

Connective tissue laboratory

Gene panels

CENTRUM MEDISCHE GENETICA UZ GENT

Center for Medical Genetics – Medical Research Building (MRB)
Ghent University Hospital
De Pintelaan 185
B-9000 Ghent
Belgium

Contact clinical information:

- Prof. Fransiska Malfait, Prof. Julie De Backer, Prof. Olivier Vanakker, Prof. Bert Callewaert and Prof. Anne De Paepe

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Contact lab information: e-mail: connective_tissue@medgen.ugent.be

- Dr. Sofie Symoens and Prof. Paul Coucke
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Sample reception: Tel: 0032 (0)9 332 24 77 – Fax: 0032 (0)9 332 65 49

Website: <https://www.cmgg.be/>

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REASONS FOR REFERRAL

- Genetic molecular analysis in patients for confirmation of a suspected clinical diagnosis.
- Mutational study and genetic counseling of at-risk relatives. The mutation in the index patient needs to be identified previously.
- Prenatal diagnosis (preferentially offered after genetic counseling). The mutation in the affected parent/sibling needs to be identified previously.

SAMPLING AND TECHNICAL INFORMATION

- We accept genomic DNA (>50 microgram) as well as EDTA blood samples (5ml). This can be sent at room temperature, but should be in the lab within 48 hours. On Fridays, samples should arrive before 15h.
- EDTA-blood should be sent to the connective tissue laboratory by express mail (FedEx/UPS).
- Prenatal samples (fetal DNA, chorion villi or amniocytes) must be sent at room temperature with a DNA/blood sample of the mother. If the mutation was identified in the father, please also add a blood sample from the father as an important positive control of the analysis. It is very important to wrap the samples safely! Receipt of the samples will be confirmed by email. **For prenatal diagnosis: please contact the laboratory three days prior to sending the samples!**

Send to :

**Center for Medical Genetics – MRB
Prof. P. Coucke – Sofie Symoens
Ghent University Hospital
De Pintelaan 185
B-9000 Ghent
Belgium**

CLINICAL INFORMATION SHEET

- Prior to the molecular analysis, we appreciate receiving clinical information. This information may be helpful in order to perform the most appropriate test.
- A signed informed consent document should be available in the patient file (can be kept by the referring clinician).

ADDITIONAL DOCUMENTS

- Clinical checklist
- Informed consent

TURN-AROUND-TIME AND FINANCIAL ISSUES

- Turn-around time (TAT) for gene panel sequencing is 2 months and starts from the receipt of all required samples. The TAT for specific mutational analysis is 6 weeks.
- The **VAT-number** of your institution is mandatory!
- Confirmation of a result in a second independent sample is not charged.

METHODOLOGY

- Molecular analysis of the requested gene panel is performed at gDNA level by means of PCR amplification of all coding exons and flanking intronic regions (20bp). The generated amplicons will be analyzed by Illumina's Sequencing By Synthesis (SBS) technology (MiSeq Personal Sequencer, Illumina).
- Detected mutants will always be confirmed by bidirectional fluorescence DNA sequencing (Sanger method).
- All amplicons need to be covered at least 31 times. Amplicons with coverage below 31x will be analyzed by bidirectional fluorescence DNA sequencing (Sanger method).
- The sensitivity of the SBS technology is > 99,9%. Deletions and duplications > 15bp cannot be detected with this technology with the same sensitivity.
- ArrayCGH analysis can be performed for most connective tissue genes mentioned in the gene panels. This arrayCGH analysis is included in the price for OI panel 1, UCMD/BM panel, Stickler panel. For all other genes, we need a new request. The array is designed to have at least three hybridization probes per exons. However, for very small exons or exons that are GC-rich, this can be less and thus possible deletions/duplications of these exons can be missed. MLPA can be performed for ABCC6. In this case, we need a new request form. The TAT of this arrayCGH is 3 months.

- Prices from January 1th, 2016 (~patients outside Belgium).

FAMILIAL THORACIC AORTIC ANEURYSM PANEL 1	€ 1.350
FBN1, COL3A1, TGFB1, TGFB2, ACTA2, SMAD3, TGFB2, MYH11, SKI (exon1), TGFB3, SMAD2	
FAMILIAL THORACIC AORTIC ANEURYSM PANEL 2	€ 1.350
MYLK, SLC2A10, NOTCH1, FBN2 (relevant exons), ADAMTS10, FBLN4(=EFEMP2), FLNA, ELN, PRKG1, MAT2A, MFAP5	
CLASSIC EHLERS-DANLOS SYNDROME PANEL	€ 1.350
COL5A1 – COL5A2	
VASCULAR EHLERS-DANLOS SYNDROME	€ 800
COL3A1	
OSTEOGENESIS IMPERFECTA PANEL 1	€ 1.350
COL1A1 - COL1A2 – IFITM5	
OSTEOGENESIS IMPERFECTA PANEL 2	€ 1.350
B3GALT6, BMP1, CREB3L1, CRTAP, FKBP10, LEPRE1, P4HB, PLOD2, PPIB, SEC24D, SERPINF1, SERPINH1, SP7, SPARC, TAPT1, TMEM38B, WNT1, XYLT2	
OSTEOPOROSIS PANEL	€ 800
LRP5, WNT1, PLS3	
BRUCK SYNDROME PANEL	€ 400
PLOD2 - FKBP10	
CUTIS LAXA PANEL	€ 1.350
ELN, FBLN4(=EFEMP2), FBLN5, LTBP4, ATP6V0A2, PYCR1, ALDH18A1, ATP7A, COG7, TALDO1, SCYL1BP1(=GORAB), NAA10, RIN2	
STICKLER PANEL	€ 1.350
COL2A1- COL11A1 - COL11A2	
BETHLEM MYOPATHIE/ULLRICH CONGENITAL MUSCULAR DYSTROPHY PANEL	€ 1.350
COL6A1 - COL6A2 - COL6A3 – COL12A1	
PORENCEPHALY PANEL	€ 1.350
COL4A1 - COL4A2	
ECTOPIA LENTIS PANEL	€ 1.350
LTBP2 - ADAMTSL4 - FBN1	
RECESSIVE EDS PANEL	€ 1.350
B3GALT6, XYLT1, B3GAT3, B4GALT7, PLOD1, FKBP14, SLC39A13, CHST14, DSE, ADAMTS2, RIN2, XYLT2	
PSEUDOXANTHOMA ELASTICUM PANEL	€ 800
ABCC6, ENPP1, GGCX, VEGFA (hotspots)	
HERITABLE DEFICIENCY OF VITAMIN K-DEPENDENT CLOTTING FACTORS	€ 400
VKORC1 – GGCX	

Informed consent

for patients willing to participate in diagnostic and scientific studies concerning heritable connective tissue and blood vessel disorders

CENTRUM MEDISCHE GENETICA UZ GENT

Subject of the study

Genetic diagnostics of heritable connective tissue- and blood vessel disorders

General information and objectives of this study

Connective tissue disorders comprise a heterogeneous group of disorders, characterized by abnormalities involving the skin, eyes, cardiovascular system, the lungs, the skeleton and joints. These disorders are often caused by specific genetic defects and are in these cases heritable. Connective tissue plays various important roles in the body such as providing strength to the different organs and tissues and enabling communication between tissues, required for their growth and normal functioning.

Connective tissue diseases can present in very different ways (according to the system(s) that is (are) mainly affected). E.g. problems of connective tissue of the bone and skeleton can result in an increased risk of fractures and bone deformities. These are important characteristics of osteogenesis imperfecta or brittle bone disease. Other heritable connective tissue disorders, such as the Ehlers-Danlos syndromes, are mainly characterized by weakness of the soft connective tissue and are associated with symptoms such as hyperelasticity and fragility of the skin, abnormal and delayed wound healing and joint hypermobility. The latter finding often leads to recurrent joint dislocations and chronic joint pain. Other types of connective tissue disorders such as Marfan syndrome are associated with dilatation and/or fragility of blood vessels.

Because your (child's) condition can be heritable, it is useful to perform genetic analysis first to confirm the diagnosis and second to perform further screening of family members.

Genetic analysis is mostly performed on blood and in some cases it can be useful to investigate other tissues (see below).

1. The aim of this study is to identify the genetic defect(s) (mutation(s)) that is (are) causing or influencing your (child's) health problems or those in (one of) your family members. This knowledge can be of importance for the treatment and management of your (child's) disease. The identification of a mutation also enables exclusion or confirmation of the diagnosis in family members who are at risk of having this condition or who have already developed symptoms. Prenatal genetic diagnostics (the genetic diagnosis of congenital or heritable disorders in the future/unborn child) can be performed when there is a significant risk for future or unborn children.

It is possible that the underlying genetic defect cannot be found at short term. When in the future new scientific insights permit to find the genetic defect responsible for your (child's) condition, this (these) analysis (analyses) can be performed on your (child's) sample and/or data received by analysis of your (child's) sample. However, this analysis will not automatically be performed. At any time you can inquire about further diagnostic and/or research modalities.

It is possible that with this genetic analysis (a) genetic variant(s) is (are) found from which is it not clear whether this (these) variant(s) is (are) responsible for your (child's) condition. In that case the options to further explore this (these) variant(s) will be discussed with you.

2. Besides analysis of the genetic defect(s) related to your disease, further studies aimed at exploring the underlying pathogenic mechanisms of this disorder can be performed on the prelevated anonymized material (see below). These studies lead to a better understanding of the mechanisms, inheritance and evolution of connective tissue disorders. This knowledge may be important for you (your child) and your family and also enables better management, treatment and care for all patients affected by this disorder.
3. These investigations can be performed on the following material that has been taken from you (your child) (check the appropriate boxes):

Blood sample

These will only be used for the study of connective tissue disorders. From this blood sample, we can extract and preserve DNA and/or generate a lymphoblast cell line (white blood cell line). The lymphoblast cell line can be preserved to extract DNA at a later time.

Skin biopsy

This biopsy is used for culturing fibroblasts (connective tissue cells). The fibroblast culture can be stored and used at a later time. Fibroblast cells can be used to study the extracellular matrix proteins they produce and can be used to extract DNA. The extracted DNA will only be used to perform genetic tests relevant to the study of connective tissue disorders.

Aortic biopsy

In case of aortic or arterial surgery, part of the aortic or arterial wall, which would normally be removed and destroyed, can be used to establish a cell culture or to perform additional analyses. As such, no extra material needs to be removed for establishing this cell culture.

Urine sample

A urine sample can be used for the diagnosis and further study of connective tissue disorders.

Skeletal muscle biopsy

This tissue is used for assessment of the respiratory chain of the mitochondria (energy production entities) and for immunohistological staining, and electron microscopy.

Your (child's) samples and data will be stored in the laboratory of the Center for Medical Genetics Ghent (Medical Research Building 1). Once the Belgian law concerning biobanking and storage of human samples of 19/12/2008 (article 22) is implemented, your (child's) samples will be stored in the biobank of the department of Medical Genetics (Medical research building 1).

It may be necessary to take a new blood sample and/or skin biopsy for study purposes when no/insufficient DNA is left in the laboratory or when no skin biopsy was performed in diagnostic setting, but that a skin biopsy is of importance for studying the underlying mechanisms of your (child's) condition.

What are the risks involved when taking part in this study?

Blood sampling

Puncturing the skin causes short lasting pain. Occasionally, some prolonged bleeding of the puncture site can occur or a bruise can appear. This will disappear within two weeks. There is a small risk of fainting or of infection at the puncture site.

Prelevation of a skin biopsy

A biopsy with a maximal diameter of 5 mm will be taken from a non-visible place, mostly at the inner side of the upper arm. The biopsy will be taken after injection of a local anesthetic. After the procedure, the skin will be sutured or Steri-strips will be applied. The injection of a local anesthetic can cause short lasting pain. There is a small risk of prolonged bleeding or wound infection after the procedure. The wound should be healed within two weeks after the procedure, and can leave a small round scar.

Prelevation of an aortic biopsy

If aortic surgery is being performed on you or your child, part of the aortic wall, that would normally be removed and destroyed, will be preserved for research purposes. As such, no extra material needs to be removed and there are no additional risks associated with this procedure.

There are no risks involved in the prelevation of a **urine sample**.

Prelevation of a muscle biopsy

A skeletal muscle biopsy is taken on the anterior muscle of the upper leg (quadriceps muscle). This is done under full anesthesia. The operation site may hurt a little in the days following the surgery. The associated risks are those of regular low-risk surgery including adverse reactions on anesthesia, local pain, bleeding, infection.

Injury resulting from participation in the study?

The researcher provides compensation and/or medical treatment in case of damage and/or injury resulting from participation in the study. For this purpose, we have a no-fault insurance in accordance with the Act of May 7th 2004 concerning experiments on humans. At that moment your (child's) data may be passed to the insurer.

What will happen with your (child's) medical information obtained during the course of this study?

In accordance with the Belgian law of December 8th 1992 en August 22th 2002, your (child's) privacy will be guaranteed and you will have access to the collected data. At your request, incorrect information can be adjusted. Representatives of the principal investigator, auditors, the ethical committee and the certified governmental instances will have direct access to your (child's) medical records to control the experimental procedures and/or data, without violating the confidentiality of these records. This access is confined within the boundaries set by the aforementioned legislation. By signing this informed consent form, you agree with this.

If information is derived from this study that is relevant for your (child's) health and/or your (child's) treatment and follow-up, the Center for Medical Genetics will invite you (and your child) to discuss these results. If information relevant to family members results from this study, we will ask you to contact your family or – if you do not wish to do this yourself – to give us permission to contact your family. If you do not wish that family members are informed, this decision will be respected.

If the study yields information that is relevant to healthcare in general, the results may be published in a scientific journal. This means that results obtained from specific clinical investigations such as echocardiography, ophthalmologic examination, medical imaging, etc. can be included after anonymization. Exceptionally, it may be relevant to publish clinical photographs. In this case, you will be asked to sign a separate informed consent form.

Who to contact in case you (your child) have additional questions about this study or you (your child) want to terminate your (child's) participation in this study?

It is recommended to directly contact the physician who enrolled you (your child) in this study. You can find his or her contact information on the last page of the informed consent form. If you are unable to reach this physician, you can contact the Center for Medical Genetics Ghent at (0032)9/332.36.03. You will be put in contact with one of the responsible investigators, as soon as possible.

Informed consent

You will receive a copy of this informed consent.

The original will be kept in your (child's) medical record at the Center for Medical Genetics Ghent.

I, _____, voluntarily give my consent for participation in this study for which analyses on my (child's) genetic material will be performed to identify genetic disorders in the context of my (child's) condition: _____.

I have received and read the patient information leaflet and I had sufficient time to ask questions. I have been sufficiently informed about the objectives of this study. I have had the opportunity to ask questions about this study and all my questions have been answered in sufficient manner.

I am aware of the fact that this study has been approved by the independent ethics committee of the Ghent University Hospital and that the study will be performed according to the rules of good clinical practice (ICH/GCP) and the Declaration of Helsinki (i.e. ethical principles regarding human experimentation). The fact that this study has been approved by the ethics committee did not influence my decision to take part in this study.

I therefore agree with the use of information derived from questioning (personal history taking), physical and technical examinations for scientific purposes only. My identity will be kept confidential, will not be disclosed and the professional confidentiality will be respected. I have been informed and consent that my personal details and medical records will be processed and stored for at least 20 years. I am aware that I have access to and can correct this information. Since these data are being processed in the context of medical-scientific purposes, I understand that access to these records can be postponed until completion of this study. If I want to access my personal data, I will contact the supervising physician, responsible for data processing.

I understand that auditors, representatives of the principal investigator, the ethics committee or the certified governmental instances may want to inspect my records to control the collected information. By signing this document, I consent to this. Furthermore, I am aware and I consent that my (child's) anonymized samples/data may be passed on to the principal investigator and may be shared with (non-)European collaborators. My privacy will be guaranteed at all time. My (child's) data/samples will not be used for commercial purposes.

I have understood the content of this research and I am prepared to participate or have my child(ren), mentioned below and represented by me, participate in this study. At any time, I will have the possibility to withdraw from this study.

(1) Consent for adults

place and date

_____,
name and signature

**(2) For patients incapable of giving consent,
represented by the legal representative**

name patient

CONSENT
place and date

_____,
name and signature of the legal representative

**(3) For child(ren) in the presence
of their parents**

name child

CONSENT
place and date

_____,
name and signature of the father

name and signature of the mother

**(4) For child(ren) not under the responsibility
of their parents**

name child

CONSENT
place and date

_____,
name and signature of tutor, relative or
legal representative

relation to the child(ren)

justification for replacing the parents

(5) For child(ren) over 12 years of age

CONSENT

place and date

**name and signature of the child over 12 years
of age:**

CONSENT

place and date

**name and signature of the child over 12 years
of age:**

(6) Consent physician

I hereby declare to have sufficiently informed the
aforementioned participant about the aims of this study.
The participant agreed to participate voluntarily by
signing and dating the informed consent form.

place and date

name and signature
