised text with the requested numbering system:

Eligible participants must fulfill the criteria set out below, as related to the sample type in question.

Peripheral blood:
1. Liver transplant recipients.
2. Evidence of acute or chronic liver disease not listed in the inclusion criteria, including, but not limited to:
1.1. Secondary sclerosing cholangitis
1.2. IgG4-related cholangitis
1.3. Viral hepatitis
1.4. Alcohol-related liver disease
1.5. Drug-induced liver disease or drug-induced sclerosing cholangitis
1.6. Hereditary haemochromatosis
1.7. Alpha-1-antitrypsin disease
1.8. Wilson disease
1.9. Budd-Chiari Syndrome
Individuals with autoimmune hepatitis, concomitant IBD, and overlapping features of sclerosing cholangitis are eligible and may be recruited to the PSC group.
3. Evidence of acute or chronic gastrointestinal disease not listed in the inclusion criteria.
4. A history of malignancy within the prior 3 years, except for individuals with:
1.1. Prior gallbladder cancer, with gallbladder removal, and without evidence of recurrence or disseminated/metastatic disease.
1.2. Prior colonic cancer, with local resection, and without evidence of recurrence or disseminated/metastatic disease.
1.3. Prior non-melanomatous skin cancer that has been resected, without evidence of recurrence or disseminated/metastatic disease.
5. If the potential participant is a member of the clinical site study team and/or his/her immediate family.
6. Women who are pregnant or less than 12 weeks post-partum.

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1.2. Prior colonic cancer, with local resection, without evidence of recurrence or disseminated /metastatic disease.
1.3. Prior non-melanomatous skin cancer that has been resected, without evidence of recurrence or disseminated/metastatic disease.
5. Previous colonic or small bowel resection.
6. If the potential participant is a member of the clinical site study team and/or his/her immediate family.
7. Women who are pregnant or less than 12 weeks post-partum.

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1.10. PBC
1.11. MASLD
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1.2. Prior colonic cancer, with local resection, without evidence of recurrence or disseminated /metastatic disease.
1.3. Prior non-melanomatous skin cancer that has been resected, without evidence of recurrence or disseminated/metastatic disease.
5. If the potential participant is a member of the clinical site study team and/or his/her immediate family.
6. Women who are pregnant or less than 12 weeks post-partum.

Date of first enrolment
15/11/2024

Date of final enrolment
15/10/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital

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Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Industry

Funder Name
Regeneron Pharmaceuticals

Alternative Name(s)
Regeneron Pharmaceuticals, Inc., Regeneron

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date