

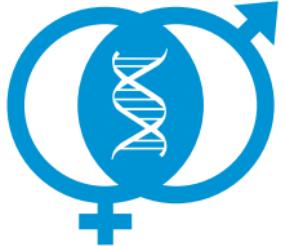
SYNLAB Medizinisches  
Versorgungszentrum  
**Humane Genetik**



## Index of Analyses

January 2019

**SYNLAB** 



SYNLAB Medizinisches  
Versorgungszentrum  
**Humane Genetik**

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By SYNLAB Medizinisches Versorgungszentrum Humane Genetik  
Medical Practice and Laboratory for Human genetics

Medical Director

**Dr. med. Dr. rer. nat.**

**Claudia Nevinny-Stickel-Hinzpeter**

Consultant Human geneticist

Postal Address

Lindwurmstrasse 23

D-80337 Munich / Germany

Telephone and Fax

Reception +49 (0)89. 54 86 29 -0

Invoicing -0

Fax -243

Molecular Genetics -554

Cytogenetics -559

Office hours

Monday – Friday 8.30 – 18.00

[info@humane-genetik.de](mailto:info@humane-genetik.de)

[www.humane-genetik.de](http://www.humane-genetik.de)

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# Preanalytics

## Testing Material

For genetic testing nuclei-containing cells of the patient are required, which are either cultivated or subjected to DNA extraction. Cells can be harvested from peripheral blood, buccal swabs, amniotic fluid, chorionic villi (CVS), or tissue samples.

In case of blood collection, no special preparation of the patient, e.g. fasting, is required. The sample may be collected at any time of the day.

The tubes should always be filled up to the measure line to guarantee an optimal ratio between blood and anticoagulants. Please invert the tubes carefully after blood collection to allow adequate mixing of blood and anticoagulants.

Blood samples should not be older than one week. Please make sure that the samples are sent to our laboratory immediately at ambient temperature, and avoid extreme temperatures during the transport.

# Preanalytics

## Cytogenetic and Molecular Cytogenetic Analyses

5 ml sterile heparin blood (infants and young children < 5 ml)  
10-15 ml amniotic fluid  
10-20 mg chorionic villi (CVS)  
Aborted fetal tissue with chorionic villi (CVS)  
Skin biopsy  
Buccal swab

## Chromosomal Microarray Analyses:

3-5 ml EDTA-blood, or 2 µg high quality DNA  
10-15 ml amniotic fluid  
10-20 mg chorionic villi (CVS)  
Aborted fetal tissue with chorionic villi (CVS)  
tissue sample, e. g. formalin-fixed paraffin embedded tissue

## Molecular Genetic Analyses

5 ml EDTA-blood (infants and young children < 3 ml)

Amniotic fluid  
Chorionic villi (CVS)  
Aborted fetal tissue  
Tissue  
Skin biopsy  
Buccal swabs

In general, EDTA-blood is the most suitable material for molecular genetic analyses. Please inquire if other genetic material is suitable for the requested analysis if blood collection is not possible.

## Kinship Analyses

3 buccal swabs or 3-5 ml EDTA-blood

# Preanalytics

## Sample Identification and Required Forms

Sample tubes and the corresponding request forms must be clearly labelled with the patient's name and date of birth for correct identification.

Our request **forms** are available for download at [www.humane-genetik.de/en/forms/](http://www.humane-genetik.de/en/forms/).

Please state the indication for the requested analysis. A short anamnesis as well as family history will significantly support our experts in performing the optimal analysis and for assessing the findings .

According to German law, the informed consent form must be signed either by the patient (or his/her legal representative) or by the referring physician. This form is mandatory for every genetic analysis and must be sent together with the sample and the request forms.

Please note that we require prepayment. Prices of our analyses are available on request [info@humane-genetik.de](mailto:info@humane-genetik.de).

If you are part of the SYNLAB group, samples may be dispatched to SYNLAB MVZ in Leinfelden, Germany, as the primary hub for all incoming samples originating in foreign countries.

Samples will then be forwarded to MVZ Humane Genetik Munich accordingly.

The spectrum of our genetic analyses is continually expanding. An updated version of the genetic analyses we currently offer can be accessed on our website [www.humane-genetik.de/en/](http://www.humane-genetik.de/en/).

Genetic analyses not offered by our laboratory can be performed in co-operation with other accredited laboratories. Please inquire.

# Molecular genetic analyses

» Cardiac diseases

## ■ Cardiac diseases

### Arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D)

OMIM:	609040, 610193, 607450, 610476
Gene:	<i>PKP2</i> , locus 12p11; <i>DSG2</i> , locus 18q12.1; <i>DSP</i> , locus 6p24.3; <i>DSC2</i> , locus 18q12.1
Inheritance:	autosomal dominant
Indication:	right- or biventricular dilation, arrhythmia, syncope, family history of sudden cardiac death
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>PKP2</i> , <i>DSG2</i> , <i>DSP</i> , <i>DSC2</i> (NGS panel, approx. 4 wks)

### Brugada syndrome, BrS1

OMIM:	601144
Gene:	<i>SCN5A</i> , locus 3p21-23
Inheritance:	usually autosomal dominant, variable penetrance
Indication:	ECG anomalies (T-wave alternans, QT-segment elevation), syncope, absence of structural cardiac disease, family history of sudden cardiac death
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>SCN5A</i> (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Cardiac diseases

## Jervell-Lange-Nielsen syndrome

OMIM: 612347, 220400

Genes: *KCNE1*, locus 21q22.1-22.2; *KCNQ1*, locus 11p15.5

Inheritance: autosomal recessive

Indication: congenital bilateral sensorineural hearing loss,  
prolongation of the QTc interval, ventricular  
tachycardia, tachyarrhythmias, ventricular fibrillation,  
syncope

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis *KCNE1*  
and *KCNQ1* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Cardiac diseases

## Cardiomyopathy (hypertrophic/dilated)

OMIM:	115197, 613426, 192600, 601494, 115195, 611880, 613690, 115200, 115196, 608751, 613251, 612954, 609599, 613172, 188380, 601493, 607487
Genes:	<i>MYBPC3</i> , locus 11p11.2; <i>MYH7</i> , locus 14q11.2; <i>TNNT2</i> , locus 1q32.1; <i>TNNI3</i> , locus 19q13.42; <i>LMNA</i> , locus 1q22; <i>TPM1</i> , locus 15q22.2; <i>MYL3</i> , locus 3p21.31; <i>MYH6</i> , locus 14q11.2; <i>BAG3</i> , locus 10q26.11; <i>ANKRD1</i> , locus 10q23.31; <i>RBM20</i> , locus 10q52.2; <i>TMPO</i> , locus 12q23.1; <i>LDB3</i> , locus 10q23.2; <i>TCAP</i> , locus 17q12;
Inheritance:	usually left ventricular hypertrophy, asymmetric septal hypertrophy, cardiac failure, progressive heart failure, sudden cardiac death, shortness of breath (particularly with exertion), chest pain, palpitations, orthostasis, syncope
Indication:	right- or biventricular dilation, arrhythmia, syncope, family history of sudden cardiac death
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>MYBPC3</i> , <i>MYH7</i> , <i>TNNT2</i> , <i>TNNI3</i> , <i>LMNA</i> , <i>MYH6</i> , <i>BAG3</i> , <i>ANKRD1</i> , <i>TMPO</i> (NGS panel, approx. 4 wks) Analysis of the genes <i>TPM1</i> , <i>MYL3</i> , <i>RBM20</i> , <i>LDB3</i> , <i>TCAP</i> available on request.

# Molecular genetic analyses

» Cardiac diseases

## Catecholaminergic polymorphic ventricular tachycardia (CPVT)

OMIM:	604772
Gene:	<i>RYR2</i> , locus 1q43
Inheritance:	autosomal dominant
Indication:	polymorphic ventricular tachycardia induced by physical activity, stress, no structural cardiac abnormalities, recurrent syncope
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>RYR2</i> (NGS panel, approx. 4 wks)

## Long QT syndrome (LQT1, LQT2, LQT3, LQT5, LQT6)

OMIM:	192500 (LQT1), 152427 (LQT2), 603830 (LQT3), 176261 (LQT5), 603796 (LQT6)
Genes:	<i>KCNQ1</i> , locus 11p15.5; <i>KCNH2</i> , locus 7q35-36; <i>SCN5A</i> , locus 3p21-23; <i>KCNE1</i> , locus 21q22.1-22.2; <i>KCNE2</i> , Locus 21q22.1-22.2
Inheritance:	usually autosomal dominant, variable penetrance
Indication:	ECG anomalies (prolongation of the QTc-interval, T-wave abnormalities), syncope, absence of structural cardiac disease, family history of sudden cardiac death
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>KCNQ1</i> , <i>KCNH2</i> , <i>SCN5A</i> , <i>KCNE1</i> , <i>KCNE2</i> (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Cardiac diseases

## Short QT syndrome (SQT1, SQT2)

OMIM: 609620, 609621

Genes: *KCNH2*, *KCNQ1*, loci 7q35-36, 11p15.5

Inheritance: usually autosomal dominant, variable penetrance

Indication: short QTc-interval in ECG, ventricular fibrillation, syncope, absence of structural cardiac disease, family history of sudden cardiac death

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing analysis *KCNH2* and *KCNQ1*  
(NGS panel, approx. 4 wks)

## Complex syndromes

### Aarskog syndrome (Faciogenital Dysplasia)

OMIM: 305400  
Gene: *FGD1*, locus Xp11.21  
Inheritance: X-linked recessive  
Indication: suspected faciogenital dysplasia, short stature, hypertelorism, shawl scrotum, and brachydactyly  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing analysis of *FGD1* (approx. 2 wks)  
deletion/duplication analysis of *FGD1* (approx. 2 wks)

### Angelman syndrome (AS)

OMIM: 105830  
Gene: *SNRPN* gene locus; *UBE3A*, Locus 15q11-13  
Inheritance: sporadic/autosomal dominant  
Indication: severe mental retardation with profound speech impairment, gait ataxia and/or tremulousness of the limbs, unique behaviour with an inappropriate happy demeanour, microcephaly and seizures, hypotonia  
Material: 3-5 ml EDTA blood  
Methods/TAT: 1<sup>st</sup> tier: methylation sensitive deletion/duplication analysis (MS-MLPA) *SNRPN*-gene locus (approx. 3 wks)  
2<sup>nd</sup> tier (for inconspicuous result from MS-MLPA): sequencing analysis of *UBE3A* (approx. 2 wks)  
3<sup>rd</sup> tier (for conspicuous result from MS-MLPA): uniparental disomy 15 (*UPD15*) analysis, parents' sample required (approx. 2 wks)

# Molecular genetic analyses

» Complex syndromes

## Beckwith-Wiedemann syndrome (BWS)

OMIM:	130650
Gene:	<i>H19/KCNQ1OT1</i> gene locus; locus 11p15.5
Inheritance:	sporadic/autosomal dominant
Indication:	macrosomia (large body size), macroglossia, visceromegaly, embryonal tumors (e.g. Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma), omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, renal abnormalities (e.g. medullary dysplasia, nephrocalcinosis, medullary sponge kidney, and nephromegaly)
Material:	3-5 ml EDTA blood
Methods/TAT:	1 <sup>st</sup> tier: methylation sensitive deletion/duplication analysis <i>H19/KCNQ1OT1</i> (MS-MLPA) (approx. 3 wks) 2 <sup>nd</sup> tier (for conspicuous result from MS-MLPA): uniparental disomy 11 ( <i>UPD11</i> ) analysis, parents' sample required (approx. 2 wks)

## Costello syndrome

OMIM:	218040
Gene:	<i>HRAS</i> , locus 11p15.5
Inheritance:	autosomal dominant
Indication:	short stature, characteristic coarse facies, redundant skin of the neck, palms, soles, and fingers, severe feeding difficulty, failure to thrive, cardiac anomalies and developmental disability
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing analysis of select regions of <i>HRAS</i> (approx. 2 wks)

# Molecular genetic analyses

» Complex syndromes

## DiGeorge syndrome

OMIM: 188400  
Loci: 22q11.2, 10p14 (*DGS2*)  
Inheritance: autosomal dominant  
Indication: congenital heart disease, particularly conotruncal malformations (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosus); palatal abnormalities, particularly velopharyngeal incompetence (VPI), submucosal cleft palate, and cleft palate, hypocalcemia  
Material: 3-5 ml EDTA blood  
Methods/TAT: deletion/duplication analysis of DiGeorge region (approx. 2 wks)

## Fragile X syndrome (Martin-Bell syndrome, FraX-A)

OMIM: 309550  
Gene: *FMR1*, locus Xq27.3  
Inheritance: X-linked  
Indication: mental retardation particularly in males, incidence 1:1250, determination of carrier status in members of risk families, clinical suspicion of premature ovarian insufficiency (POI) or FraX-associated tremor/ataxia syndrome (FXTAS)  
Material: 3-5 ml EDTA blood  
Methods/TAT: 1<sup>st</sup> tier: fragment length analysis (approx. 2 wks) and Southern Blot analysis for the determination of the CGG-repeat length in the promotor region of *FMR1* (approx. 3 wks),  
prenatal analysis: approx. 1 wk  
2<sup>nd</sup> tier: sequencing analysis (approx. 3 wks) and methylation sensitive deletion/duplication analysis (MS-MLPA) *FMR1* locus (approx. 3 wks)

# Molecular genetic analyses

» Complex syndromes

## Fragile X syndrome (FraX-E)

OMIM: 309548  
Gene: *AFF2*, locus Xq28  
Inheritance: X-linked  
Indication: mental retardation particularly in males, analysis of the carrier status in families with positive family history for Fragile X syndrome  
Material: 3-5 ml EDTA blood  
Methods/TAT: fragment length analysis (approx. 2 wks) and Southern Blot analysis for the determination of the GCC-repeat length in the *AFF2* gene (approx. 3 wks), prenatal analysis: approx. 1 wk

## Hypoparathyroidism, Deafness, and Renal Disease (HDR)

OMIM: 146255  
Gene: *GATA3*, locus 10p15  
Inheritance: autosomal dominant  
Indication: hypocalcemia, tetany, hearing loss (usually bilateral ranging from mild to profound impairment), renal disease manifestations: nephrotic syndrome, cystic kidney, renal dysplasia, hypoplasia or aplasia, pelvicalyceal deformity, vesicoureteral reflux, chronic renal failure, hematuria, proteinuria and renal scarring  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing (approx. 2 wks) and deletion/duplication analysis *GATA3* (approx. 2 wks)

# Molecular genetic analyses

» Complex syndromes

## Kallmann syndrome

- OMIM: 308700, 147950, 610628, 244200  
Genes: *ANOS1*, *FGFR1*, *PROK2*, *PROKR2*, loci Xp22.3,  
8p11.2-p11.1, 3p13, 20p12.3  
Inheritance: X-linked recessive (*ANOS1*), autosomal dominant  
(*FGFR1*, *PROK2*, *PROKR2*)  
Indication: idiopathic or isolated hypogonadotropic  
hypogonadism (IHH) and anosmia or hyposmia  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*ANOS1*, *FGFR1*, *PROK2*, *PROKR2* (NGS panel,  
approx. 4 wks)

## LEOPARD syndrome

- OMIM: 151100  
Gene: *PTPN11*, locus 12q24.1  
Inheritance: autosomal dominant  
Indication: LEOPARD = lentiginosis, ECG-abnormalities,  
ocular hypertelorism, pulmonary stenosis,  
abnormal genitalia, retarded growth, deafness  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing analysis *PTPN11*, *RAF1*, *BRAF*  
(NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Complex syndromes

## Noonan Syndrom

	OMIM:	Loci:
NS 1	163950	<i>PTPN11</i> , locus 12q24.1
NS 3	609942	<i>KRAS</i> , locus 12p12.1
NS 4	610733	<i>SOS1</i> , locus 2p22.1
NS 5	611553	<i>RAF1</i> , locus 3p25.2
NS 7	613706	<i>BRAF</i> , locus 7q34;
NS 8	615355	<i>RIT1</i> , locus 1q22

Inheritance: autosomal dominant

Indication: congenital heart defect, pulmonary stenosis, cardiac hypertrophy, short stature, triangular shaped face, hypertelorism, cryptorchidism, in some cases slight mental retardation

Material: 3-5 ml EDTA blood

Methods/TAT: 1<sup>st</sup> tier: (basic) sequencing analysis of *PTPN11*  
2<sup>nd</sup> tier: (comprehensive) sequencing analysis *SOS1*, *RAF1*, *KRAS*, *BRAF*, *RIT1*  
(NGS panel, approx. 4 wks)

## Osler-Rendu-Weber disease

OMIM: 187300, 600376

Genes: *ENG*, *ACVRL1*, loci 9q34.11, 12q13.13

Inheritance: autosomal dominant

Indication: hereditary hemorrhagic telangiectasia, arteriovenous malformations, nosebleeding, gastrointestinal bleeding

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing (approx. 2 wks per gene) and deletion/duplication analysis *ENG* and *ACVRL1* (approx. 2 wks)

# Molecular genetic analyses

» Complex syndromes

## Prader-Willi syndrome (PWS)

OMIM:	176270
Gene:	<i>SNRPN</i> , locus 15q11-13, UPD 15
Inheritance:	sporadic/autosomal dominant
Indication:	severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and gradual development of morbid obesity, delayed motor milestones and language development, cognitive impairment, hypogonadism and genital hypoplasia
Material:	3-5 ml EDTA blood
Methods/TAT:	1 <sup>st</sup> tier: methylation sensitive deletion/duplication analysis (MLPA) <i>SNRPN</i> locus (approx. 3 wks) 2 <sup>nd</sup> tier (for conspicuous result from MS-MLPA): uniparental disomy 15 ( <i>UPD15</i> ) analysis, parents' sample required (approx. 2 wks)

## Proteus syndrome

OMIM:	176920
Gene:	<i>AKT1</i> , locus 14q32.3
Inheritance:	de novo, mosaicism for a somatic activating mutation in the <i>AKT1</i> gene
Indication:	asymmetric and disproportionate overgrowth of body parts, connective tissue nevi, epidermal nevi, dysregulated adipose tissue, vascular malformations, cerebriform connective tissue nevus
Material:	skin punch or tissue from affected region
Methods/TAT:	Sequencing analysis of select regions of <i>AKT1</i> (approx. 2 wks)

# Molecular genetic analyses

» Complex syndromes

## Rett syndrome

OMIM:	312750
Gene:	<i>MECP2</i> , locus Xq28
Inheritance:	X-linked dominant
Indication:	mental retardation particularly in females, normal psychomotor development during the first six to 18 months of life, followed by a short period of developmental stagnation, then rapid regression in language and motor skills, autism, repetitive, stereotypic hand movements
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing (approx. 2 wks) and deletion/duplication analysis analysis <i>MECP2</i> (approx. 2 wks)

## Silver-Russell syndrome (SRS)

OMIM:	180860
Gene:	<i>H19/IGF2</i> gene locus; locus 11p15.5
Inheritance:	sporadic/autosomal dominant
Indication:	intrauterine growth retardation accompanied by postnatal growth deficiency, proportionately short stature, normal head circumference, fifth-finger clinodactyly, typical facial features and limb-length asymmetry that may result from hemihypotrophy
Material:	3-5 ml EDTA blood
Methods/TAT:	methylation sensitive deletion/duplication analysis (MS-MLPA) <i>H19/IGF2</i> gene locus (approx. 3 wks) and several loci of chromosome 7 (approx. 3 wks)

# Molecular genetic analyses

» Complex syndromes

## Sotos syndrome

OMIM: 117550  
Gene: *NSD1*, locus 5q35  
Inheritance: autosomal dominant  
Indication: typical facial appearance, macrocephaly, overgrowth (height and head circumference  $\geq 2$  SD above the mean), learning disability ranging from mild to severe  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing (approx. 3 wks) and deletion/duplication analysis *NSD1* (approx. 2 wks)

## Thrombocytopenia-absent radius syndrome (TAR)

OMIM: 274000  
Gene: *RBM8A*, locus 5q35  
Inheritance: autosomal recessive  
Indication: reduced number of platelets, thrombocytopenia, absence of the radius but preservation of the thumb  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of select regions of *RBM8A* (approx. 2 wks) and deletion/duplication analysis of *RBM8A* (approx. 2 wks)

# Molecular genetic analyses

» Complex syndromes

## Williams-Beuren syndrome

OMIM:	194050, 609757
Gene:	<i>WBSCR</i> region, locus 7q11.2
Inheritance:	autosomal dominant
Indication:	cardiovascular disease, supravalvular aortic stenosis (SVAS), elastin arteriopathy, peripheral pulmonary stenosis, hypertension, distinctive facies, mental retardation (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism and early puberty)
Material:	3-5 ml EDTA blood
Methods/TAT:	deletion/duplication analysis of <i>WBSCR</i> region (approx. 2 wks)

## ■ Connective Tissue Disorders

### Ehlers-Danlos syndrome (Arthrochalasia type)

OMIM: 130060  
Genes: *COL1A1*, *COL1A2*, loci 17q21.32, 7q22.1  
Inheritance: autosomal dominant  
Indication: severe generalized joint hypermobility, recurrent subluxations, congenital hip dislocation, skin hyperextensibility, atrophic scars  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*COL1A1* and *COL1A2* (NGS panel, approx. 4 wks)

### Ehlers-Danlos syndrome types (classic type)

OMIM: 130000, 130010  
Gene: *COL5A1*, *COL5A2*, loci 9q34, 2q31  
Inheritance: autosomal dominant  
Indication: joint hypermobility, hyperextensible skin, atrophic and "cigarette paper" scars  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*COL5A1*, *COL5A2* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Connective Tissue Disorders

## Ehlers-Danlos syndrome (kyphoscoliotic type)

OMIM: 225400  
Gene: *PLOD1*, locus 1p36  
Inheritance: autosomal recessive  
Indication: generalized joint laxity, progressive scoliosis, scleral fragility and globe rupture, muscle hypotonia at birth, tissue fragility  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*PLOD1* (NGS panel, approx. 4 wks)

## Ehlers-Danlos syndrome (vascular type)

OMIM: 130050  
Gene: *COL3A1*, locus 2q31  
Inheritance: autosomal dominant  
Indication: skin hyperextensibility, atrophic scarring, easy bruising, thin and translucent skin, joint hypermobility, rupture of inner organs and arteries, facial appearance: hollow cheeks, prominent staring eyes, pinched nose, lobeless ears  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*COL3A1* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Connective Tissue Disorders

## Marfan/Loeys-Dietz-Syndrom

- OMIM: 154700, 609192, 610168  
Genes: *FBN1*, locus 15q21.1; *TGFBR1*, locus 9q22;  
*TGFBR2*, locus 3p22  
Inheritance: autosomal dominant  
Indication: connective tissue weakness, bone overgrowth with disproportionately long extremities and joint laxity, aortic root dilatation, aortic aneurysm, myopia, ectopia lentis, typical facial dysmorphic features (hypertelorism, cleft palate/bifid uvula, craniosynostosis), aggressive arterial/aortic aneurysm, arterial tortuosity  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*FBN1*, *TGFBR1*, *TGFBR2* (NGS panel, approx 4 wks)

## Osteogenesis Imperfecta

- OMIM: 166200, 166210  
Genes: *COL1A1*, *COL1A2*, loci 17q21.32, 7q22.1  
Inheritance: autosomal dominant  
Indication: increased bone fragility with variable severity, blue sclera, dentinogenesis imperfecta, hearing impairment  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*COL1A1*, *COL1A2* (NGS panel, approx. 4 wks)

## ■ Endocrinology

### Congenital adrenal hyperplasia (CAH)

#### 21-Hydroxylase deficiency

OMIM: 201910  
Gene: *CYP21A2*, locus 6p21.3  
Inheritance: autosomal recessive  
Indication: Congenital adrenal hyperplasia, salt wasting, precocious puberty or adrenarche, virilization, hirsutism  
Material: 3-5 ml EDTA blood  
Methods/TAT: deletion/duplication analysis (approx. 2 wks) and sequencing analysis of *CYP21A2* (approx. 2 wks), prenatal analysis altogether approx. 1 wk

#### Steroid 11-beta-Hydroxylase deficiency

OMIM: 202010  
Gene: *CYP11B1*, locus 8q24.3  
Inheritance: autosomal recessive  
Indication: low renin hypertension, hypokalemia, hyperandrogenemia, virilization, genital ambiguity in females  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis and *CYP11B1* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Endocrinology

## 17-alpha-Hydroxylase deficiency

OMIM: 202110  
Gene: *CYP17A1*, locus 10q24.32  
Inheritance: autosomal recessive  
Indication: impaired cortisol synthesis, low renin  
hypertension, hypokalemia, metabolic alkalosis  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis and  
*CYP17A1* (NGS panel, approx. 4 wks)

## 3-beta-Hydroxysteroid Dehydrogenase 2 deficiency

OMIM: 201810  
Gene: *HSD3B2*, locus 1p12  
Inheritance: autosomal recessive  
Indication: severe salt wasting, genital ambiguity in males and  
females  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis and  
*HSD3B2* (NGS panel, approx. 4 wks)

## P450 Oxidoreductase deficiency

OMIM: 201810  
Gene: *POR*, Locus 7q11.32  
Inheritance: autosomal recessive  
Indication: genital ambiguity (virilization of females,  
undervirilization of males), bone malformations  
resembling Antley-Bixler syndrome  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis and  
*POR* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Endocrinology

## Hyperinsulinism

→ please refer to "Metabolic diseases"

## Hyperproinsulinemia

→ please refer to "Metabolic diseases"

## Kallmann syndrome

→ please refer to "Complex syndromes"

## Maturity-Onset Diabetes of the Young (MODY)

→ please refer to "Metabolic diseases"

## Neonatal Diabetes (Permanent/transient)

→ please refer to "Metabolic diseases"

## Obesity (early onset)

OMIM: 614963, 155541, 155540, 176830, 614962, 614963

Genes: *MC4R*, *MC3R*, *POMC*, *LEPR*, *LEP*, loci 18q21.32,  
20q13.2, 2p23.3, 1p31.3, 7q32.1

Inheritance: autosomal dominant (*MC4R*, *MC3R*), autosomal  
recessive (*POMC*, *LEPR*, *LEP*)

Indication: severe and early onset obesity, increased lean  
mass, increased linear growth, hyperphagia, and  
severe hyperinsulinemia

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis  
*MC4R*, *LEPR*, *MC3R*, *POMC*, *LEP* (NGS panel,  
approx. 4 wks)

## ■ Eye diseases

### Leber's hereditary optic neuropathy (LHON)

OMIM: 535000  
Genes: *MTND1*, *MTND4*, *MTND6*, mitochondrial genome  
Inheritance: mitochondrial  
Indication: bilateral, painless, subacute visual failure that develops during young adult life, unilateral or bilateral optic neuropathy, centrocecal scotoma  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of the common variants m.11778G>A, m.3460G>A, m.14484T>C (approx. 2 wks)

### Optic Atrophy 1 (*OPA1*)

OMIM: 165500  
Gene: *OPA1*, locus 3q29  
Inheritance: autosomal dominant  
Indication: bilateral neuropathy of the optic nerve, scotoma  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing (approx. 2 wks) and deletion/duplication (approx. 2 wks) analysis of *OPA1*

## Fertility disorders

### Habitual miscarriages

#### Factor V, Leiden variant

OMIM: 227400  
Gene: *F5*, Locus 1q23  
Inheritance: polygenic/multifactorial  
Indication: thrombosis, habitual miscarriages  
Material: 3-5 ml EDTA blood  
Methods/TAT: real-time-PCR genotyping of the Leiden variant  
c.1601G>A; p.Arg534Gln in the *F5* gene mittels  
(approx. 1 wk)

#### Mannose binding lectin (MBL)

OMIM: 614372  
Gene: *MBL2*, locus 10q21.1  
Inheritance: polygenic/multifactorial  
Indication: recurrent preterm births due to chorioamnionitis  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *MBL2*, detection of the  
haplotypes HYPA, HYPD, LYPA, LYQA, LXPA, LYPB,  
LYQC (approx. 2 wks)

## Male infertility

### Azoospermia factor (AZF)

OMIM: 415000  
Gene: AZF-locus Yq11  
Inheritance: Y-chromosomal  
Indication: infertility due to non-obstructive azoospermia,  
oligozoospermia, cryptozoospermia  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR; detection of microdeletions in the AZF region  
(approx. 2 wks)

### Congenital bilateral aplasia of the vas deferens (CBAVD)

OMIM: 277180  
Gene: CFTR, locus 7q31.3  
Inheritance: autosomal recessive  
Indication: infertility due to obstructive azoospermia  
Material: 3-5 ml EDTA blood  
Methods/TAT: detection of 40 common variants in the CFTR gene  
(approx. 2 wks), sequencing and deletion/duplication  
analysis CFTR (NGS panel, approx. 4 wks)

## Gastrointestinal diseases

### Celiac disease

OMIM: 146880, 604305  
Gene: Major Histocompatibility Complex *DQA1*, *DQB1*,  
locus 6p21.3  
Inheritance: polygenic/multifactorial  
Indication: gluten-sensitive enteropathy, malabsorption  
resulting from inflammatory injury to the mucosa  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequence specific PCR (SSP) (approx. 2 wks)

### Inflammatory bowel disease (Crohn disease)

OMIM: 266600  
Gene: *NOD2*, locus 16q12.1  
Inheritance: polygenic/multifactorial  
Indication: relapsing intestinal inflammation  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing analysis of *NOD2*, detection of  
the variants p.(Arg702Trp), p.(Gly908Arg),  
p.(Leu1007Profs\*2) (approx. 2 wks)

## Hematology

### **α-Thalassemia**

OMIM: 141800  
Genes: *HBA1, HBA2*, locus 16pter-p13.3  
Inheritance: autosomal, variable phenotype  
Indication: microcytic hypochromic anemia  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing (approx. 2 wks) and deletion/duplication analysis (approx. 2 wks) *HBA1, HBA2*

### **β-Thalassemia**

OMIM: 141900  
Gene: *HBB*, locus 11p15.5  
Inheritance: autosomal, variable phenotype  
Indication: microcytic hypochromic anemia, increased amounts of hemoglobin A2 (HbA2) and F (HbF)  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing (approx. 2 wks) and deletion/duplication analysis (approx. 2 wks) *HBB*

### **Glucose-6-Phosphate Dehydrogenase Deficiency**

OMIM: 305900  
Gene: *G6PD*, locus Xq28  
Inheritance: X-chromosomal recessive  
Indication: anemia (nonspherocytic hemolytic anemia), hemolytic episodes, favism  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing (approx. 2 wks) and deletion/duplication (approx. 2 wks) analysis *G6PD*

# Molecular genetic analyses

» Hematology

## Sickle Cell Anemia

OMIM: 603903

Gene: *HBB*, locus 11p15.5

Inheritance: autosomal recessive

Indication: suspected sickle cell anemia

Material: 3-5 ml EDTA blood

Methods/TAT: Real-time-PCR detection of the variants HbS (p.(Glu7Val)) and HbC (p.(Glu7Lys)) (approx. 1 wk)

# Molecular genetic analyses

» Hemophilia

## Hemophilia

### Hemophilia A

OMIM: 306700  
Gene: *F8*, locus Xq28  
Inheritance: X-chromosomal recessive  
Indication: excessive bleeding after injury or surgery, muscle or joint hemorrhage  
Material: 3-5 ml EDTA blood  
Methods/TAT: 1<sup>st</sup> tier: PCR and inverse PCR to detect inversions of introns 1 and 22 (approx. 2 wks)  
2<sup>nd</sup> tier: sequencing and deletion/duplication analysis *F8* (NGS panel, approx. 4 wks)

### Hemophilia B

OMIM: 306900  
Gene: *F9*, locus Xq27.1  
Inheritance: X-chromosomal recessive  
Indication: excessive bleeding after injury or surgery, muscle or joint hemorrhage  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis *F9* (NGS panel, approx. 4 wks)

### Von-Willebrand disease

OMIM: 193400, 613554, 277480  
Gene: *VWF*, locus 12p13.31  
Inheritance: autosomal recessive and autosomal dominant  
Indication: hemorrhagic diathesis, conspicuous result from biochemical blood clotting analysis  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis *VWF* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Hereditary cancer syndromes

## ■ Hereditary cancer syndromes

For analyses of hereditary cancer syndromes we kindly request information regarding the personal and family medical history of the patient or counselee. Please find the respective form on our website.

### Familial adenomatous polyposis (FAP)

OMIM: 611731 (FAP1), 608456 (FAP2)

Genes: *APC*, locus 5q22.2, *MUTYH*, locus 1p34.1

Inheritance: autosomal dominant (*APC*) and autosomal recessive (*MUTYH*)

Indication: suspected classic or attenuated FAP, flat adenoma syndrome, suspected Gardner syndrome or Turcot syndrome, suspected classic FAP with extracolonic manifestations

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis *APC*, *MUTYH* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Hereditary cancer syndromes

## Hereditary Breast/Ovary cancer (HBOC)

OMIM:	113705, 600185, 604373, 613399, 610355
Genes:	<i>BRCA1</i> , locus 17q21; <i>BRCA2</i> , locus 13q12.3; <i>CHEK2</i> , locus 22q12; <i>RAD51C</i> , locus 17q22; <i>PALB2</i> , locus 16p12.2
Inheritance:	autosomal dominant
Indication:	suspected hereditary breast/ovarian cancer, positive family history for early onset breast/ ovarian cancer, bilateral breast cancer, male family members with breast cancer. Analysis may facilitate therapeutic decision regarding Olaparib
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>BRCA1</i> , <i>BRCA2</i> , <i>CHEK2</i> , <i>RAD51C</i> , <i>PALB2</i> (NGS panel, approx. 4 wks)

## Hereditary Breast Cancer, rare predisposition

OMIM:	114480
Genes:	<i>CDH1</i> , locus 16q22.1; <i>TP53</i> , locus 17p13.1; <i>STK11</i> , locus 19p13.3; <i>PTEN</i> , locus 10q23.31; <i>ATM</i> , locus 11q22.3
Inheritance:	autosomal dominant
Indication:	breast cancer with positive family history of breast cancer and further tumor entities
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>CDH1</i> , <i>TP53</i> , <i>STK11</i> , <i>PTEN</i> , <i>ATM</i> (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Hereditary cancer syndromes

## Hereditary non-polyposis colorectal cancer (HNPCC)

- OMIM: 120435, 609310, 614350, 614337  
Genes: *MSH2*, locus 2p21-16; *MLH1*, locus 3p21; *MSH6*,  
locus 2p16; *PMS2*, locus 7p22.1  
Inheritance: autosomal dominant  
Indication: positive family history for colon cancer or  
HNPCC-associated tumors, patient fulfills the  
updated Bethesda Guidelines (2004) or the classic  
Amsterdam Criteria  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*MLH1*, *MSH2*, *MSH6*, *PMS2* (NGS panel, approx.  
4 wks)

## Hereditary diffuse gastric cancer

- OMIM: 137215  
Gene: *CDH1*, locus 16q22.1  
Inheritance: autosomal dominant  
Indication: signet ring carcinoma, family history of gastric  
cancer and lobular breast cancer  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*CDH1* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Hereditary cancer syndromes

## Juvenile Polyposis syndrome

OMIM: 174900

Genes: *BMPR1A*, locus 10q23.2, *SMAD4*, locus 18q21.2

Inheritance: autosomal dominant

Indication: hamartomatous polyps of the gastrointestinal tract, secondary anemia due to bleeding of polyps

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis  
*BMPR1A*, *SMAD4* (NGS panel, approx. 4 wks)

## Li-Fraumeni syndrome

OMIM: 151623

Gene: *TP53*, locus 17p13.1

Inheritance: autosomal dominant

Indication: early onset of tumors, multiple tumors within an individual, and multiple affected family members, variety of tumor types rather than site-specific cancers. Tumors are usually soft tissue sarcomas and osteosarcomas, breast cancer, brain tumors, leukemia, adrenocortical carcinoma

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis *TP53* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Hereditary cancer syndromes

## Multiple endocrine neoplasia type I, MEN1

OMIM: 131100  
Gene: *MEN1*, locus 11q13.1  
Inheritance: autosomal dominant  
Indication: tumors of parathyroids, pancreatic islets, duodenal endocrine cells and the anterior pituitary  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*MEN1* (NGS panel, approx. 4 wks)

## Multiple endocrine neoplasia type II, MEN2

OMIM: 171400  
Gene: *RET*, locus 10q11.2  
Inheritance: autosomal dominant  
Indication: isolated medullary carcinoma of the thyroid (MTC, C-Cell carcinoma), pheochromocytoma, hyperparathyroidism  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing analysis *RET* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Hereditary cancer syndromes

## Neurofibromatosis

### Neurofibromatosis type 1, *NF1*

OMIM: 162200  
Gene: *NF1*, locus 17q11.2  
Inheritance: autosomal dominant  
Indication: multiple café au lait spots (>5 mm), axillary and inguinal freckling, multiple discrete dermal neurofibromas, iris Lisch nodules  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis *NF1* (NGS panel, approx. 4 wks)

### Neurofibromatosis type 2, *NF2*

OMIM: 101000  
Gene: *NF2*, locus 22q12.2  
Inheritance: autosomal dominant  
Indication: vestibular schwannoma followed by tinnitus, hearing loss, balance dysfunction, meningiomas, ependymomas, astrocytoma  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis *NF2* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Hereditary cancer syndromes

## Peutz-Jeghers syndrome

OMIM: 175200  
Genet: *STK11*, locus 19p13.3  
Inheritance: autosomal dominant  
Indication: gastrointestinal hamartomatous polyps,  
mucocutaneous hyperpigmentation of mouth, eyes,  
nostrils, and fingers  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis *STK11*  
(NGS panel, approx. 4 wks)

## PTEN hamartoma tumor syndrome

OMIM: 158350, 153480  
Gene: *PTEN*, locus 10q23.31  
Inheritance: autosomal dominant  
Indication: includes Cowden syndrome (multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium), Bannayan-Riley-Ruvalcaba syndrome (multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium), *PTEN*-related Proteus syndrome (PS), and Proteus-like syndrome (congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi)  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis *PTEN* (NGS panel, approx. 4 wks), methylation sensitive deletion/duplication analysis (MS-MLPA) *PTEN* (approx. 3 wks)

# Molecular genetic analyses

» Hereditary cancer syndromes

## Tuberous sclerosis

OMIM:	191100, 613254
Genes:	<i>TSC1</i> , <i>TSC2</i> , loci 9q34.31, 16p13.3
Inheritance:	autosomal dominant
Indication:	hamartomas in multiple organs (brain, skin, heart, kidneys, lung), epilepsy, learning difficulties, behavioural problems, autism, renal angiomyolipoma
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>TSC1</i> , <i>TSC2</i> (NGS panel, approx. 4 wks)

## Von-Hippel-Lindau syndrome, *VHL*

OMIM:	193300
Gene:	<i>VHL</i> , locus 3p25.3
Inheritance:	autosomal dominant
Indication:	retinal angioma, cerebellar or spinal cord hemangioblastoma, renal cell carcinoma, pheochromocytoma
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing analysis of <i>VHL</i> (approx. 2 wks) deletion/duplication analysis of <i>VHL</i> (approx. 2 wks)

# Molecular genetic analyses

» HLA-associated disorders

## ■ Immune disorders

### Behçet syndrome

OMIM: 109650  
Gene: Major Histocompatibility Complex, locus 6p21.3  
Inheritance: polygenic/multifactorial  
Indication: recurrent oral and/or genital aphthous ulcers, inflammation of gastrointestinal tract, central nervous system, vascular system, lungs, and kidneys  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequence specific PCR (SSP) (approx. 2 wks)

### Celiac disease

→ please refer to "Gastrointestinal diseases"

### HLA-B27 associated diseases

OMIM: 142800  
Gene: Major Histocompatibility Complex, locus 6p21.3  
Inheritance: polygenic/multifactorial  
Indication: suspected Bechterew disease, spondyloarthropathy, psoriatic arthritis  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequence specific PCR (SSP) (approx. 2 wks)

# Molecular genetic analyses

» HLA-associated disorders/Intersexuality

## Narcolepsia

OMIM: 142857  
Gene: Major Histocompatibility Complex, locus 6p21.3  
Inheritance: polygenic/multifactorial  
Indication: hypersomnia, daytime sleepiness, cataplexy  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequence specific PCR (SSP) (approx. 2 wks)

## ■ Intersexuality

### Congenital adrenal hyperplasia (CAH)

→ please refer to "Endocrinology"

## SRY

OMIM: 480000  
Gene: SRY, locus Yp11.3  
Inheritance: Y-chromosomal  
Indication: primary amenorrhea, gonadal dysgenesis,  
suspected XX-males, suspected testicular  
feminization  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR (approx. 2 wks)

## Kidney diseases

### Alport syndrome

OMIM: 303630, 203780, 104200  
Genes: *COL4A5*, locus Xq22.3; *COL4A4*, locus 2q36.3;  
*COL4A3*, Locus 2q36.3  
Inheritance: X-chromosomal (*COL4A5*), autosomal dominant/  
recessive (*COL4A4*, *COL4A3*)  
Indication: micro- or macrohematuria, proteinuria with  
progression to end stage renal disease, focal  
thickening or splitting of the glomerular basement  
membrane, progressive bilateral sensorineural  
hearing loss, anterior lenticonus  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*COL4A5*, *COL4A3*, *COL4A4* (NGS panel, approx.  
4 wks)

### Adult dominant polycystic kidney disease (ADPKD)

OMIM: 613095, 173900  
Genes: *PKD1*, locus 16p13.3; *PKD2*, locus 4q22.1  
Inheritance: autosomal dominant  
Indication: multiple renal and liver cysts, with further  
complication of hypertension  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*PKD1*, *PKD2* (NGS panel, approx. 8 wks)

# Molecular genetic analyses

» Kidney diseases

## Autosomal recessive polycystic kidney disease (ARPKD)

OMIM: 263200  
Gene: *PKHD1*, locus 6p12.3-p12.2  
Inheritance: autosomal recessive  
Indication: enlarged, echogenic kidneys with fusiform dilatation of the collecting ducts in the neonatal period, oligohydramnios and Potter sequence, pulmonary hypoplasia  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*PKHD1* (NGS panel, approx. 4 wks)

## Renal glucosuria

OMIM: 233100  
Gene: *SLC5A2*, locus 16p11.2  
Inheritance: autosomal dominant, autosomal recessive  
Indication: glucosuria with no signs of hyperglycemia or tubular dysfunction  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *SLC5A2* (approx. 2 wks)

## Liver diseases

### Crigler-Najjar syndrome type I/II

OMIM: 143500, 606785  
Gene: *UGT1A1*, locus 2q37  
Inheritance: autosomal recessive  
Indication: Hyperbilirubinemia, congenital familial nonhemolytic jaundice with kernicterus  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing analysis of *UGT1A1* (approx. 2 wks)

### Hemochromatosis

OMIM: 235200 (*HFE1*), 602390 (*HFE2A*), 613313 (*HFE2B*),  
604250 (*HFE3*), 606069 (*HFE4*)  
Gene: *HFE*, locus 6p22.2; *HJV*, locus 1q21; *HAMP*, locus 19q13; *TFR2*, locus 7q22.1; *SLC40A1*, locus 2q32  
Inheritance: autosomal recessive (*HFE1*, *HFE2A+B*, *HFE3*),  
autosomal dominant (*HFE4*)  
Indication: increased serum ferritin and transferrin saturation, in advanced disease stages liver fibrosis, cirrhosis, bronzed skin, diabetes  
Material: 3-5 ml EDTA blood  
Methods/TAT: 1<sup>st</sup> tier (basic analysis): Real-time PCR, detection of the most common variants p.(Cys282Tyr), p.(His63Asp) and p.(Ser65Cys) (approx. 1 wk)  
2<sup>nd</sup> tier (comprehensive analysis): sequencing and deletion/duplication analysis *HFE*, *HJV*, *HAMP*, *TFR2*, *SLC40A1* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Liver diseases

## Hyperbilirubinemia, Gilbert syndrome

OMIM: 143500

Gene: *UGT1A1*, locus 2q37

Inheritance: autosomal recessive

Indication: hyperbilirubinemia, congenital familial nonhemolytic jaundice with kernicterus

Material: 3-5 ml EDTA blood

Methods/TAT: PCR and fragment analysis, detection of the TA-repeat-expansion in the promoter of *UGT1A1* (approx. 2 wks)

## Wilson disease

OMIM: 277900

Gene: *ATP7B*, locus 13q14.3

Inheritance: autosomal recessive

Indication: hepato-, splenomegaly, movement disorders (tremor, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement), Kayser-Fleischer ring

Material: 3-5 ml EDTA blood

Methods/TAT: Real-time-PCR, detection of the most common variant p.(His1069Gln) (approx. 1 wk), sequencing and deletion/duplication analysis *ATP7B* (NGS panel, approx. 4 wks)

## Lung diseases

### Alpha1-Antitrypsin deficiency

OMIM: 107400  
Gene: *SERPINA1*, locus 14q32.1  
Inheritance: autosomal recessive  
Indication: chronic obstructive pulmonary disease (COPD)  
in adults, liver disease in children and adults,  
emphysema, prolonged jaundice, liver disease in  
adults, manifest as cirrhosis and fibrosis  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR detection of the variants Pi\*S and  
Pi\*Z (approx. 1 wk) sequencing (approx. 2 wks)  
and deletion/duplication (approx. 2 wks) analysis  
*SERPINA1*

### Cystic Fibrosis (CF)

OMIM: 219700  
Gene: *CFTR*, locus 7q31.2  
Inheritance: autosomal recessive  
Indication: obstructive lung disease, bronchiectasis, exocrine  
pancreas insufficiency, elevated sweat chloride  
concentration, meconium ileus  
Material: 3-5 ml EDTA blood  
Methods/TAT: ▪ Real-time-PCR detection of the most common  
variant p.(Phe508del) (approx. 1 wk)  
▪ panel for 40 common variants (approx. 2 wks)  
▪ sequencing and deletion/duplication analysis  
*CFTR* (NGS panel, approx. 4 wks)

## Metabolic diseases

### Apolipoprotein A1

OMIM: 107680  
Gene: *APOA1*, locus 11q23  
Inheritance: autosomal dominant  
Indication: early identification of at-risk patients for atherosclerosis, assessment of the risk for myocardial infarction and peripheral obstructive disease  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *APOA1* (approx. 2 wks)

### Apolipoprotein B

OMIM: 107730  
Gene: *APOB*, locus 2p24  
Inheritance: autosomal dominant  
Indication: dyslipoproteinemia, hypercholesterolemia  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR detection of the most common variants p.(Arg3527Gln), p.(Arg3527Trp), p.(Arg3558Cys) (approx. 1 wk)

### Apolipoprotein E

OMIM: 107741  
Gene: *APOE*, locus 19q13.2  
Inheritance: autosomal dominant  
Indication: dyslipoproteinemia, hypercholesterolemia, Alzheimer's disease  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR for genotyping of *APOE*-alleles E2, E3, E4 (approx. 1 wk)

# Molecular genetic analyses

» Metabolic diseases

## Fabry disease, $\alpha$ -Galactosidase-A deficiency

OMIM:	301500
Gene:	<i>GLA</i> , locus Xq22
Inheritance:	X-linked
Indication:	males with less than 1% $\alpha$ -galactosidase enzyme activity, periodic crises of severe pain in the extremities (acroparesthesias), appearance of vascular cutaneous lesions (angiofibromas), hypohidrosis, characteristic corneal and lenticular opacities, and proteinuria, gradual deterioration of renal function to end-stage renal disease
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing analysis of <i>GLA</i> (approx. 2 wks) deletion/duplication analysis of <i>GLA</i> (approx. 2 wks)

## Familial hypercholesterolemia

OMIM:	143890, 603776
Genes:	<i>LDLR</i> , <i>PCSK9</i> , <i>LDLRAP1</i> , loci 19p13.2, 1p32.3. 1p36.11
Inheritance:	autosomal dominant ( <i>LDLR</i> , <i>PCSK9</i> ), autosomal recessive ( <i>LDLRAP1</i> )
Indication:	Hypercholesterolemia, tendinous xanthomas, corneal arcus, premature atherosclerosis and coronary artery disease
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>LDLR</i> , <i>PCSK9</i> , <i>LDLRAP1</i> (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Metabolic diseases

## Fructose intolerance

→ please refer to "Nutrigenetics"

## Gaucher disease

OMIM: 608013, 230800, 230900, 231000, 231005

Gene: *GBA*, locus 1q22

Inheritance: autosomal recessive

Indication: presence of Gaucher cells (intracellular accumulation of glucosylceramide), hepatosplenomegaly, pancytopenia, neurologic manifestations

Material: 3-5 ml EDTA blood

Methods/TAT: Sequencing analysis of *GBA* (approx. 4 wks)

## Glucose-6-Phosphate Dehydrogenase Deficiency

→ please refer to "Hematology"

## Hyperinsulinism

### severe neonatal type

OMIM: 600509, 600937  
Genes: *ABCC8, KCNJ11*, loci 11p15.1, 11p15.1  
Inheritance: autosomal recessive  
Indication: persistent hypoglycemia in the first years of life,  
severe refractory hypoglycemia in the first 48  
hours of life  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*ABCC8, KCNJ11* (NGS panel, approx. 4 wks)

### mild type

OMIM: 138130, 138079  
Genes: *GLUD1, GCK*, loci 10q23.3, 7p15-p13  
Inheritance: autosomal dominant  
Indication: persistent hypoglycemia in the first years of  
life, Hyperinsulinism–hyperammonaemia (HI/  
HA) syndrome, nonspecific symptoms including  
seizures, hypotonia, poor feeding and apnea  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*GLUD1, GCK, HNF4A* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Metabolic diseases

## Hyperproinsulinemia

OMIM:	613370
Gene:	<i>INS</i> , locus 11p15.5
Inheritance:	autosomal dominant
Indication:	circulating proinsulin, apparent insulin resistance with hyperglycemia and hyperinsulinemia but good response to insulin treatment
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>INS</i> (NGS panel, approx. 4 wks)

## Lactose intolerance

→ please refer to "Nutrigenetics"

## Maturity-Onset Diabetes of the Young (MODY)

OMIM: 606391

	OMIM:	Loci:
MODY 1	125850	<i>HNF4A</i> , locus 20q12-q13.1
MODY 2	125851	<i>GCK</i> , locus 7p13
MODY 3	600496	<i>HNF1A</i> , locus 12q24.2
MODY 4	606392	<i>PDX1</i> , locus 13q12.1
MODY 5	137920	<i>HNF1B</i> , locus 17q12
MODY 6	606394	<i>NEUROD1</i> , locus 2q31
MODY 7	603301	<i>KLF11</i> , locus 2p25.1
MODY 8	609812	<i>CEL</i> , locus 9q34.13
MODY 9	612225	<i>PAX4</i> , locus 7q32.1
MODY 10	176730	<i>INS</i> , locus 11p15.5
MODY 11	613375	<i>BLK</i> , locus 8p32.1
MODY 13	616329	<i>KCNJ11</i> , locus 11p15.1

# Molecular genetic analyses

» Metabolic diseases

Inheritance: autosomal dominant

Indication: in general: positive family history of diabetes, early manifestation (before the age of 25), no beta cell autoimmunity

MODY 1: severe hyperglycemia, low HDL cholesterol and triglycerides, high LDL cholesterol

MODY 2: mild hyperglycemia (since birth) without progression, gestational diabetes

MODY 3: severe hyperglycemia, glucosuria, high HDL cholesterol

MODY 5: characteristic phenotype of diabetes mellitus and non-diabetic renal disease (renal dysplasia, renal cysts), genital malformations and liver dysfunction

MODY 4, 6-13: rare MODY types

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis  
*HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, INS, BLK, ABCC8, KCNJ11*  
(NGS panel, approx. 4 weeks)

# Molecular genetic analyses

» Metabolic diseases

## MCAD Deficiency (Medium-Chain Acyl-CoA Dehydrogenase)

OMIM: 201450

Gene: ACADM, locus 1p31

Inheritance: autosomal recessive

Indication: positive acylcarnitine screening in newborn screening, hypoketotic hypoglycemia, vomiting, lethargy triggered by a common illness, seizures, hepatomegaly and acute liver disease, onset typically between three and 24 months of age

Material: 3-5 ml EDTA blood

Methods/TAT: 1<sup>st</sup> tier: sequencing analysis of select regions of ACADM (approx. 1 wk)

2<sup>nd</sup> tier: sequencing analysis of remaining regions of ACADM (approx. 1 wk) and deletion/duplication analysis of ACADM (approx. 2 wks)

# Molecular genetic analyses

» Metabolic diseases

## Neonatal diabetes (permanent/transient)

OMIM:	600509, 600937
Genes:	<i>ABCC8</i> , <i>KCNJ11</i> , locus 11p15.1; <i>INS</i> , Locus 11p15.5; <i>GCK</i> , locus 7p15-13; chromosomal region 6q24
Inheritance:	autosomal dominant for <i>KCNJ11</i> , autosomal dominant or autosomal recessive for <i>ABCC8</i> and <i>INS</i> , autosomal recessive for <i>GCK</i>
Indication:	Hyperglycemia in the first 6 months of life, intrauterine growth retardation, low birth weight, failure to thrive, deficiency of subcutaneous adipose tissue, low C-peptide levels
Material:	3-5 ml EDTA blood
Methods/TAT:	sequencing and deletion/duplication analysis <i>KCNJ11</i> , <i>ABCC8</i> , <i>INS</i> , <i>GCK</i> (NGS panel, approx. 4 wks), <i>UPD6</i> (methylation sensitive MLPA, approx. 3 wks)

## Obesity (early onset)

→ please refer to "Endocrinology"

# Molecular genetic analyses

» Metabolic diseases

## Osteoporosis

OMIM: 166710, 120150, 601769  
Genes: *COL1A1*, *VDR*, loci 17q21.31-q22, 12q12-q14  
Inheritance: polygenic/multifactorial  
Indication: osteoporosis, genotyping before starting a hormone substitution therapy to assess the risk for osteoporosis  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of the Sp1 polymorphism in the *COL1A1* gene (approx. 2 wks),  
Sequencing analysis of the Bsml polymorphism in the *VDR* gene (approx. 2 wks)

## Phenylketonuria (PKU)/Hyperphenylalaninemia

OMIM: 261600, 233910  
Gene: *PAH*, locus 11q22.3  
Inheritance: autosomal recessive  
Indication: positive phenylalanine screening in newborn:  
plasma phenylalanine concentrations higher than 800 µmol/L, hyperphenylalaninemia  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing analysis of *PAH* (approx. 2 wks),  
deletion/duplication analysis of *PAH* (approx. 2 wks)

# Molecular genetic analyses

» Metabolic diseases

## Porphyria

	OMIM:	Locus:	Inheritance:
Acute intermittent Porphyria	176000	<i>HMBS</i> , locus 11q23.3	autosomal dominant
Variegate Porphyria	176200	<i>PPOX</i> , locus 1q23.3	autosomal dominant
Porphyria cutanea tarda	176100	<i>UROD</i> , locus 1p34.1	autosomal dominant
Erythropoietic Protoporphyria	177000	<i>FECH</i> , locus 18q21.31	autosomal recessive
Doss Porphyria	612740	<i>ALAD</i> , locus 9q32	autosomal recessive
congenital erythropoietic Porphyria	263700	<i>UROS</i> , locus 10q26	autosomal recessive
X-chromosomal dominant	300752	<i>ALAS2</i> , locus Xp11.21	X-chromosomal dominant
Coproporphyrinia	121300	<i>CPOX</i> , locus 3q11.2	autosomal recessive

Indication: neurovisceral attacks (abdominal pain, gastrointestinal dysfunction, and neurological disturbances), passage of dark urine, cutaneous manifestations (increased photosensitivity, blistering, skin fragility with chronic scarring of sun-exposed areas, postinflammatory hyperpigmentation), hypertrichosis

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis  
*HMBS*, *PPOX*, *UROD*, *FECH*, *ALAD*, *UROS*, *ALAS2*, *CPOX* (NGS panel, approx. 4 weeks)

## Mitochondrial diseases

### Chronic progressive external ophthalmoplegia (CPEO), Kearns-Sayre syndrome (KSS), Pearson syndrome

OMIM: 530000, 557000

Locus: mitochondrial genome

Inheritance: maternal, with variable penetrance

Indication: suspected mitochondrial disease, pigmentary retinopathy, progressive external ophthalmoplegia (PEO), sideroblastic anemia and exocrine pancreas dysfunction, ptosis, paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness, cardiomyopathy

Material: muscle biopsy, 3-5 ml EDTA blood

Methods/TAT: Long range PCR, detection of deletions (approx. 2 wks) PCR-RFLP, quantification; detection of the variant m.3243G>A (approx. 2 wks)

### Leber hereditary optic neuropathy (LHON)

→ please refer to "Eye diseases"

# Molecular genetic analyses

» Mitochondrial diseases

## Leigh-/Neuropathy, ataxia, retinitis pigmentosa (NARP syndrome)

OMIM:	256000, 551500
Gene:	<i>MT-ATP6</i> , mitochondrial genome
Indication:	Decompensation (often with lactic acidosis) during an intercurrent illness typically associated with psychomotor retardation or regression, neurological features include hypotonia, spasticity, movement disorders (including chorea), cerebellar ataxia, and peripheral neuropathy
Inheritance:	maternal, with variable penetrance
Material:	3-5 ml EDTA blood
Methods/TAT:	PCR-RFLP, quantification; detection of the variants m.8993T>G and m.8993T>C (approx. 2 wks)

## Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), Diabetes-Deafness syndrome

OMIM:	540000
Gene:	<i>MT-TL1</i> , mitochondrial genome
Inheritance:	maternal, with variable penetrance
Indication:	generalized tonic-clonic seizures that are often associated with stroke-like episodes of transient hemiparesis or cortical blindness, atypical diabetes, deafness, recurrent headaches, cardiac failure, renal failure
Material:	3-5 ml EDTA blood
Methods/TAT:	PCR-RFLP, quantification; detection of the variant m.3243G>A (approx. 2 wks)

# Molecular genetic analyses

» Mitochondrial diseases

## Myoclonic epilepsy associated with ragged-red fibers (MERRF) syndrome

OMIM: 545000

Gene: *MT-TK*, mitochondrial genome

Inheritance: maternal, with variable penetrance

Indication: myoclonus epilepsy (ragged-red fibers in the muscle biopsy), generalized epilepsy, ataxia, weakness, dementia, hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White syndrome (WPW)

Material: 3-5 ml EDTA blood

Methods/TAT: PCR-RFLP, quantification; detection of the variant m.8344A>G (approx. 2 wks)

# Molecular genetic analyses

» Neurodegenerative diseases

## ■ Neurodegenerative diseases

For analyses of neurodegenerative diseases we kindly request information regarding the personal and family medical history of the patient or counselee. Please find the respective form on our website.

### Ataxia telangiectasia

OMIM: 208900  
Gene: *ATM*, locus 11q22.3  
Inheritance: autosomal recessive  
Indication: progressive cerebellar ataxia, oculomotor apraxia, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, frequent infections, leukemia and lymphoma  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis of *ATM* (NGS panel, approx. 4 wks)

### Autosomal dominant adult-onset demyelinating leukodystrophy (ADLD)

OMIM: 169500  
Gene: *LMNB1*, locus 5q23.2  
Inheritance: autosomal dominant  
Indication: onset in the fourth or fifth decade of life, early autonomic abnormalities, pyramidal and cerebellar dysfunction, in neuroimaging symmetric demyelination of the CNS, lack of astrogliosis  
Material: 3-5 ml EDTA blood  
Methods/TAT: deletion/duplication analysis of *LMNB1* (approx. 2 wks)

# Molecular genetic analyses

» Neurodegenerative diseases

## Cerebral Autosomal Dominant/Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL/ARASIL)

OMIM: 125310

Gene: *NOTCH3*, locus 19p13.12; *HTRA1*, locus 10q26.13

Inheritance: autosomal dominant

Indication: history of migraine headache, onset of cerebrovascular disease progressing to dementia, diffuse white matter lesions and subcortical infarcts in neuroimaging

Material: 3-5 ml EDTA blood

Methods/TAT: Methods/TAT: sequencing and deletion/duplication analysis of *NOTCH3*, *HTRA1* (NGS panel, approx. 4 wks)

## Friedreich Ataxia

OMIM: 229300

Gene: *FXN*, locus 9q21.11

Inheritance: autosomal recessive

Indication: progressive gait and limb ataxia, limb muscle weakness, absent lower limb reflexes, extensor plantar responses, dysarthria, and decreased vibratory sense and proprioception, onset between 5 and 25 years

Material: 3-5 ml EDTA blood

Methods/TAT: 1<sup>st</sup> tier: PCR, fragment analysis for determination of the GAA-repeat length of the *FXN* gene (approx. 3 wks)

2<sup>nd</sup> tier: sequencing (approx. 2 wks) and deletion/duplication analysis *FXN* (approx. 2 wks)

# Molecular genetic analyses

» Neurodegenerative diseases

## Huntington disease

OMIM: 143100  
Gene: *HTT*, locus 4p16.3  
Inheritance: autosomal dominant  
Indication: hyperkinesia, choreatic movements, disturbance of speech, dementia  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR, fragment analysis: identification of the CAG-repeat length/CGG repeat length of *HTT* (approx. 2 wks)

## Spinocerebellar ataxias

### Spinocerebellar ataxia type 1 (SCA1)

OMIM: 164400  
Gene: *ATXN1*, locus 6p22.3  
Inheritance: autosomal dominant  
Indication: cerebellar and upper motor neuron signs, extensor plantar responses, onset in the third or fourth decade of life  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR, fragment analysis: identification of the CAG-repeat length of *ATXN1* (approx. 2 wks)

# Molecular genetic analyses

» Neurodegenerative diseases

## Spinocerebellar ataxia type 2 (SCA2)

OMIM: 183090  
Gene: ATXN2, locus 12q24.12  
Inheritance: autosomal dominant  
Indication: progressive cerebellar ataxia, nystagmus, slow saccadic eye movements, ophthalmoparesis, parkinsonism, presence of pyramidal signs, onset in the fourth decade  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR, fragment analysis: identification of the CAG-repeat length of ATXN2 (approx. 2 wks)

## Spinocerebellar ataxia type 3 (SCA3), Machado-Joseph disease (MJD)

OMIM: 109150  
Gene: ATXN3, locus 14q32.12  
Inheritance: autosomal dominant  
Indication: progressive cerebellar ataxia, dystonic-rigid syndrome, spasticity, and ocular movement abnormalities  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR, fragment analysis: identification of the CAG-repeat length of ATXN3 (approx. 2 wks)

# Molecular genetic analyses

» Neurodegenerative diseases

## Spinocerebellar ataxia type 6 (SCA6)

OMIM: 183086  
Gene: *CACNA1A*, locus 19p13.13  
Inheritance: autosomal dominant  
Indication: gait unsteadiness, stumbling, and imbalance,  
slowly progressive cerebellar ataxia, dysarthria,  
and nystagmus, dysarthria, upper-limb  
incoordination, intention tremor, dysarthria,  
dysphagia, onset in the fourth decade  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR, fragment analysis: identification of the  
CAG-repeat length of *CACNA1A* (approx. 2 wks)

## Spinocerebellar ataxia type 7 (SCA7)

OMIM: 183086  
Gene: *ATXN7*, locus 3p14.1  
Inheritance: autosomal dominant  
Indication: progressive cerebellar ataxia, dysarthria,  
dysphagia, cone-rod and retinal dystrophy with  
progressive central visual loss resulting in  
blindness  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR, fragment analysis: identification of the  
CAG-repeat length of *ATXN7* (approx. 2 wks)

# Molecular genetic analyses

» Neuromuscular diseases/Neuropathies

## ■ Neuromuscular diseases/Neuropathies

### Charcot-Marie-Tooth disease (CMT)

	OMIM:	Loci:
CMT1A	118220	<i>PMP22</i> , locus 17p11.2
CMT1B	118200	<i>MPZ</i> , locus 1q23.3
CMT1C	601098	<i>LITAF</i> , locus 16p13.13
CMT1D	607678	<i>EGR2</i> , locus 10q21.3
CMT1X	302800	<i>GJB1</i> , locus Xq13.1
CMT2A	609260	<i>MFN2</i> , locus 1p36.22
CMT2A1	118210	<i>KIF 1B</i> , locus 1p36.22
CMT2B1	605588	<i>LMNA</i> , locus 1q22
CMT2D	601472	<i>GARS</i> , locus 7p14.3
CMT2E/1F	607684	<i>NEFL</i> , locus 8p21.2

### Basic analysis Charcot-Marie-Tooth disease type 1A (CMT1A)

Inheritance: autosomal dominant

Indication: demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity, pes cavus foot deformity, bilateral foot drop, age of onset 5-25 years

Material: 3-5 ml EDTA blood

Methods/TAT: deletion/duplication analysis of *PMP22* (approx. 2 weeks)

# Molecular genetic analyses

» Neuromuscular diseases/Neuropathies

## comprehensive analysis Charcot-Marie-Tooth disease

Inheritance: autosomal dominant (CMT1B, C, D, CMT2A, 2A1, 2B1, 2D, 2E/1F), X-chromosomal dominant (CMT1X)

Indication: CMT1: demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity

CMT2: axonal peripheral sensorimotor neuropathy with early and more severe involvement of the lower extremities than the upper extremities, distal upper-extremity involvement as the neuropathy progresses, more prominent motor deficits than sensory deficits, normal nerve conduction velocity

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis  
*PMP22, MPZ, LITAF, EGR2, GJB1, MFN2, KIF1B, LMNA, GARS, NEFL* (NGS panel, approx. 4 weeks)

# Molecular genetic analyses

» Neuromuscular diseases/Neuropathies

## Hereditary neuropathy with liability to pressure palsies (HNPP)

OMIM:	162500
Gene:	<i>PMP22</i> , locus 17p11.2
Inheritance:	autosomal dominant
Indication:	repeated focal pressure neuropathies such as carpal tunnel syndrome, peroneal palsy with foot drop, age of onset usually in the second or third decade of life
Material:	3-5 ml EDTA blood
Methods/TAT:	deletion/duplication analysis of <i>PMP22</i> (approx. 2 wks) sequencing analysis of <i>PMP22</i> (approx. 2 wks)

## Muscular dystrophy type Duchenne/Becker (*DMD/BMD*)

OMIM:	310200, 300376
Gene:	<i>DMD</i> , locus Xp21
Inheritance:	X-linked recessive
Indication:	progressive proximal muscular dystrophy, pseudohypertrophy, increase in serum concentration of creatine phosphokinase (CK), myofiber degeneration with fibrosis and fatty infiltration in muscle biopsy, cardiomyopathy
Material:	3-5 ml EDTA blood
Methods/TAT:	1 <sup>st</sup> tier: deletion/duplication analysis of <i>DMD</i> (approx. 2 wks) 2 <sup>nd</sup> tier: sequencing analysis of <i>DMD</i> (NGS panel, approx. 4 wks)

## Myotonic dystrophy

### Myotonic dystrophy type 1, Steinert disease

OMIM: 160900  
Gene: *DMPK*, locus 19q13.32  
Inheritance: autosomal dominant  
Indication: muscle weakness and wasting, myotonia, muscular dystrophy, cataract, hypogonadism and often cardiac conduction abnormalities  
Material: 3-5 ml EDTA blood  
Methods/TAT: 1<sup>st</sup> tier: PCR and fragment analysis; determination of the CTG-repeat length of *DMPK* (short repeat ranges) (approx. 2 wks)  
2<sup>nd</sup> tier: Southern blot; determination of the CTG-repeat length of *DMPK* (long repeat ranges) (approx. 3 wks)

### Myotonic dystrophy type 2/ proximal myotonic myopathy (PROMM)

OMIM: 602668  
Gene: *CNBP*, locus 3q21  
Inheritance: autosomal dominant  
Indication: myotonia and muscle dysfunction, muscular dystrophy, cataract, onset usually in the third decade of life  
Material: 3-5 ml EDTA blood  
Methods/TAT: 1<sup>st</sup> tier: PCR and fragment analysis; determination of the CCTG-repeat length of *CNBP* (short repeat ranges) (approx. 2 wks)  
2<sup>nd</sup> tier: Southern blot; determination of the CCTG-repeat length of *CNBP* (long repeat ranges) (approx. 3 wks)

# Molecular genetic analyses

» Neuromuscular diseases/Neuropathies

## Spinal and Bulbar Muscular Atrophy (SBMA), Kennedy disease

OMIM: 313200

Gene: *AR*, locus Xq12

Inheritance: X-linked recessive

Indication: proximal muscle weakness, muscle atrophy, fasciculations, gynecomastia, testicular atrophy, and reduced fertility as a result of mild androgen insensitivity

Material: 3-5 ml EDTA blood

Methods/TAT: PCR, fragment analysis; determination of the CAG-repeat length of *AR* (approx. 2 wks)

## Spinal muscular atrophy types I/II/III

OMIM: 253300, 253550, 253400

Gene: *SMN1*, locus 5q31.2

Inheritance: autosomal recessive

Indication: suspected Werdnig-Hoffmann disease or Kugelberg-Welander disease, severe proximal progressive muscle weakness, hypotonia, psychomotor delay, joint laxity, onset ranging from before birth to adolescence or young adulthood

Material: 3-5 ml EDTA blood

Methods/TAT: deletion/duplication analysis of *SMN1* and *SMN2* (approx. 2 wks), prenatal analysis (approx 1 wk)

## Nutrigenetics

### Celiac disease

→ please refer to "Gastrointestinal diseases"

### Fructose intolerance

OMIM: 229600  
Gene: *ALDOB*, locus 9q22.3  
Inheritance: autosomal recessive  
Indication: nausea and abdominal pain after eating fruits and fructose/sucrose-containing foods, fructose-/saccharose-intolerance; hypoglycemia, vomiting, nonspecific liver dysfunction  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing (approx. 2 wks) and deletion/duplication analysis analysis *ALDOB* (approx. 2 wks)

### Lactose intolerance

OMIM: 223100  
Gene: *LCT*, locus 2q21  
Inheritance: autosomal recessive  
Indication: lactose intolerance, abdominal symptoms, including stomach cramps, bloating and flatulence after intake of lactose-containing food  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR detection of the polymorphism -13910C>T of *LCT* (approx. 1 wk)

## Pancreatic diseases

### Hereditary pancreatitis

OMIM: 167800

Genes: *PRSS1*, *SPINK1*, *CFTR*, loci 7q35, 5q32, 7q31.2

Inheritance: autosomal dominant, incomplete penetrance (*PRSS1*), autosomal recessive, incomplete penetrance (*SPINK1*), autosomal recessive (*CFTR*)

Indication: recurrent episodes of pancreatic attacks, which can progress to chronic pancreatitis, abdominal pain, nausea and vomiting, elevated amylase and lipase serum concentrations in children, obstructive lung disease, bronchiectasis, exocrine pancreas insufficiency, elevated sweat chloride concentration, meconium ileus

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis  
*PRSS1*, *SPINK1*, *CFTR* (NGS panel, approx. 4 wks)

## ■ Periodic fever

### Chronic neurologic cutaneous and articular syndrome (CINCA)/neonatal onset multisystemic inflammatory disease (NOMID)

OMIM: 607115  
Gene: *NLRP3*, locus 1q44  
Inheritance: autosomal dominant  
Indication: severe chronic inflammatory disease of early onset, cutaneous symptoms, central nervous system involvement and arthropathy  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*NLRP3* (NGS panel, approx. 4 wks)

### Familial cold autoinflammatory syndrome (FCAS)

OMIM: 120100  
Gene: *NLRP3*, locus 1q44  
Inheritance: autosomal dominant  
Indication: cold urticaria, recurrent attacks of a maculopapular rash associated with arthralgias, myalgias, fever and chills, and swelling of the extremities after exposure to cold  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*NLRP3* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Periodic fever

## Familial mediterranean fever (FMF)

OMIM: 249100

Gene: *MEFV*, locus 16p13

Inheritance: autosomal recessive

Indication: recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis, amyloidosis

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis  
*MEFV* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Periodic fever

## Hyper-IgD syndrome (HIDS)

OMIM: 260920  
Gene: *MVK*, locus 12q24  
Inheritance: autosomal recessive  
Indication: recurrent febrile attacks with no fixed periodicity,  
accompanied by abdominal pain and arthralgia,  
increased IgD levels ( $>100$  IU/ml)  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis *MVK*  
(NGS panel, approx. 4 wks)

## Muckle-Wells syndrome

OMIM: 191900  
Gene: *NLRP3*, locus 1q44  
Inheritance: autosomal dominant  
Indication: episodic skin rash, arthralgias, and fever  
associated with late-onset sensorineural deafness  
and renal amyloidosis  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing and deletion/duplication analysis  
*NLRP3* (NGS panel, approx. 4 wks)

# Molecular genetic analyses

» Periodic fever

## Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), familial Hibernian fever

OMIM: 142680

Gene: *TNFRSF1A*, locus 12p13.2

Inheritance: autosomal dominant

Indication: episodes of autoinflammation usually associated with fever, abdominal pain, myalgia, exanthema, arthralgia/arthritis and ocular involvement

Material: 3-5 ml EDTA blood

Methods/TAT: sequencing and deletion/duplication analysis  
*TNFRSF1A* (NGS panel, approx. 4 wks)

## ■ Pharmacogenetics

### 5-Fluorouracil (5FU)- toxicity

OMIM: 274270  
Gene: *DPYD*, locus 1p22  
Inheritance: autosomal dominant  
Indication: risk assessment for toxicity for cancer patients for whom 5-Fluorouracil-based chemotherapy is planned  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR to detect the exon 14 skipping variant (c.1905+1G>A) of *DPYD* (approx. 2-3 days)

### Statin-induced myopathy (*SLCO1B1*), haplotype

#### *SLCO1B1\*5*

OMIM: 604843  
Gene: *SLCOB1*, locus 12p12.1  
Inheritance: polygenic/multifactorial  
Indication: risk assessment for myopathy during treatment with statins  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *SLCO1B1*, detection of haplotype *SLCO1B1\*5* (approx. 2 wks)

# Molecular genetic analyses

» Pharmacogenetics

## Thiopurin S-Methyltransferase Deficiency

OMIM: 610460  
Gene: *TPMT*, locus 6p22.3  
Inheritance: autosomal dominant  
Indication: risk assessment for toxicity for cancer patients for whom azathioprine, 6-mercaptopurine and 6-thioguanine based chemotherapy is planned  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR detection of the variants c.238G>C, c.460G>A and c.719A>G, haplotypes TPMT\*1, TPMT\*2, TPMT\*3A, TPMT\*3B, TPMT\*3C)  
(approx. 2-3 days)

## Irinotecan toxicity

OMIM: 191740  
Gene: *UGT1A1*, locus 2q37 (see also Hyperbilirubinemia, Gilbert syndrome)  
Inheritance: autosomal recessive  
Indication: risk assessment for toxicity for cancer patients for whom irinotecan based chemotherapy is planned  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR and fragment analysis to detect the TA-expansion in the promoter of *UGT1A1*  
(approx. 2 wks)

# Molecular genetic analyses

» Short stature

## ■ Short stature

### Achondroplasia

OMIM: 100800  
Gene: *FGFR3*, locus 4p16.3  
Inheritance: autosomal dominant  
Indication: disproportionate short stature, short limbs, frontal bossing, mid face hypoplasia, lumbar lordosis, short fingers  
Material: 3-5 ml EDTA blood  
Methods/TAT: 1<sup>st</sup> tier: sequencing analysis of *FGFR3*, detection of the variants c.1138G>A and c.1138G>C (approx. 2 wks)  
2<sup>nd</sup> tier: sequencing analysis of remaining regions of *FGFR3* (approx. 2 wks)

### Hypochondroplasia

OMIM: 146000  
Gene: *FGFR3*, locus 4p16.3  
Inheritance: autosomal dominant  
Indication: disproportionate short stature, slight lumbar lordosis, reduced extensibility of the elbows, symptoms similar to achondroplasia but milder appearance  
Material: 3-5 ml EDTA blood  
Methods/TAT: 1<sup>st</sup> tier: sequencing analysis of *FGFR3*; detection of the variants c.1620C>A, c.1620C>G, c.1619A>C and c.1619A>G (approx. 2 wks)  
2<sup>nd</sup> tier: sequencing analysis of remaining regions of *FGFR3* (approx. 2 wks)

# Molecular genetic analyses

» Short stature

## ***SHOX* deficiency**

OMIM: 312865  
Gene: *SHOX/SHOXY*, locus Xpter-p22.32/Ypter-p11.2  
Inheritance: pseudo-autosomal dominant  
Indication: idiopathic short stature, Leri-Weill syndrome,  
Langer mesomelic dysplasia  
Material: 3-5 ml EDTA blood  
Methods/TAT: deletion/duplication analysis of *SHOX* and PAR1  
(approx. 2 wks) sequencing analysis of *SHOX*  
(approx. 2 wks)

## **Silver-Russell syndrome (SRS)**

→ please refer to "Complex syndromes"

## **Thanatophoric dysplasia**

OMIM: 187600  
Gene: *FGFR3*, locus 4p16.3  
Inheritance: autosomal dominant  
Indication: usual perinatal or neonatal lethal condition;  
short ribs and narrow thorax, macrocephaly,  
hypotonia, type I characterized by micromelia and  
bent femurs, type II characterized by micromelia,  
straight femurs, cloverleaf skull deformity  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *FGFR3* (approx. 2 wks)

# Molecular genetic analyses

» Thrombophilia/Atherosclerosis

## ■ Thrombophilia/Atherosclerosis

### Angiotensin converting enzyme (ACE)

OMIM: 106180  
Gene: *ACE*, locus 17q23  
Inheritance: polygenic/multifactorial  
Indication: risk assessment for coronary artery disease,  
hypertension  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR, genotyping of the deletion/insertion  
polymorphism in intron 16 of *ACE* (ACE I/D)  
(approx. 2 wks)

### Antithrombin III deficiency (AT3D)

OMIM: 613118  
Gene: *SERPINC1*, locus 1q25.1  
Inheritance: autosomal dominant  
Indication: risk assessment for venous thromboembolic  
disease, severe thrombophilia  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing analysis of *SERPINC1* (approx. 2 wks)  
deletion/duplication analysis of *SERPINC1*  
(approx. 2 wks)

# Molecular genetic analyses

» Thrombophilia/Atherosclerosis

## **β-Fibrinogen**

OMIM: 134830  
Gene: *FGB*, Locus 4q28  
Inheritance: polygenic/multifactorial  
Indication: elevated fibrinogen levels  
Material: 3-5 ml EDTA blood  
Methods/TAT: PCR-RFLP, genotyping of the polymorphism c.-455G>A in the *FGB* gene (approx. 2 wks)

## **Factor V, APC resistance**

OMIM: 188055  
Gene: *F5*, locus 1q23  
Inheritance: autosomal dominant  
Indication: thrombophilia due to activated protein C resistance, family history of thrombosis  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR genotyping of the Leiden variant p.[Arg534Gln], legacy p.Arg506Gln, of *F5*, Sequencing analysis of *F5* (approx. 1 wk), genotyping of the variant p.[His1327Arg], legacy H1299R, HR2 haplotype (approx. 2 wks)

## **Factor XIII, A1 subunit**

OMIM: 134570  
Gene: *F13A1*, locus 6p25.1  
Inheritance: polygenic/multifactorial  
Indication: assessment of the protective effect of the variant p.[Val35Leu], legacy V34L, against myocardial infarction  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *F13A1*, genotyping of the variant p.[Val35Leu], legacy V34L (approx. 2 wks)

# Molecular genetic analyses

» Thrombophilia/Atherosclerosis

## Glycoprotein Ia (Integrin α-2), IIIa (Integrin β-3)

OMIM: 192974, 173470

Genes: *ITGA2*, locus 5q11.2, *ITGB3*, locus 17q21.32

Inheritance: polygenic/multifactorial

Indication: risk assessment for venous thromboembolic disease

Material: 3-5 ml EDTA blood

Methods/TAT: Real-time-PCR genotyping of the variant c.759C>T (legacy c.807C>T) of *ITGA2* (approx. 1 wk)

Real-time-PCR genotyping of the variant HPA-1a/1b c.176C>T; p.Leu59Pro (legacy c.1565C>T; p.Leu33Pro) of *ITGB3* (approx. 1 wk)

## Homocystinemia

OMIM: 236250

Gene: *MTHFR*, locus 1p36.3

Inheritance: autosomal recessive

Indication: homocystinuria, homocysteinemia

Material: 3-5 ml EDTA blood

Methods/TAT: Real-time-PCR genotyping of the variants p.(Ala222Val) and p.(Glu429Ala) of *MTHFR* (approx. 1 wk)

# Molecular genetic analyses

» Thrombophilia/Atherosclerosis

## Plasminogen-Activator-Inhibitor type 1, PAI1

OMIM: 173360  
Gene: *SERPINE1*, locus 7q22.1  
Inheritance: polygenic/multifactorial  
Indication: risk assessment for thrombophilia, usually in combination with *F5* genotyping  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR genotyping of the polymorphism 4G/5G in the promotor region of *SERPINE1* (approx. 1 wk)

## Prothrombin, Factor II

OMIM: 176930  
Gene: *F2*, locus 11q11  
Inheritance: autosomal dominant  
Indication: risk assessment for thrombophilia  
Material: 3-5 ml EDTA blood  
Methods/TAT: Real-time-PCR genotyping of the variant G20210A in the 3'UTR of *F2* (approx. 1 wk)

## Protein C deficiency

OMIM: 176860, 612304  
Gene: *PROC*, locus 2q14.3  
Inheritance: autosomal recessive and autosomal dominant  
Indication: severe thrombophilia  
Material: 3-5 ml EDTA blood  
Methods/TAT: sequencing analysis of *PROC* (approx. 2 wks)  
deletion/duplication analysis of *PROC* (approx. 2 wks)

# Molecular genetic analyses

» Thrombophilia/Atherosclerosis

## Protein C receptor, PROCR

OMIM: 600646  
Gene: *PROCR*, locus 20q11.22  
Inheritance: polygenic/multifactorial  
Indication: venous thromboembolism and myocardial infarction  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *PROCR* (approx. 2 wks)

## Protein Z deficiency

OMIM: 614024  
Gene: *PROZ*, locus 13q34  
Inheritance: polygenic/multifactorial  
Indication: thrombophilia  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *PROZ* (approx. 2 wks)

## Protein Z dependent protease inhibitor

OMIM: 605271  
Gene: *SERPINA10*, locus 14q32.13  
Inheritance: polygenic/multifactorial  
Indication: venous thromboembolism and myocardial infarction  
Material: 3-5 ml EDTA blood  
Methods/TAT: Sequencing analysis of *SERPINA10* (approx. 2 wks)

# Molecular genetic analyses

» Thrombophilia/Atherosclerosis

## Thrombomodulin defect

OMIM: 614486

Gene: *THBD*, locus 20p11.21

Inheritance: polygenic/multifactorial

Indication: venous thromboembolism and myocardial infarction

Material: 3-5 ml EDTA blood

Methods/TAT: Sequencing analysis of *THBD* (approx. 2 wks)

# Molecular genetic analyses

» Uniparental disomies

## ■ Uniparental disomies

### Uniparental disomies 2, 6, 7, 11, 14, 15

- OMIM: *UPD6* 601410, *UPD7* 180860, *UPD11* 130650,  
*UPD14* 608149, *UPD15* 105830, 176270
- Indication: Beckwith-Wiedemann syndrome; Silver-Russell syndrome; PWS/AS; neonatal diabetes
- Material: 3-5 ml EDTA blood of patient and both parents
- Methods/TAT: microsatellite analysis, segregation analysis (approx. 2 wks) or methylation sensitive deletion/duplication analysis (MS-MLPA) (approx. 3 wks)

# Kinship Analyses

» Kinship Analyses

- Loci: 20 polymorphic STRs in the human genome
- Purpose: Paternity and/or maternity testing,  
monozygotic/dizygotic twins
- Material: 3-5 ml EDTA blood or at least two buccal swabs
- Methods/TAT: PCR, microsatellite (STR) analysis (approx.  
2-3 wks)

## Prenatal chromosome diagnostics

### Chromosome analysis from amniotic fluid

Indication: advanced maternal age, conspicuous ultrasound and/or biochemical findings, clarification of conspicuous or unclear results from non-invasive prenatal test (NIPT), fetal malformation, parental chromosomal structural changes, preceding abortion or stillbirth, birth of children with chromosomal changes, birth of children with congenital malformations, mutagen exposure before or during pregnancy, psychological distress, neural tube defects, viral infections of the embryo

Material: 10-15 ml amniotic fluid, sealed original syringe, not centrifuged

Methods/  
TAT: Cell culture of amniotic cells, preparation of chromosomes, G-banded chromosome analysis (approx. 1-2 wks). In case of inconspicuous cytogenetic findings and abnormal fetal ultrasound a chromosomal microarray analysis with the platform Infinium CytoSNP-850K (Illumina) may be carried out (approx. 1-2 wks).

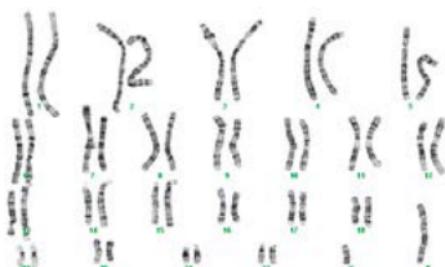


Figure: Inconspicuous male chromosomes (karyotype: 46,XY)

# Cytogenetics and molecular cytogenetics

» Prenatal chromosome diagnostics

## Chromosome analysis from chorionic villi sampling (CVS)

Indication: early prenatal diagnostics (from the 10<sup>th</sup> week of pregnancy), advanced maternal age, preceding abortion or stillbirth, parental chromosomal structural changes, conspicuous first-trimester-screening, conspicuous ultrasound findings, birth of children with congenital malformations, mutagen exposure before or during pregnancy, psychological distress, known familial gene mutations

Material: 10-20 mg chorionic villi, in transport medium or in sterile heparin-added physiological NaCl-solution

Methods/  
TAT: direct preparation or preparation after 24 hr-culture, long-term culture to rule out a placenta-fetus-mosaic and to assess the fine structure of chromosomes, preparation of chromosomes, G-banded chromosome analysis (rapid diagnosis after 6-24 hrs, final diagnosis 1-2 wks) In case of inconspicuous cytogenetic findings and abnormal fetal ultrasound, a chromosomal microarray analysis with the platform Infinium CytoSNP-850K (Illumina) may be carried out (approx. 1-2 wks).

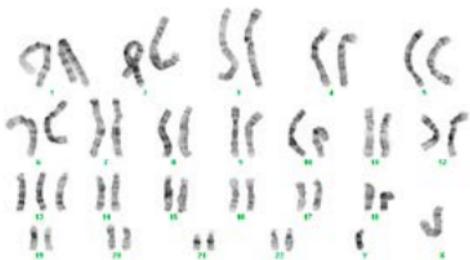


Figure: Male chromosomes with an additional chromosome 13 (trisomy 13) (karyotype: 47,XY,+13)

## ■ Postnatal chromosome diagnostics

### Chromosome analysis from peripheral lymphocytes

Indication: involuntary childlessness, sterility, suspicion of gonosomal chromosomal changes, suspicion of structural chromosomal changes, habitual miscarriages, birth of children with chromosomal abnormalities, conspicuous prenatal karyotype of the unborn child, suspicion of a dysmorphic syndrome indicated by prenatal ultrasound findings, known familial chromosomal changes

Material: 2-5 ml heparin-blood

Methods/TAT: culture of peripheral lymphocytes (48 hrs, 72 hrs), G-banded chromosome analysis (approx. 1-2 wks)

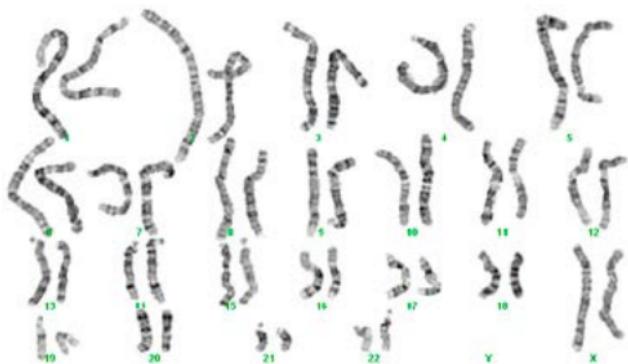


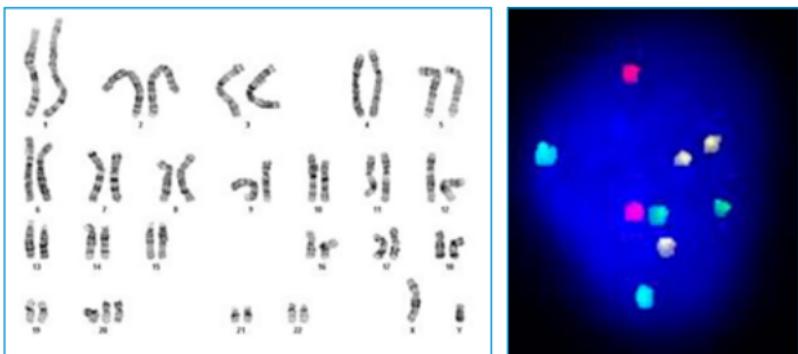
Figure: Inconspicuous female chromosomes (karyotype: 46,XX)

# Cytogenetics and molecular cytogenetics

» Postnatal chromosome diagnostics

## Chromosome analysis from products of conception

- Indication: involuntary childlessness, miscarriages after IVF/  
ICSI, preceding miscarriages, known parental  
chromosomal changes, preceding births of  
children with chromosomal changes
- Material: products of conception, 2-5 ml EDTA-blood from  
the mother
- Methods/TAT: cell culture, G-banded chromosome analysis.  
In case of cell culture failure, a chromosomal  
microarray on fetal DNA is performed. If  
necessary, fluorescence in situ hybridization  
(FISH) with specific probes on native embryonic  
cells is used for exclusion of polyploidy (approx.  
1-8 wks).



Left figure: Verification of a trisomy 22 after fluorescence in situ hybridization in native cells of chorionic villi preparations from products of conception [chromosome 22: gold, chromosome 13: red, chromosome 21: green, chromosome 16: aqua].

Right figure: Male chromosomes with a trisomy 20 [karyotype: 47,XY,+20]

## Molecular cytogenetics

### Fluorescence in situ hybridization (FISH)

#### Rapid prenatal diagnostics

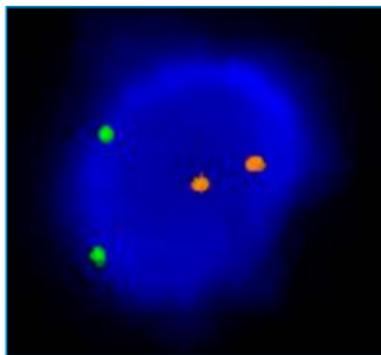
Loci: 13q14 (RB1), 21q22 (DSCR), 18p11-q11 (D18Z1),  
Xp11-q11 (DXZ1), Yp11-q11 (DYZ3)

Indication: advanced maternal age, conspicuous ultrasound  
and/or biochemical findings, clarification of  
conspicuous or unclear results from non-invasive  
prenatal test (NIPT), psychological distress

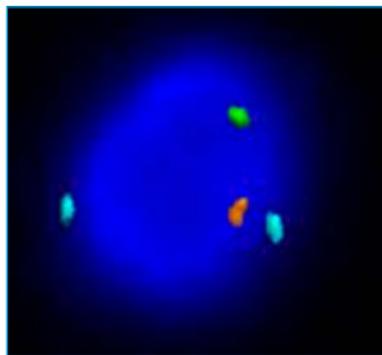
Material: native amniotic cells

Methods/TAT: preparation of native amniotic cells, prescreening  
for the most frequent aneuploidies with  
fluorescence in situ hybridization using specific  
probes for chromosomes 13, 18, 21, X, and Y  
(approx. 4-24 hrs)

The prenatal FISH test is always performed in combination with  
conventional chromosome analysis.



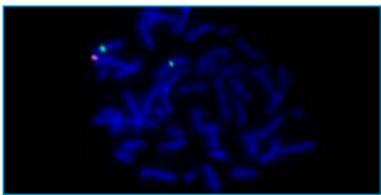
Left figure: Inconspicuous signal pattern in a native amniotic cell after a fluorescence in situ hybridization with specific probes for chromosomes 21 (red) and 13 (green)



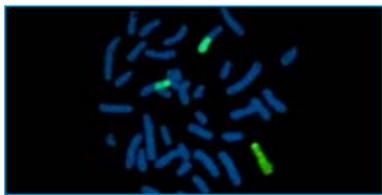
Right figure: Inconspicuous male signal pattern after hybridization with specific probes for chromosomes 18 (aqua), Y (orange), and X (green)

## Microdeletion-diagnostics, screening for mosaicism, chromosome “painting”

- Loci: depending on the indication and preliminary findings, e.g. Wolf-Hirschhorn syndrome (4p16.3), Cri-du-Chat (5p15.2), Williams-Beuren syndrome (7q11), Prader-Willi/Angelman syndrome (15q11-q13), Lissencephaly/Miller-Dieker syndrome (17p13.3), Smith-Magenis syndrome (17p11.2), DiGeorge/Catch22 syndrome (22q11.2), Kallmann syndrome (Xp22.3), sex reversal (Yp11.23), X-linked ichthyosis, and others on request
- Indication: suspected microdeletion syndrome, chromosomal translocation, exclusion of mosaics, complex chromosomal rearrangements, detection of a familial microdeletion (e.g. chromosomal rearrangement with participation of the chromosome region critical for Down syndrome)
- Material: heparin blood, amniotic fluid, chorionic villi, products of conception, buccal swabs, skin biopsy
- Methods/TAT: cell culture, preparation of chromosomes, hybridization with appropriate fluorescence-marked DNA-probes, fluorescence microscopy (approx. 1-5 days).



Left figure: Confirmation of a deletion of the *SHOX*-region (red signal) in the short arm of one of the two X chromosomes using FISH



Right figure: Presentation of a balanced reciprocal translocation between chromosomes 4 and 6 after FISH with a „painting“ probe specific for chromosome 4 (green signal)

# Cytogenetics and molecular cytogenetics

» Molecular cytogenetics

## Subtelomere analysis

- Loci: FISH probes: Subtelomere-regions of all chromosomes
- Indication: Suspicion of chromosomal dysmorphic syndrome of unclear origin, developmental retardation, mental retardation, phenotypic features, habitual miscarriages
- Material: 2-5 ml heparin blood
- Methods/TAT: Fluorescence in situ hybridization with subtelomere-specific probes (whole panel) always in context with a conventional chromosome analysis, single probe diagnostics on request (approx. 1-2 wks)

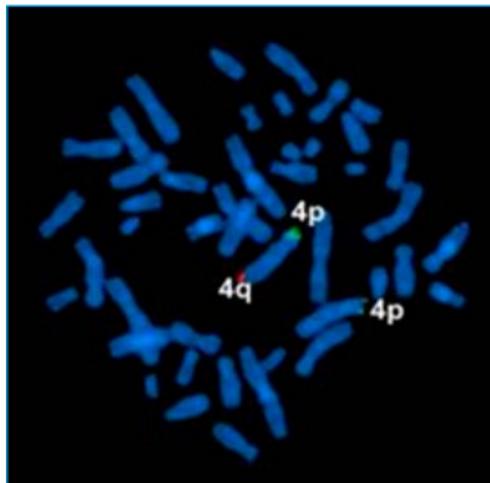


Figure: Confirmation of a deletion in the subtelomeric region of the long arm of one chromosome 4 [red signal in 4q]

# Chromosomal microarray diagnostics

» Molecular cytogenetics

Indication: Mental retardation, pre- and postnatal growth retardation, specific growth anomalies (e.g. microcephaly, microsomia or macrocephaly, macrosomia), two or more facial dysmorphies (e.g. hypertelorism, nose and ear anomalies), congenital anomalies (e.g. heart defect, hand defects, hypospadias), cerebral seizures, behavioural abnormalities

Material: 3-5 ml fresh EDTA blood; To validate detected imbalances an additional heparin blood sample (3-5 ml) might be needed; To clarify the origin of a detected imbalance, parental blood samples (3-5 ml heparin or EDTA blood) might be necessary.

Methods/TAT: high-resolution chromosomal microarray (Infinium CytoSNP-850K, Illumina), detection of genomic imbalances and copy-neutral loss of heterozygosity (LOH) events in the whole genome (approx. 2-8 wks)

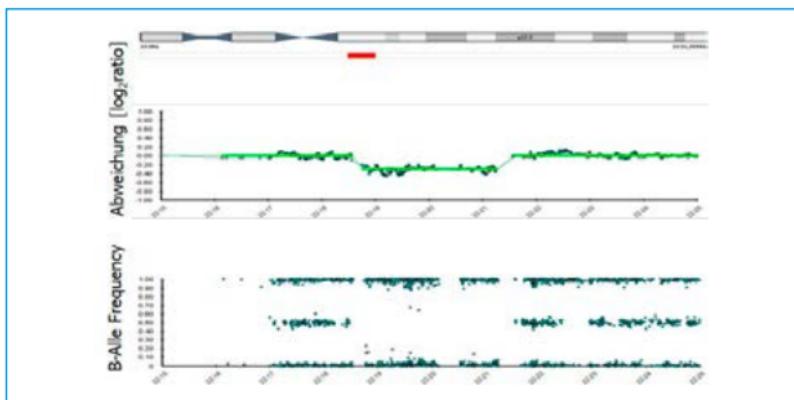


Figure: ideogram of chromosome 19. Heterozygous loss of genetic material, a deviation from the base line.

# Quality assurance

Since the founding of our laboratory in the year 2000 we have established quality control procedures, which not only comply with the highest quality standards but also guarantee a continuous improvement of our quality procedures. An essential part of our quality assurance is the regular participation in internal and external quality assessment schemes. In this way, quality, safety and reliability of our services are assured to be on the highest level for the benefit of the patients.

## Molecular Genetics

The department of Molecular Genetics successfully participates in external quality assessment schemes of the European Molecular Genetics Quality Network (EMQN), the Reference Institute for Bioanalytics (RfB), of GenQA (Genomics Quality Assessment), INSTAND and the Deutsche Gesellschaft für Abstammungsbegutachtung (DGAB). Apart from that we carry out interlaboratory comparisons with cooperating laboratories for certain analyses for which external quality assessment is not available.

- 11p Imprinting disorders (BWS/SRS)
- 5-Flurouracil (5FU)-toxicity (*DPYD*)
- Alpha1-Antitrypsin Deficiency (*SERPINA1*)
- Alport syndrome
- Angiotensin converting enzyme (*ACE*)
- Apolipoprotein B
- Apolipoprotein E
- Autosomal dominant polycystic kidney disease
- AT3 deficiency
- Breast-ovarian cancer, familial
- Celiac disease
- CADASIL
- Charcot-Marie-Tooth disease
- Congenital adrenal hyperplasia
- Cystic fibrosis
- DiGeorge syndrome
- DNA-sequencing (Sanger and NGS methods)

# Quality assurance

- Duchenne muscular dystrophy
- Ehlers-Danlos syndrome
- Fabry disease
- Familial adenomatous polyposis colon cancer
- Factor V
- Factor XIII
- Familial hypercholesterolemia
- *FGFR3* related disorders
- Fragile X syndrome
- Friedreich ataxia
- Gaucher disease
- Gilbert syndrome
- Glucose-6-Phosphate Dehydrogenase Deficiency
- Glycoprotein Ia
- Glycoprotein IIIa
- Hemochromatosis
- Hemophilia A
- Hereditary non-polyposis colon cancer (HNPCC)
- Hereditary pancreatitis
- Hereditary recurrent fevers
- HLAB27
- Homocysteinemia (*MTHFR*)
- Huntington disease
- Hypertrophic cardiomyopathies
- Inflammatory bowel (Crohn) disease (*NOD2*)
- Kinship analyses
- Lactose intolerance (*LCT*)
- Leber's hereditary optic neuropathy
- Long QT syndrome
- Marfan syndrome
- Monogenic diabetes (MODY)
- Multiple Endocrine Neoplasia Type 1 and 2
- Myotonic dystrophy type I
- Neurofibromatosis type 1
- Noonan syndrome
- Osteogenesis Imperfecta
- Osteoporosis
- Phenylketonuria
- Plasminogen-Activator-Inhibitor type 1, PAI1
- Porphyrias
- Prader Willi/Angelman syndrome
- Protein C deficiency
- Prothrombin (Factor II)
- Short Stature Homeobox gene (*SHOX* deficiency)
- Spinal muscular atrophy
- Spinocerebellar ataxias
- $\beta$ -Fibrinogen
- Thalassemia,  $\alpha$ - and  $\beta$
- Thiopurin S-Methyltransferase Deficiency (*TPMT*)
- Von-Hippel-Lindau syndrome
- Wilson disease
- Y-chromosome microdeletions

# Quality assurance

## Cytogenetics and Molecular Cytogenetics

The department of cytogenetics and molecular cytogenetics successfully participates in external quality assessment schemes of the GenQA (Genomics Quality Assessment) and the BVDH e.V. (Association of German Human Genetics Laboratories e.V.).

- GenQA Amniotic Fluid
- GenQA CVS
- GenQA Products of Conception (G-banded only)
- GenQA Blood
- GenQA FISH rapid aneuploidy
- BVDH Labororientierte QS Postnatal
- BVDH Labororientierte QS Pränatal (Amnion)

## Chromosomal Microarray

Regular and successful participation in external quality assessment schemes of GenQA (Genomics Quality Assessment).

- GenQA Products of Conception
- GenQA Constitutinal microarray analysis – postnatal
- GenQA Prenatal Microarray

# Quality assurance

## DAkkS – Accreditation

Our Laboratory is accredited by the "DAkkS" (Deutsche Akkreditierungsstelle GmbH). All molecular Genetic and cytogenetic examinations are accredited according to DIN EN ISO 15189:2014. All examinations for kinship analyses are accredited according to DIN EN ISO/IEC 17025:2005.



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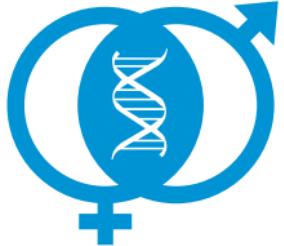
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<i>PROCR</i>	88	<i>TMPO</i>	10
<i>PROK2</i>	17	<i>TNFRSF1A</i>	79
<i>PROKR2</i>	17	<i>TNNI3</i>	10
<i>PROZ</i>	88	<i>TNNT2</i>	10
<i>PRSS1</i>	75	<i>TP53</i>	37, 39
<i>PTEN</i>	37, 42	<i>TPM1</i>	10

<i>TPMT</i> . . . . .	81, 101
<i>TSC1</i> . . . . .	43
<i>TSC2</i> . . . . .	43
<i>UBE3A</i> . . . . .	13
<i>UGT1A1</i> . . . . .	48, 49, 81
<i>UPD11</i> . . . . .	14, 90
<i>UPD14</i> . . . . .	90
<i>UPD15</i> . . . . .	13, 19, 90
<i>UPD6</i> . . . . .	58, 90
<i>UPD7</i> . . . . .	90
<i>UROD</i> . . . . .	60
<i>UROS</i> . . . . .	60
<i>VDR</i> . . . . .	59
<i>VHL</i> . . . . .	43
<i>VWF</i> . . . . .	35
<i>WBSCR</i> . . . . .	22



SYNLAB Medizinisches  
Versorgungszentrum  
**Humane Genetik**

Medical director:

**Dr. med. Dr. rer. nat.**

**Claudia Nevinny-Stickel-Hinzpeter**

Fachärztin für Humangenetik

Lindwurmstraße 23  
80337 München / Germany

T **+49** (0)89. 54 86 29-0

F **+49** (0)89. 54 86 29-243

[info@humane-genetik.de](mailto:info@humane-genetik.de)  
[www.humane-genetik.de](http://www.humane-genetik.de)

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