Human genetics of myocarditis: overall, after mRNA COVID-19 vaccination, and after SARS-CoV-2 infection

First published: 21/01/2026

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000728

Study ID

1000000728

DARWIN EU® study

No

Study countries

United States

Study description

This is a non-interventional, retrospective case-control genetic association study using secondary data from the US-based Helix Research Network (HRN) Myocarditis Registry, where patients with myocarditis (cases) and patients without myocarditis (controls) will be identified.
Cases and controls will be individuals who previously consented to participate in genetic research studies and for whom clinical information is available.
The study will include the below three cohorts of cases.
• Cohort A – post-mRNA COVID-19 vaccination myocarditis cases: myocarditis within 14 days of mRNA vaccination
• Cohort B – post-SARS-CoV-2 infection myocarditis cases: myocarditis within 8 weeks of SARS-CoV-2 infection
• Cohort C – acute/viral myocarditis cases: myocarditis unrelated to COVID-19 vaccination or SARS-CoV-2 infection
Controls will be individuals without myocarditis who previously consented to participate in the HRN.

Study status

Ongoing

Research institutions and networks

Institutions

Pfizer

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Institution

Helix, Inc.

Contact details

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Primary lead investigator

Scott Kelly

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 06/06/2023

Actual: 06/06/2023

Study start date

Planned: 19/01/2026

Actual: 20/01/2026

Date of final study report

Planned: 15/08/2026

Sources of funding

- Pharmaceutical company and other private sector

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Other study registration identification numbers and links

C4591078

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Hypothesis generation (including signal detection)

Data collection methods:

Secondary use of data

Study design:

This is a retrospective case-control genetic association study where patients with myocarditis (cases) and patients without myocarditis (controls) will be identified using the Helix Research Network (HRN) Myocarditis Registry. Cases and controls will be individuals who previously consented.

Main study objective:

To identify genetic variants associated with myocarditis among three populations (after mRNA COVID-19 vaccination, after SARS-CoV-2 infection, and acute/viral myocarditis unrelated to COVID-19 vaccination or SARS-CoV-2 infection) by performing a retrospective case-control study evaluating:

a) The role of rare coding variants using a genome-wide approach by testing if rare loss-of-function or missense variants predicted to be damaging in one or more genes are more prevalent in cases of myocarditis after mRNA COVID-19 vaccination compared to controls.

b) The role of HLA alleles by testing whether an HLA allele is significantly enriched among cases versus controls (using HLA class I genes and four HLA class II genes - HLA-DPB1, HLA-DQA1, HLA-DQB1, and HLA-DRB1).

c) The role of common variants by conducting a genome-wide association analysis to examine if any common variants are significantly enriched among cases compared to controls.

d) The role of rare coding variants in 3 sets of candidate genes (CD36, IL1

pathway, cardiomyopathy genes) that have each been linked to myocarditis in the literature.

Study Design

Non-interventional study design

Case-control

Study drug and medical condition

Medicinal product name

COMIRNATY

Study drug International non-proprietary name (INN) or common name

COVID-19 MRNA VACCINE (NUCLEOSIDE-MODIFIED)

Anatomical Therapeutic Chemical (ATC) code

(J07BN01) covid-19, RNA-based vaccine

covid-19, RNA-based vaccine

Medical condition to be studied

Myocarditis

Population studied

Short description of the study population

The study will include the below three cohorts of cases.

• Cohort A – post-mRNA COVID-19 vaccination myocarditis cases: myocarditis within 14 days of mRNA vaccination

• Cohort B – post-SARS-CoV-2 infection myocarditis cases: myocarditis within 8 weeks of SARS-CoV-2 infection

• Cohort C – acute/viral myocarditis cases: myocarditis unrelated to COVID-19 vaccination or SARS-CoV-2 infection

Controls will be individuals without myocarditis who previously consented to participate in the HRN.

Participants previously consented to be in the HRN research study and the HRN myocarditis registry sub-study between March 2018 and July 2025. After consent, participants submitted a sample for sequencing.

Age groups

- Adolescents (12 to < 18 years)
- Adults (18 to < 65 years)
  - Adults (18 to < 46 years)
  - Adults (46 to < 65 years)
- Adults (65 to < 75 years)

Estimated number of subjects

10.000

Study design details

Setting

This study will mostly use the US-based HRN Myocarditis Registry, originally consisting of electronic health records (EHR), case report forms (CRF), questionnaire, and genetic (whole exome sequencing) data on individuals with

and without myocarditis. The data was collected from participants who consented to the HRN protocol between 1 April 2018 and 25 July 2025 and provided saliva, buccal, or blood samples for germline Exome+® sequencing. Additionally, select pediatric participant data may be incorporated from a secondary pediatric study under a data sharing agreement.

The HRN study is an umbrella encompassing multiple research projects led by Helix and the following health systems in the US: Renown Health, HealthPartners, the Medical University of South Carolina, WellSpan Health, Nebraska Medicine, St. Luke's University Health Network, Sanford Health, and the Ohio State University. To construct the HRN Myocarditis Registry specifically, Helix previously reached out to physicians and healthcare organizations (members of the HRN and additional new contacts) to identify potential myocarditis cases.
Sequencing data from whole Exome+ sequencing was typically generated and available 3 months following consent and return of a biological sample from the participants. Phenotype data including electronic health records data was updated on a quarterly basis for participants part of the HRN study and data from the data freeze of October 2025 will be used for this analysis. Data collected via eCRF was collected once for cases only, after a myocarditis diagnosis and between 2023 and 2025.

Comparators

Not applicable.

Outcomes

The outcome of interest is the diagnosis of myocarditis (Myocarditis after vaccination, Myocarditis after SARS-CoV-2 infection and Myocarditis not related to COVID-19) and the key covariates include age, sex, vaccine dose, and other

known risk factors.

Data analysis plan

A variety of genomic analysis methods will be executed, including a genome-wide rare-variant, genome-based analysis (to identify rare variants), an HLA analysis, and a genome-wide association study (to identify common variants).

To address the Primary Objective, whole exomes were processed through a bioinformatic pipeline in order to generate an analysis-ready genomic dataset. Using exome data, various genetic analyses will be performed, including rare-variant gene-based collapsing analyses (to identify rare variants), HLA-WAS (to investigate beyond simple single nucleotide polymorphisms in the HLA region), GWAS (to identify common variants), and a candidate gene approach to investigate specific genes and pathways including CD36, the IL1 pathway, and cardiomyopathy genes. Descriptive statistics will be presented to characterize patients (cases and controls) in terms of demographics and clinical characteristics at the time of the index myocarditis diagnosis.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

Helix Research Network (HRN) Myocarditis Registry

Data sources (types)

Biobank

Disease registry

Laboratory tests and analyses

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown