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

Submission date
03/06/2025

Registration date
16/07/2025

Last Edited
15/07/2025

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Nutritional, Metabolic, Endocrine

☐ Prospectively registered
☐ Protocol
☐ Statistical analysis plan
☐ Results
☐ Individual participant data
☒ 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 2025

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

Who is the main contact?
garrabou@clinic.cat

Study website
http://www.pku.cat

Contact information

Type(s)
Public, Scientific, Principal Investigator

Contact name
Dr Glòria Garrabou

ORCID ID
https://orcid.org/0000-0001-8973-9933

Contact details
Casanova. 143
Barcelona
Spain
08036
+34 (0)93 227 54 00 - 2907
garrabou@clinic.cat

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
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

Secondary study design

Case-control study

Study setting(s)

Hospital, Laboratory

Study type(s)

Prevention

Participant information sheet

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 measure
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

Secondary outcome measures
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

Overall study start date
17/12/2019

Completion date
10/03/2025

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

Age group
Mixed

Lower age limit
2 Years

Upper age limit
98 Years

Sex
Both

Target number of participants
130

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

Sponsor details

Carrer de la TV3, s/n
Sant Joan Despí
Spain
08970
+34 (0)934 99 93 33
fundaciomaratotv3@ccma.cat

Sponsor type
Charity

Website
http://www.tv3.cat/marato

Funder(s)

Funder type
Charity

Funder Name
Fundació la Marató de TV3

Alternative Name(s)
TV3 Marathon Foundation, Marathon Foundation, Fundació la Marató

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Spain

Results and Publications

Publication and dissemination plan
For dissemination of the project results, the following channels may be available:
1. Indexed journals: At least three original articles will be published in first quartile journals. Written by researchers in reference journals in the field of congenital metabolic diseases, neurology, neuroimaging, metabolism, cardiovascular risk, microbiology, etc (Journal of Inherited Metabolic Disease, Neuroimage). The selection will be adapted to the maximum possible impact based on the results obtained, with the objective of disseminating the results and generating synergies that allow revalidating and applying these results both in clinical practice and in future projects
2. Scientific conferences: Multiple oral and written communications, will be sent to the main

national and international scientific conferences about congenital metabolism errors (Spanish Association of Congenital Metabolism Errors (AECOM), Society for the study of inborn errors of Metabolism (SSIEM), where the results obtained will be presented, the therapeutic recommendations extracted, as well as inciting to continue and revalidate the most outstanding findings Minority Disease Meetings under the auspices of SEMI and the Catalan Society of Minority Diseases
3. The most outstanding results that may be of interest to society will be disseminated through communications on the web portals (Hospital Clinic, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), University of Barcelona and Hospital San Juan de Dios) and in social networks (Twitter, Facebook, LinkedIn and Instagram). Publications are made in three languages (Catalan, Spanish and English)
4. Diffusion to the state media: Of the most outstanding results that may be of interest to the public. Press conferences will be organised and press releases will be sent to the media
5. Scientific dissemination actions among PKU patients through annual meetings with the association of patients and family members
6. Outreach actions at events such as "Minority Disease Day", science week, thematic weeks

Intention to publish date

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