

# Understanding how phenylketonuria affects the brain, heart, metabolism, and gut from childhood to adulthood

<b>Submission date</b> 03/06/2025	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered
<b>Registration date</b> 16/07/2025	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Protocol
<b>Last Edited</b> 13/04/2026	<b>Condition category</b> Nutritional, Metabolic, Endocrine	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
		<input type="checkbox"/> Individual participant data
		<input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Phenylketonuria (PKU) is a common inherited condition where the body cannot properly break down an amino acid called phenylalanine. This happens because of a missing enzyme, which leads to harmful conditions. PKU mainly affects the brain, but secondary effects may involve the heart and alternative tissues. Current treatments include a special low-protein diet and medication, but not everyone responds well. This study aims to better understand the effects of PKU on the brain and heart, and how differences in gut bacteria and metabolism may affect symptoms and treatment success.

### Who can participate?

The study will include people diagnosed with PKU or a related condition called hyperphenylalaninemia, including both children and adults living in Catalonia.

### What does the study involve?

Participants will undergo tests using the latest technology to assess brain function and heart health. Researchers will also analyze participants' gut bacteria, metabolic and bioenergetic profiles to see how these relate to their symptoms and treatment responses.

### What are the possible benefits and risks of participating?

Taking part may give participants more detailed information about their health and could help improve future treatments. The tests involve some time and effort but do not carry significant risks.

### Where is the study run from?

Fundació La Marató de TV3 in Catalonia (Spain)

### When is the study starting and how long is it expected to run for?

December 2019 to March 2027

Who is funding the study?  
Fundació La Marató de TV3 (Spain)

Who is the main contact?  
garrabou@clinic.cat

## Contact information

### Type(s)

Public, Scientific, Principal investigator

### Contact name

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## Additional identifiers

### Protocol serial number

18/C/2020

## Study information

### Scientific Title

Phenylketonuria: from childhood to adults through brain functional connectomics, cardiovascular changes, metabolomic and intestinal microbiota characteristics

### Acronym

PKU.CAT

### Study objectives

We propose the present study in order to progress in the knowledge of phenylketonuria (PKU), and we hypothesize that, in patients with PKU, compared with a control population of the same age and sex of our cultural and genetic environment:

1. The specific neuropsychological alterations of patients with PKU correlate with the structural and functional connectivity patterns observed in MRI, and with the metabolic control of the disease (diet adherence and Phe concentrations).
2. The metabolic and cardiovascular risk of these patients is largely explained by the higher prevalence of obesity, insulin resistance, diabetes, and arterial hypertension, factors that, in turn, are related to the metabolic control of the disease: adherence to the PKU diet and Phe

concentrations. In turn, the in-depth characterization of the cardiovascular risk phenotype will allow the establishment of standardized recommendations to define specific prevention strategies for this group of patients at high cardiovascular risk.

3. The intestinal microbiota diversity profile and the metabolic products generated by it (metabolomics) are characteristic in this population and explain part of the neuropsychological, cardiometabolic phenotypic variability and of both dietary and tetrahydrobiopterin therapeutic response (BH4).

### **Ethics approval required**

Ethics approval required

### **Ethics approval(s)**

approved 18/06/2018, Hospital Clinic de Barcelona (Villaroel, 170, Barcelona, 08036, Spain; +34 93 227 54 00 - 1437; proceic@clinic.cat), ref: HCB/2020/0552

### **Study design**

Multicenter observational case-control study

### **Primary study design**

Observational

### **Study type(s)**

Prevention

### **Health condition(s) or problem(s) studied**

Phenylketonuria

### **Interventions**

Multicenter observational and controlled study for the cross-sectional analysis of both patients and age/sex-paired controls, either of pediatric and adult age. In the case of adult PKU patients, those with poor metabolic control were longitudinally followed up before and after a dietary or pharmacological therapeutic intervention.

### **Intervention Type**

Other

### **Primary outcome(s)**

1. Neurological impairment measured using neuropsychological tests (Behavior Rating Inventory of Executive Function for Adults (BRIEF-A), Arithmetic subtest, Vocabulary subtests from the Wechsler Adult Intelligence Scale – IV edition (WAIS-IV)) at baseline, 36 months
2. Cardiovascular risk measured using carotid ultrasound, electrocardiography, continuous blood pressure monitoring, Oral Glucose Tolerance Test (OGTT) at baseline, 36 months

### **Key secondary outcome(s)**

1. Microbiota diversity is measured using stool sample analysis at baseline and 36 months
2. Individual metabolomic profiles are measured using blood and urine sample analysis at baseline and 36 months
3. Mitoquines and oxidative stress levels are measured using ELISA (GDF15, Humanin) and colorimetric assays (TBARS, 8-OHdG, TAC) at baseline and 36 months
4. Nutritional status is measured using clinical nutritional assessment, dietary intake record, and body composition analysis (DEXA) at baseline and 36 months

5. Liver morphology and elasticity are measured using liver ultrasound and elastography at baseline and 36 months
6. Physical activity levels are measured using the International Physical Activity Questionnaire (IPAQ) at baseline and 36 months
7. Dietary intake patterns are measured using the Food Frequency Questionnaire (FFQ-143) at baseline and 36 months
8. Cardiovascular health is measured using electrocardiography and ambulatory blood pressure monitoring (ABPM) at baseline and 36 months
9. Brain structure and function are measured using brain magnetic resonance imaging (MRI) at baseline and 36 months

**Completion date**

10/03/2027

## Eligibility

**Key inclusion criteria**

Pediatric (<18 years old) and adult patients (≥18 years old) with a genetic diagnosis of PKU or hyperphenylalaninemia (PKU group)

**Participant type(s)**

Healthy volunteer, Patient

**Healthy volunteers allowed**

No

**Age group**

Mixed

**Lower age limit**

2 years

**Upper age limit**

98 years

**Sex**

All

**Total final enrolment**

127

**Key exclusion criteria**

1. Intelligence quotient below 70 according to the WAIS/WISC tests
2. Pregnancy or planning a pregnancy during the study period
3. Active cancer
4. Severe chronic hepatic disease
5. Acute cardiovascular event in the 6 months prior to study inclusion
6. Common MRI contraindications
7. Creatinine levels ≥2.0 mg/dL

**Date of first enrolment**

01/06/2020

**Date of final enrolment**

31/12/2024

## Locations

**Countries of recruitment**

Spain

**Study participating centre**

Hospital Clinic of Barcelona and Hospital Sant Joan de Deu

Villaroel, 170

Barcelona

Spain

08036

## Sponsor information

**Organisation**

Fundació La Marató de TV3

## Funder(s)

**Funder type**

Charity

**Funder Name**

Fundació la Marató de TV3

**Alternative Name(s)**

TV3 Marathon Foundation, Marathon Foundation, Fundació la Marató, Fundació La Marató de 3Cat, 3Cat Marathon Foundation

**Funding Body Type**

Government organisation

**Funding Body Subtype**

Trusts, charities, foundations (both public and private)

**Location**

Spain

## Results and Publications

### Individual participant data (IPD) sharing plan

The study results (raw datasets) will be published in open-source data registries (i.e. Ensembl) and derived findings/conclusions in open-science journals aligned to DORA and Co-ARA guidelines

### IPD sharing plan summary

Stored in publicly available repository

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes