Zentrum für Kardiovaskuläre
Genetik und Gendiagnostik

Genetic Assessment in Patients with a Large Aorta

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Genetic Assessment in Patients with a Large Aorta

Zentrum für Kardiovaskuläre Genetik und Gendiagnostik

Why?

When?

Where?

Why?

Why is important the genetic assessment of patients with large aorta?

Why is important to know which gene is mutated?

Why is important to know the diseases-causing mutation?

Why is Genetic Testing Important?

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- To make an accurate diagnosis
- To know the genetic background of the aortic disease: Requirement for targeted management and therapy
- To clarify whether the aortic disease is inherited: clarification on unclear phenotype, presymptomatic genetic testing, prenatal diagnosis, and preimplantation genetic diagnosis (in Switzerland only by using polar bodies => applicable for affected females)
- For mutation databases and special studies (genotype-phenotype studies, understanding of the molecular pathogenesis and phenotypic variability of aortic diseases)

Hereditary Aortic Diseases

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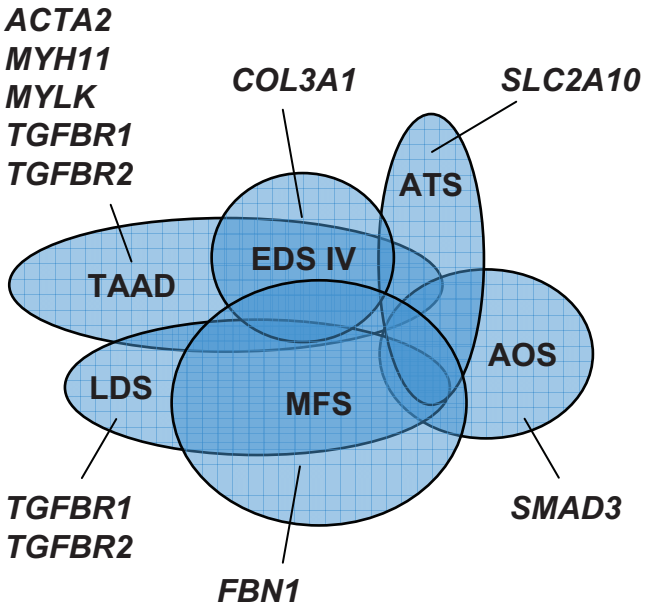

But several other genes have been associated with hereditary aneurysm conditions in humans and/or in mouse models, such as *ACVRL1, COL1A1, COL1A2, COL4A1, COL4A5, EFEMP2, ELN, ENG, FLNA, GAA, GLA, GJA1, JAG1, KLF15, KLF2, LOX, MED12, NF1, NOS3, NOTCH1, NPHP3, PKD1, PKD2, PLOD1, PLOD3, PTPN11, S100A12,* and *TSC2*

Loeys-Dietz aortic aneurysm syndrome (LDS) characterized by arterial aneurysms, tortuous arteries, Marfanoid habitus, and craniofacial features;

Familial thoracic aortic aneurysms and dissections (TAAD), in which the phenotype is essentially restricted to the aorta;

Vascular type of Ehlers–Danlos syndrome (EDS IV), characterized by arterial rupture, thin/translucent skin, extensive bruising, characteristic facial appearance, and intestinal/uterine rupture;

Aneurysms-osteoarthritis syndrome (AOS), a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis;

Autosomal recessive **arterial tortuosity syndrome** (ATS) characterized by elongation, tortuosity, kink, and aneurysm formation in the major arteries.

Hereditary Aortic Diseases

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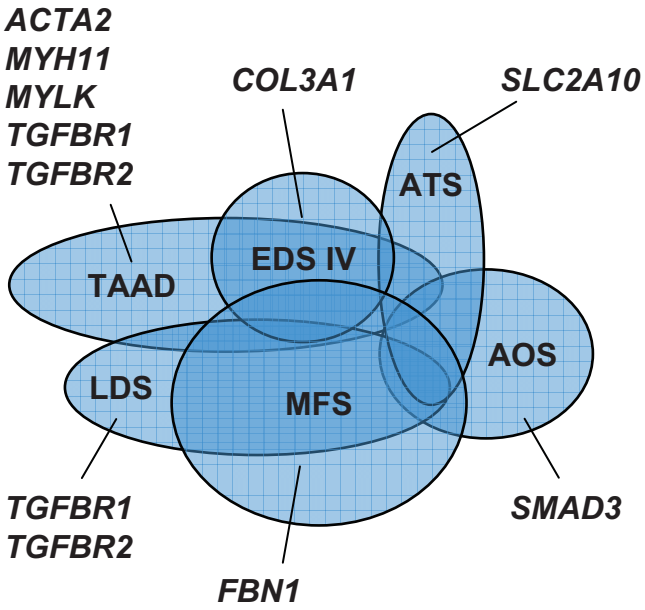

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In the presence of artic aneurysm/dissection and absence of other discriminating clinical features, only genetic testing can distinguish aortic diseases, allowing accurate diagnosis.

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Targeted Management

- Individuals with an aortic disease-causing mutation require regular surveillance and appropriate mode of life
- Individuals with a *TGFBR1/2* mutation (TGF *β* receptor defects) tend to rupture at younger age and smaller aortic diameters, requiring more frequent imaging
- Mutations in the genes *COL3A1, MYLK, and SMAD3* can result in aortic dissection and/or rupture with little to no aortic enlargement
- Individuals with a *COL3A1* mutation require special care (fragile tissue, spontaneous arterial rupture)

Targeted Therapy

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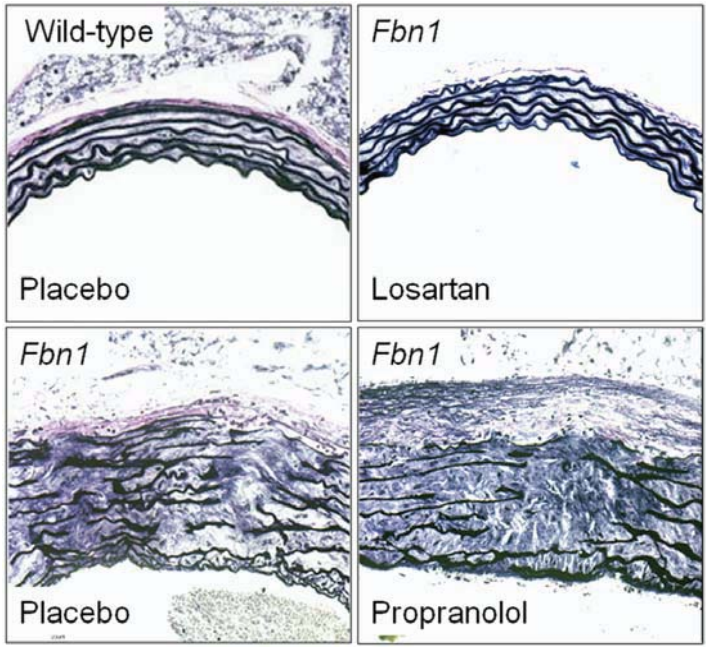
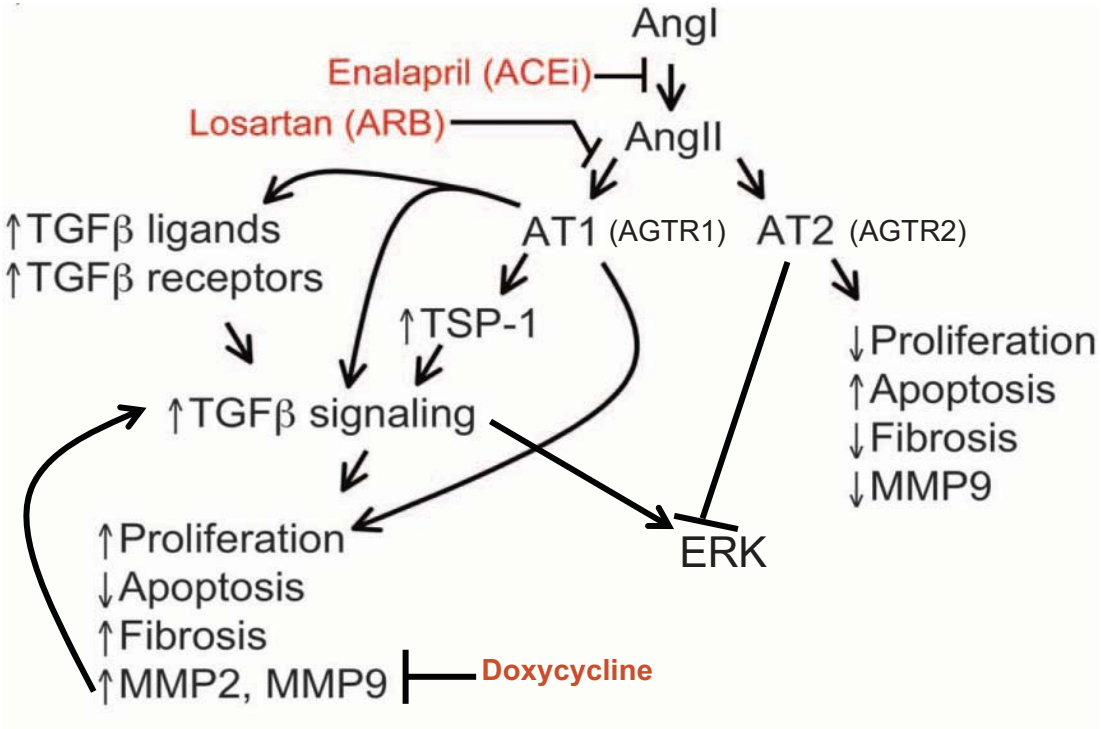


Matt *et al.* 2008, J Thorac Cardiovasc Surg 135:389-94

Postnatal treatment with losartan, propranolol, or placebo in mice with *Fbn1* mutation (p.C1039G). Verhoeff–van Gieson staining.



Whereas patients with mutations leading to increased level of TGF-beta could benefit from a treatment with **losartan**, patients with mutations leading to increased proteolysis in the aortic wall may respond to a drug therapy with **doxycycline** (inhibitor of matrix metalloproteases).

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1. Aortic Aneurysm at Young Age

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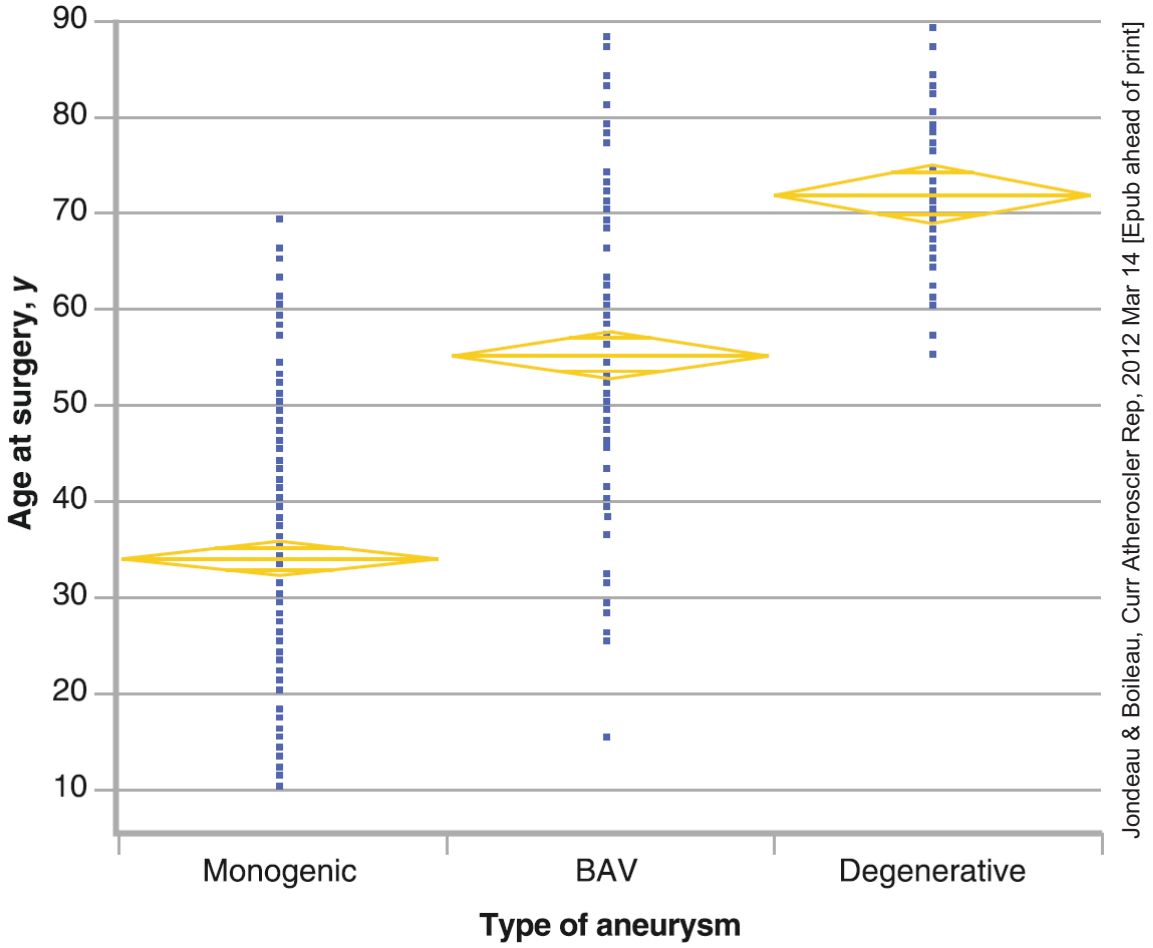

Different groups of patients with thoracic aortic aneurysm according to their age at surgery. BAV—bicuspid aortic valve

2. Clinical Signs Suggesting Aortic Disease

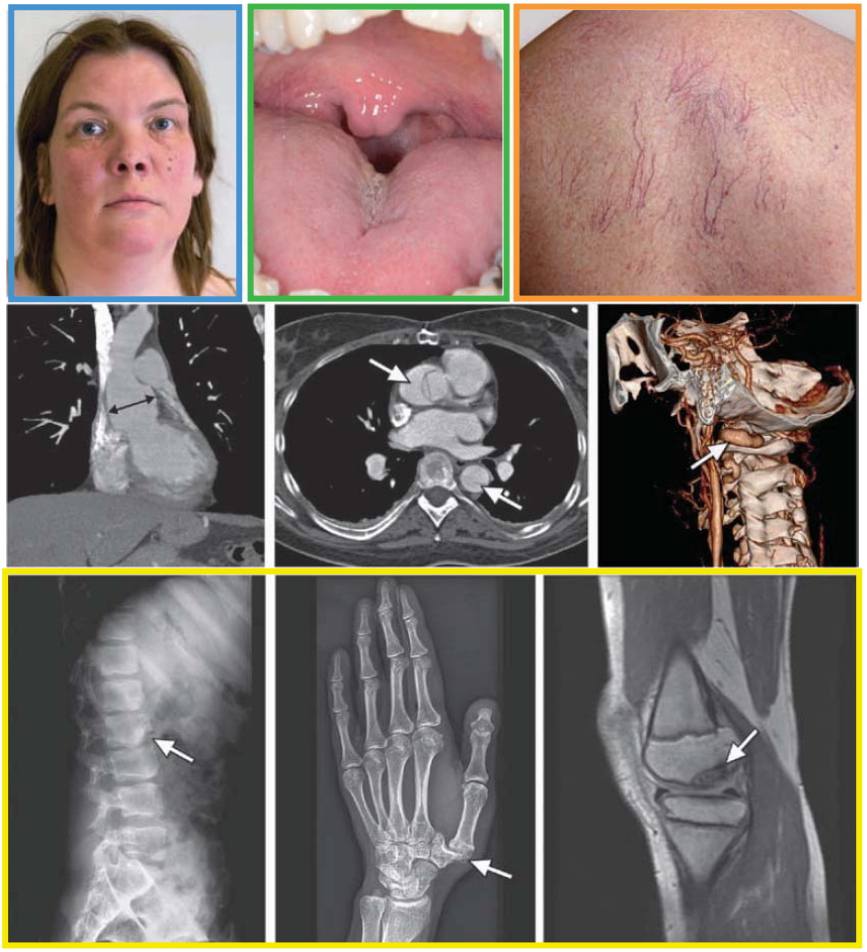

Table 2 Comparison of the main clinical features in aneurysm syndromes

Features	AOS (%) $N = 27$	LDS type I[11] (%) $N = 40$	LDS type II[11] (%) $N = 12$	MFS[19] (%) $N = 1,013$
Cardiovascular				
Aortic root aneurysm/ dissection	58	98	100	77
Aneurysms of other vessels	41	52	73	7
Arterial tortuosity	53	84	67	–
Mitral valve abnormalities	59	29[b]	–	54
Congenital heart disease	9	35	–	–
Other heart diseases	32[a]	–	–	–
Skeletal				
Pectus deformity	16	68	–	59
Scoliosis	43	50	–	53
Joint laxity (Beighton score ≥5)	19	68	100	63
Joints				
Osteoarthritis ≥ 1 joint	100	–	–	–
Intervertebral disc degeneration	90	–	–	–
OCD or meniscal abnormalities	72	–	–	–
Craniofacial				
Hypertelorism	37	90	0	–
Abnormal palate/uvula	58	90	25	–
Craniosynostosis	0	48	0	–
Skin/integument				
Velvety skin	67	28	82	-
Herniae	50	–	36	10
Other				
Ectopia lentis	0	0	–	54

[a]Left ventricular hypertrophy and atrial fibrillation. [b]Based on 16 cases[5]. –, not reported in referred articles.

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AOS, Aneurysms-osteoarthritis syndrome; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome

3. Aortic Aneurysm in Family Members

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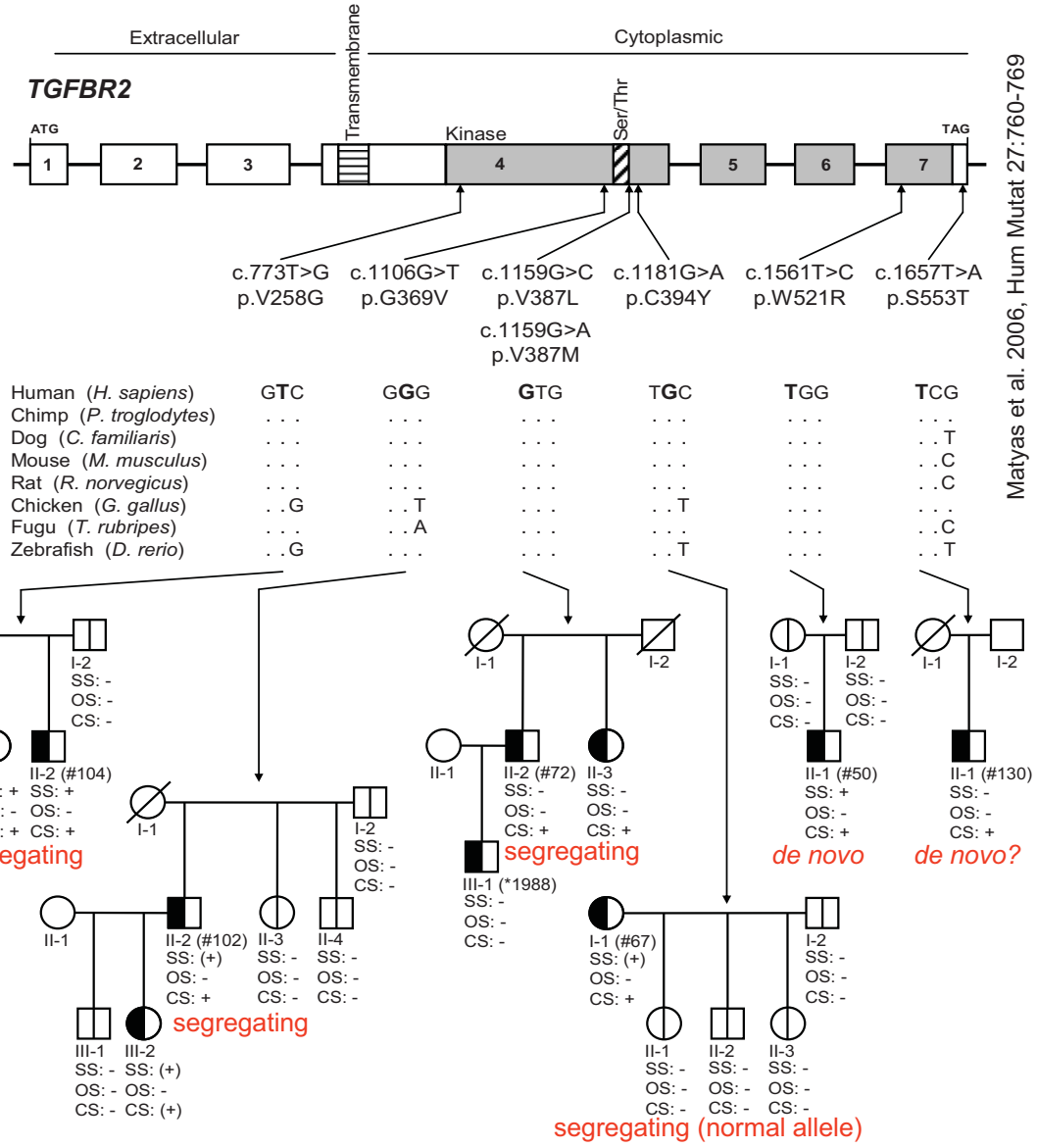

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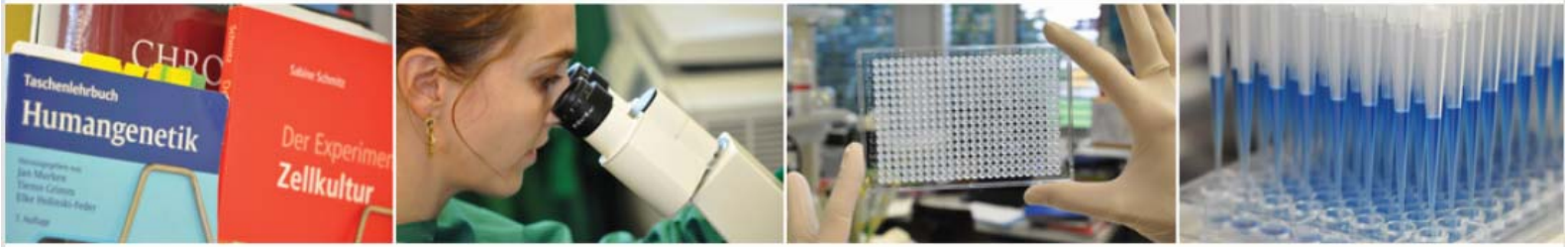
Startseite | Gendiagnostik | Genetische Beratung | Forschung - Research | Lehre | Organisation | Kontakt



Willkommen

Das Zentrum für Kardiovaskuläre Genetik und Gendiagnostik ist schweizweit das erste und einzige Zentrum, welches auf die molekulare Gendiagnostik und die Erforschung genetisch bedingter Aortenkrankheiten und deren klinische Konsequenzen, wie Aneurysmen und Dissektionen, spezialisiert ist.

Unsere Kompetenz beruht auf langjähriger Erfahrung auf diesem Gebiet:

- 1999 – 2002 Kinderspital Zürich (UZH)
- 2003 – 2010 Institut für Medizinische Genetik (UZH)
- 2010 – 2011 Institut für Medizinische Molekulargenetik (UZH)
- ab 2012 Zentrum für Kardiovaskuläre Genetik und Gendiagnostik

Unsere Stärke liegt darin, dass die Haupttätigkeitsbereiche des Zentrums – Forschung, Lehre, Gendiagnostik und interdisziplinäre Beratung – ineinandergreifen, zusammenarbeiten und sich dadurch gegenseitig unterstützen und vorwärtsbringen.

Das Leitbild des Zentrums finden Sie **» hier (pdf)** — Weitere Information **» (pdf)**

Unsere Meinung zu Internet-Gentests **» (pdf)** — Personalisierte Medizin **» (pdf)**

Anschrift

Zentrum für Kardiovaskuläre Genetik und Gendiagnostik
Wagistrasse 25
CH-8952 Schlieren ZH

Direkt zu

- **» Anmeldeformular**
- **» Gendiagnostikangebote**
- **» Polkörperdiagnostik**
- **» Sprechstundenvereinbarung**
- **» Forschungsschwerpunkte**
- **» Publikationen**
- **» Masterarbeitangebote**

Genetikzentrum für Aortenkrankheiten

Das Zentrum für Kardiovaskuläre Genetik und Gendiagnostik arbeitet mit renommierten Institutionen und führenden Klinikern und Forschern in der Schweiz und im Ausland zusammen . **» Mehr**

Aortenkrankheiten – seltene Krankheiten

Aortenkrankheiten, wie beispielsweise das Marfan Syndrom, gehören zu den seltenen Krankheiten. **» Mehr**

www.genetikzentrum.ch | www.orphangenetics.ch | www.orphangene.ch

www.genetikzentrum.ch

Zentrum für Kardiovaskuläre Genetik und Gendiagnostik

Angebot

Anmeldeformular

Untersuchungsmaterial

Polkörperdiagnostik

Links & Downloads

Angebot

Wir bieten molekulargenetische DNA-Untersuchungen bei folgenden Krankheiten und Genen an:

• Acromicric & Geleophysic Dysplasias (» **AD & GD**)	*FBN1*
• Aneurysma Osteoarthrose Syndrom (» **AOS**)	*SMAD3*
• Arterientortuositätssyndrom (» **ATS**)	*SLC2A10*
• Barth Syndrom (» **BTHS**)	*TAZ*
• Birt-Hogg-Dubé Syndrom (» **BHD**) / Pneumothorax	*FLCN*
• Ehlers-Danlos Syndrom Typ IV (» **EDS IV**)	*COL3A1*
• Hirn-Aneurysmata (» **IA**)	*COL3A1, TGFBR3*
• Kongenitale kontrakturale Arachnodaktylie (» **CCA**)	*FBN2*
• Linsenektopie (» **EL**)	*FBN1*
• Loeys-Dietz-Aortenaneurysma Syndrom (» **LDS**)	*TGFBR1, TGFBR2*
• Marfan Syndrom (» **MFS**) » **mehr**	*FBN1*
• Mitralklappenprolaps (» **MVP**)	*FBN1*
• Morbus Fabry (in Zusammenarbeit mit » **IMD** und » **KISPI**) » **mehr**	*GLA*
• Noonan Syndrom (» **NS1**)	*PTPN11*
• Progeroid Syndrom ähnliche Lipodystrophie » **mehr**	*FBN1*
• Shprintzen-Goldberg Syndrom (» **SGS**)	*FBN1, TGFBR1, TGFBR2*
• Stiff-Skin Syndrom (» **SSS**)	*FBN1*
• Thorakale Aneurysmen und Dissektionen der Aorta (» **TAAD**)	*FBN1, TGFBR1, TGFBR2, ACTA2, MYH11, MYLK, EFEMP2*
• Thorakales Aortenaneurysma mit Ductus arteriosus persistens (» **PDA**)	*MYH11*
• Triple-X Syndrom (» **47,XXX**)	47,XXX
• Turner Syndrom (» **TS**)	45,X
• XXY Syndrom (» **Klinefelter Syndrom**) / XYY Syndrom (» **47,XYY**)	47,XXY / 47,XYY
• Weill-Marchesani Syndrom, autosomal-dominant (» **WMS**)	*FBN1*

Weitere Gendiagnostikangebote:

- Kopplungsuntersuchungen bei Familien mit einer segregierenden Krankheit
- Polkörperdiagnostik (PKD; nur nach Voranmeldung) » **mehr**
- Nach Rücksprache können wir DNA-Untersuchungen auch für weitere monogene Krankheiten anbieten

Stiftung für Menschen mit seltenen Krankheiten

www.stiftung-seltene-krankheiten.ch

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Leiter: PD Dr. Gabor Matyas, FAMH Medizinische Genetik

Stellvertreterin: Caroline Henggeler, FAMH Medizinische Genetik

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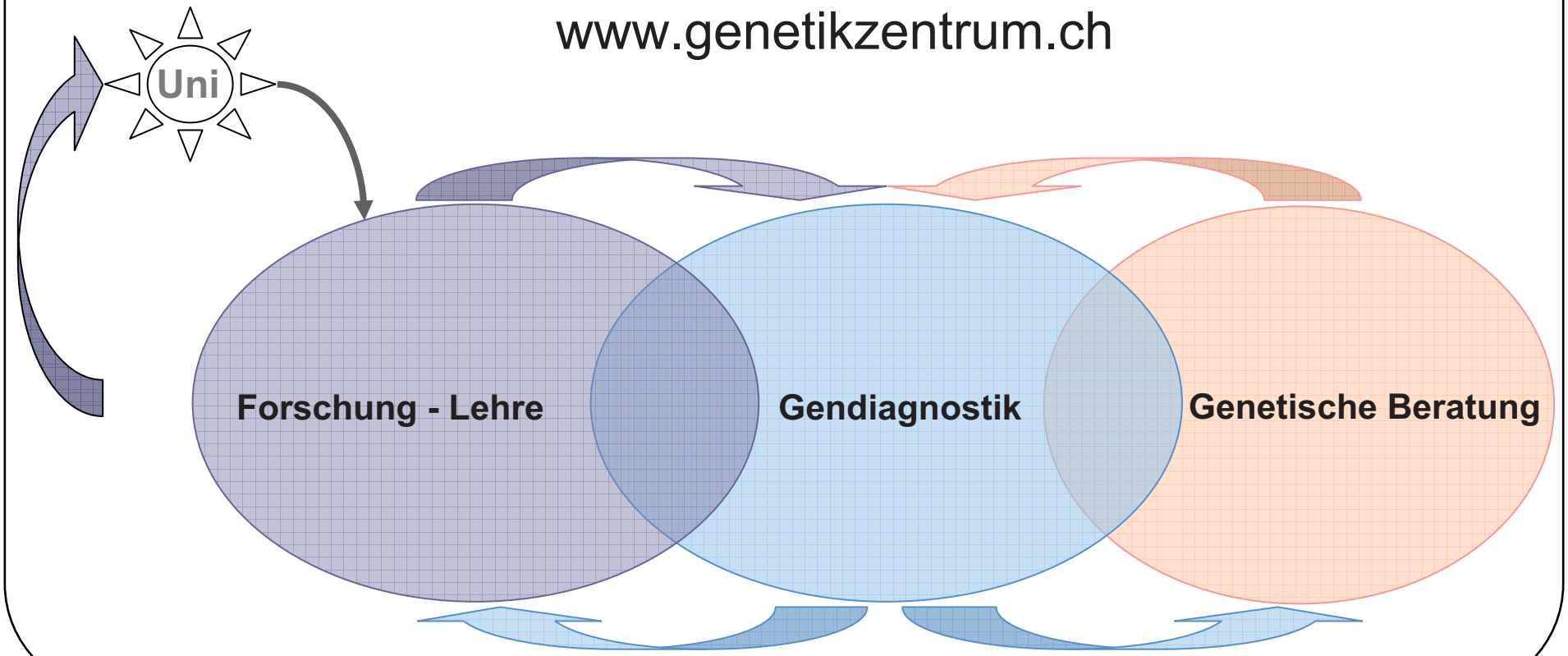

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Thank you for your attention!

Our opinion about internet gene tests:
http://www.genetikzentrum.ch/view/userfiles/files/Sonntag_Nr4_Interview.pdf

«Die Zukunft der Medizin liegt in der Genetik:
Es ist immer offensichtlicher, dass sich die Medizin in Prävention, Diagnose und Therapie an der Genetik orientieren muss.»
(Prof. Dr. med. Jan Murken, Klinikum der Universität München)