# Biochemical characterisation of TSC1 and TSC2 variants identified in patients with tuberous sclerosis complex

Published: 05-07-2007
Last updated: 17-08-2024

Pathogenic, non-truncating TSC1 and TSC2 mutations can be distinguished from non-pathogenic changes by studying their effects on the TSC1-TSC2 protein complex, and on splicing of the TSC1 and TSC2 mRNAs. Functional characterisation of unclassified...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Chromosomal abnormalities, gene alterations and gene variants |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON31326

**Source**
ToetsingOnline

**Brief title**
Characterisation of TSC1 and TSC2 variants

### Condition

- Chromosomal abnormalities, gene alterations and gene variants

**Synonym**
tuberous sclerosis complex; Bourneville's disease

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Erasmus MC, Universitair Medisch Centrum Rotterdam
**Source(s) of monetary or material Support:** Congressionally-Directed Medical Research Program;US Army Medical Research and Materiel Command

## Intervention

**Keyword:** TSC1, TSC2, tuberous sclerosis complex, unclassified variant

## Outcome measures

### Primary outcome

Studies are performed when unclassified TSC1 or TSC2 variants have been

identified. Study endpoint is the determination of pathogenicity of the TSC1

and TSC2 gene variants in individuals with TSC.

### Secondary outcome

not applicable

# Study description

### Background summary

After identification of TSC1 and TSC2, the genes that are mutated in individuals with tuberous sclerosis (TSC), we demonstrated that the TSC1 and TSC2 gene products form a protein complex. We characterised this complex and demonstrated that pathogenic missense mutations disrupt the complex. In addition, we performed mutation analysis on a cohort of >650 TSC index patients. In the majority of cases we identified the pathogenic mutation. However, in >50 cases it was impossible to ascertain from the genetic data alone whether specific sequence changes were pathogenic. We labelled these changes 'unclassified variants'.
Since the identification of the role of the TSC1-TSC2 complex in regulating signal transduction through mTOR, and the demonstration that the complex is a GTPase activating protein (GAP) for rheb, we have analysed the effect of different unclassified TSC1 and TSC2 variants on the activity of the TSC1-TSC2 complex. This has the potential to extend the diagnostic service that can be offered to TSC patients and their families.

### Study objective

Pathogenic, non-truncating TSC1 and TSC2 mutations can be distinguished from non-pathogenic changes by studying their effects on the TSC1-TSC2 protein complex, and on splicing of the TSC1 and TSC2 mRNAs. Functional characterisation of unclassified TSC1 and TSC2 variants will complement

existing diagnostic tests and enable appropriate clinical care and counselling for more TSC patients and their relatives. We hypothesise that specific non-truncating TSC1 and TSC2 mutations will be associated with a mild TSC phenotype. Characterisation of multiple TSC1 and TSC2 variants will also help define the structural and catalytic domains in TSC1 and TSC2.

### Study design

Observational study.

### Study burden and risks

Each participant has provided a blood sample for the isolation of genomic DNA as part of the standard genetic consultation procedure. TSC1 and TSC2 mutation screening is performed by the Section of DNA Diagnostics within the Department of Clinical Genetics at the Erasmus Medical Center. The mutation screening procedure is not part of the research project. In approximately 20 specific cases where a potential splice site mutation, or a mutation affecting transcription, is identified, a skin biopsy (3 mm) will be requested. This is a very minor surgical procedure carried out under local anaesthetic with negligable rsks to the patient. Temporary discomfort and some scar tissue are possible.
The study is non-therapeutic. However, a potential benefit is that patients and their relatives will obtain better information regarding their TSC1 or TSC2 mutation status.

## Contacts

**Public**
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 50
3015 GE Rotterdam
NL
**Scientific**
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 50
3015 GE Rotterdam
NL

# 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)

## Inclusion criteria

Individuals with tuberous sclerosis complex in whom potential splice site mutations have been identified will be asked to provide a skin biopsy.

## Exclusion criteria

Individuals with tuberous sclerosis complex where the routine, diagnostic genetic/DNA analysis has identified the pathogenic mutation.

# Study design

## Design

**Study type:** Observational invasive

| | |
|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Diagnostic |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 01-07-2008 |
| Enrollment: | 20 |
| Type: | Actual |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 05-07-2007 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

## 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 | NL16537.078.07 |