Solve the Unsolved

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Integrating genomic (WES/WGS) and other -omics technology in order to find the genetic cause, in 500 patients (children and adults) with an unexplained metabolic phenotype in whom standard care (genetic and metabolic evaluation) did not provide a...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON55505

Source
ToetsingOnline

Brief title
StU

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism
- Mental impairment disorders

Synonym
inborn errors of metabolism and inherited metabolic disorder

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ?

Intervention

Keyword: diagnosis, gene, inborn error of metabolism, treatment

Outcome measures

Primary outcome

Identification of a genetic variant and alignment with its biochemical and

phenotypical abnormalities.

Secondary outcome

Evaluating the diagnostic yield of combined WES/WGS and omics techniques.

Study description

Background summary

Inborn Errors of Metabolism (IEM) are monogenic conditions in which the impairment of a biochemical pathway is intrinsic to the pathophysiology of the disease. Organ dysfunction results from intoxication and/or storage, as well as a shortage of energy and building blocks. Rapid diagnosis of IEM enables initiation of targeted treatment (e.g. diet) slowing down or stopping the degenerative nature of the disease, resulting in significantly reduction of morbidity and mortality. A diagnosis also enables prognostication, access to community services and accurate genetic counselling for the patient and his/her family.
Diagnosing IEM can be a major challenge, because of phenotypic heterogeneity and complex, expensive, diagnostic tests. Whole exome/ genome sequencing (WES/WGS) has revolutionized diagnostics of rare diseases and IEM, but still gives a negative/inconclusive result in >50% of cases. Addition of other omics technologies (metabolomics, glycomics, lipidomics, epigenomics, transcriptomics, proteomics) with integrated bio informatics has increased yield, as it may point to the defective pathway allowing scrutinizing genes in genomic data or vice versa: it generates evidence of the deleterious functional impact of a VUS.

In this study we will unite our national expertise and apply a multi-omics approach to solve the unsolved genetic basis of patients with a metabolic phenotype on a larger scale.

Study objective

Integrating genomic (WES/WGS) and other -omics technology in order to find the genetic cause, in 500 patients (children and adults) with an unexplained metabolic phenotype in whom standard care (genetic and metabolic evaluation) did not provide a diagnosis.

Study design

A prospective, diagnostic (deep phenotyping, WES/WGS and pan-omics) multicenter cohort study.

Patients with unexplained metabolic phenotypes are referred (on paper) and discussed by the Solve the Unsolved (StU) team. After informed consent, clinical phenotyping, bioinformatic reanalysis of WES data and additional metabolomics will be performed in all participants. In case of no diagnosis, a tailor made diagnostic plan is made combining deep WES, WGS, glycomics, lipidomics, epigenomics, transcriptomics and/or proteomics Combination of these studies can lead to: 1) a known IEM, 2) a candidate variant, 3) still no diagnosis.

In case of a variant, additional functional studies (enzymatic assays, targeted omics, CRISPR/CAS, cell lines) will be used to confirm the effect of the genetic variant on protein function leading to definite. If still undiagnosed matchmaking (genetic/phenotypical) through international databases might lead to diagnosis.

Study burden and risks

The study involves collection of clinical data, reanalysis of previously analysed genetic data, additional *omics* and functional testing.
All participants will have at least 1 and at maximum 3 clinical study visits (located at the hospital of treatment) and maximum 2 telephone appointments with the arts-onderzoeker. Whenever possible clinical study visits will be combined with regular hospital visits.

Clinical data (clinical history, family history, physical examination, consultations, additional laboratory and/or radiological investigations) will be collected. A physical examination, blood and urine sampling will be performed in all participants at their first study visit. Any other already available biological samples (eg stored cell lines, dried blood spots, cerebrospinal fluid (CSF)) will be collected for re-analysis. In a selection of patients a skin biopsy will be performed at the 2nd clinical study visit for the use of functional studies.

The additional study visit and diagnostic procedures (e.g. blood, urine sampling and skin biopsy) and its associated risks, as well as renewed (false) hope/uncertainty about finding a diagnosis are potential burdens for

participants. The potential benefit for all participants include: the opportunity to establish a diagnosis providing information on prognosis, (refinement of) management, genetic counselling with precise recurrence risk and option(s) for prenatal diagnosis.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Patients (any age/gender/race) with an unexplained metabolic phenotype defined as: neurological symptoms and/or abnormalities on (physical) examination suggestive of an inborn error of metabolism (energy deficiency, intoxication type or storage type) AND / OR
one or more of the following suggesting a deficient metabolic pathway or process:
• abnormal metabolites in body fluids (CSF, urine, blood)
• functional studies at a biochemical/cellular level which indicates a metabolic deficiency (e.g. respiratory chain complex analysis)
• organ dysfunction (e.g. liver or kidney failure)
• abnormalities on imaging (neuro-imaging (including spectroscopy); X-rays (dysostoses or other bone abnormalities); ultrasound (enlarged liver/spleen))
• a VUS (variant of unknown significance) in a gene involved in metabolism

Exclusion criteria

after discussion by the Solve the Unsolved team the patient is suspected to have:
- a genetic condition for which there is a simpler and more cost-effective test available for diagnosis
- a complex genetic disorder (caused by a combination of multiple genes and/or environmental influences)
- a condition that is thought to be caused by factors that are non-genetic, such as infection, injury or toxic exposure
• he/she is unable to follow the study protocol (e.g. additional blood samples)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-12-2019
Enrollment:	500
Type:	Actual

Ethics review

Approved WMO Date:	24-06-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	06-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL67721.018.19