ISRCTN13103571 https://doi.org/10.1186/ISRCTN13103571

Understanding the genetic causes and clinical aspects of being born with a mutation in the TP53 gene in Sweden

Submission date 03/10/2019	**Recruitment status** Recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 14/10/2019	**Overall study status** Ongoing	
Last Edited 14/04/2025	**Condition category** Genetic Diseases	

Plain English summary of protocol

Background:
Individuals who are born with a mutation in their TP53 gene in all of their cells (germline mutation) have an increased risk of developing cancer. Some individuals have a high risk of breast cancer and it is unclear if these families also have an increased risk of other adult-onset cancer types. Other individuals have a high risk of many cancer types from childhood and young adulthood, mainly cancers of the bone and soft tissues, breast, brain- and/or cancer in the adrenal gland. This combination of cancers in a family is known as Li-Fraumeni syndrome (LFS). Today, we do not understand why some families with TP53 mutations have adult-onset breast cancer while others develop LFS. Recent reports have indicated that mutation carriers may benefit from a surveillance program.

Aims:
This study aims to characterise germline TP53 mutations from all possible perspectives in order to understand the implications of these mutations and to improve the treatment, surveillance and clinical follow-up of patients with germline TP53 mutations.

Who can participate?
All individuals of any age who carry a germline TP53 mutation (detected in e.g. normal blood cells) and who are able to provide informed consent are able to participate. In addition, children who have a parent with a germline TP53 mutation, but who have not undergone genetic testing themselves are able to participate.

What does the study involve?
The study involves four parts. Clinical information on cancer diagnoses, treatment, follow-up, genetic testing results and family history will be collected in a registry for all participants.
In addition, participants can opt to: (1) donate blood/tissue samples for the molecular analyses and for circulating biomarkers for cancer; (2) participate in the surveillance programme with clinical examination and whole-body MRI for adults and ultrasound of the abdomen and urinary sample for children; and (3) fill out three questionnaires that measure quality of life, cancer worry and benefits/risks of surveillance.

What are the possible benefits and risks of participating?
We do not know yet if there is any advantage in participating in the study. If the surveillance program turns out to be beneficial, then the participants will have benefited from this during the study period and we hope will then continue with the same protocol after the study is terminated. On the other hand, if the surveillance program turns out to not be beneficial, then the participants have not benefitted (and perhaps even suffered more anxiety) and also will not be able to continue with the surveillance program after termination of the study. The blood samples entail a small discomfort, but can be taken together with other samples if possible. All analyses are done within the research setting and this will take many years, so will not benefit the participants directly, but may improve their medical care in the future.

Where is the study run from?
The coordinating centre is Clinical Genetics, Karolinska University Hospital, Stockholm.
The participating centres are:
1. Norrlands University Hospital in Umeå
2. Akademiska Sjukhuset in Uppsala
3. Sahlgrenska University Hospital in Göteborg
4. Universitetssjukhuset Linköping
5. Skånes Universitetssjukhus Lund

When is the study starting and how long is it expected to run for?
The study started up in Stockholm 2017 and has started/will start in the rest of the country in 2019. The study will continue until 2026.

Who is funding the study?
This study is supported by the Stockholm County Council and we are applying for further funding.

Who is the main contact?
1. Emma Tham, emma.tham@sll.se, Principal investigator, Consultant in Clinical Genetics, Ph.D. Karolinska University Hospital
2. Svetlana Bajalica Lagercrantz, Svetlana.lagercrantz@ki.se, Principal investigator, Chief physician Oncology/Clinical Genetics, Assistant Professor, Karolinska University Hospital

Contact information

Type(s)
Scientific

Contact name
Dr Emma Tham

ORCID ID
https://orcid.org/0000-0001-6079-164X

Contact details
Department of Clinical Genetics
Karolinska University Hospital
Stockholm
Sweden
17176

+46851770455
emma.tham@sll.se

Type(s)
Scientific

Contact name
Dr Svetlana Bajalica Lagercrantz

Contact details
Department of Clinical Genetics
Karolinska University Hospital
Stockholm
Sweden
17176
+46 851770000
svetlana.lagercrantz@ki.se

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Molecular Characterization and Clinical Aspects of Germline TP53 Mutations in the Swedish Constitutional TP53 Cohort.

Acronym
SWEP53

Study objectives
1. Germline TP53 mutations are probably underdiagnosed in clinical practice and that by increasing awareness of this rare condition may improve diagnosis
2. Whole-body MRI/ultrasound/urinary tests can detect cancer at an earlier stage than symptoms and have an acceptable level of incidental findings
3. Circulating biomarkers can detect cancer at an early stage in these high-risk families
4. The quality of life and psychosocial health of TP53-carriers in an intensive surveillance program is better than without intensive surveillance
5. Genetic and environmental factors modulate risk for cancer in TP53-families
6. p53-reactivating compounds can have an anti-cancer effect on short term cell cultures from tumours originating from patients with germline TP53 mutations.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/11/2015, Ethical review board of Stockholm (Swedish Ethical Review Authority, Etikprövningsmyndigheten, Box 2110, 750 02 Uppsala, Sweden; +46-10-475 08 00; registrator@etikprovning.se), ref: 2015/1600-31 with addition 2018/1690-32

Study design
Observational

Primary study design
Observational

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Germline TP53 mutation carriers

Interventions
The study involves four parts. Clinical information on cancer diagnoses, treatment, follow-up, genetic testing results and family history will be collected in a registry for all participants.

In addition, participants can opt to: (1) donate blood/tissue samples for the molecular analyses and for circulating biomarkers for cancer; (2) participate in the surveillance programme with clinical examination and whole-body MRI for adults and ultrasound of the abdomen and urinary sample for children; and (3) fill out three questionnaires that measure quality of life, cancer worry and benefits/risks of surveillance.

Whole-body MRI and standardised clinical examination is added to standard breast cancer surveillance. Blood samples for cell free DNA are collected at the same time as the surveillance. Participants fill out psychosocial questionnaires.

Intervention Type
Other

Primary outcome(s)
TNM and clinical stage measured by reviewing medical records, histopathology and radiological reports

Key secondary outcome(s))
1. Number and distribution of detected premalignant lesions based on MRI examination for adults or ultrasound of the abdomen for children at baseline, at annual examination or by any radiological method used if symptoms arise during the interval between controls
2. The proportion of R0 / R1 / R2 tumor surgery based on surgical and radiological reports
3. Location and number of incidental findings that lead to additional examinations with radiology and/or invasive techniques after image diagnostics in the control program (i.e. on MRI examination or ultrasound examination at baseline or at annual examination)
4. Number of benign tumors detected using MRI/ultrasound at baseline or at annual examination
5. Tumor aggression (growth in serial imaging and information from histopathology report)

6. Measures of psychosocial health, i.e. compare year 5 with year 0 using SF36 Health Survey (widely used world-wide to measure patient reported outcomes), Cancer worry scale (Lerman C, 1994, Douma KH, 2010, Lammens CRM, 2010) and a questionnaire addressing the benefits and barriers to surveillance (Lammens CRM, 2010; Champion VL, 1984; Kash KM, 1992; Madalinska JB, 2007)
7. Measuring the penetrance, onset age, tumor spectrum, heredity, genotype-phenotype correlations of TP53 mutation carriers in Sweden to characterize the Swedish TP53 families based on review of medical records, pedigree data and genetic testing results
8. Practical feasibility of a national image-diagnostic surveillance program based on feedback from the radiologists, oncologists, pediatric oncologists and genetics departments at our annual workshops
9. Characterize the significance of new TP53 variants using cell-lines in the laboratory to test new TP53 variants
10. Discover modifying genetic/environmental factors using data from the risk factor questionnaire (local form) filled in at inclusion in the study and from genetic tests performed on the samples taken as part of this study
11.Investigate whether cell free DNA is a reliable biomarker for early cancer detection by analysing tumour-specific genetic changes in the blood at diagnosis of cancer and at all time points prior to cancer diagnosis to determine if cell free DNA could detect a cancer earlier than symptoms or MRI/ultrasound.
12. Test whether TP53 activating agents have an anti-tumor effect in vitro

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. All carriers of a pathogenic TP53 germline variant over the age of 15 years OR all children (0-18 years) who have 50% risk of inheriting a pathogenic TP53 germline variant
2. Able to provide informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
All

Sex
All

Total final enrolment
60

Key exclusion criteria
1. Individuals with a TP53 germline variant of unknown pathogenicity

Date of first enrolment
01/01/2017

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
Sweden

Study participating centre
Karolinska University Hospital
Clinical Genetics
Stockholm
Sweden
17 176

Study participating centre
Norrlands University Hospital
Clinical Genetics
Umeå
Sweden
90737

Study participating centre
Akademiska Sjukhuset
Clinical Genetics
Uppsala
Sweden
75185

Study participating centre
Sahlgrenska University Hospital
Clinical Genetics
Göteborg
Sweden
41345

Study participating centre

Skånes Universitetssjukhus Lund
Clinical genetics
Lund
Sweden
22242

Study participating centre
Universitetssjukhuset Linköping
Clinical genetics
Linköping
Sweden
58185

Sponsor information

Organisation
Stockholms Läns Landsting

ROR
https://ror.org/02zrae794

Funder(s)

Funder type
Government

Funder Name
Stockholms Läns Landsting

Alternative Name(s)
Stockholm County Council

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Sweden

Funder Name
investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	cancer worry, perceived benefits and risks to surveillance and overall health	05/01/2023	07/11/2023	Yes	No
Results article	sub-study of WB-MRI findings generated by the baseline examination	14/01/2022	07/11/2023	Yes	No
Abstract results	conference abstract	17/06/2019	11/10/2019	No	No
Other publications	rationale and design	13/01/2020	19/04/2021	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes