AWMGS
All Wales Medical Genomics Service

Aortopathy (Marfan, Aortopathy and Connective Tissue Disorders) 23 Gene Panel

Background

This panel includes genes where mutations can cause various disorders relating to defects in the connective tissue; the tissue that connects, supports, binds or separates other tissues or organs. This group of disorders have different combinations of symptoms with varying degrees of severity, but they all involve medical problems affecting the heart. The syndromes covered by this panel include Marfan, and various forms of Loeys-Dietz and Ehlers-Danlos (we also offer a separate panel for Ehlers-Danlos, which covers all forms of this condition). Inheritance patterns vary depending upon the specific type and the mutated gene involved, although many are autosomal dominant which means that there is a 50% chance of a parent with the gene mutation passing it onto their child. See the support links below for more details about this group of syndromes.

Genes

ACTA2	COL5A1	FBN1	MYH11	SLC2A10	TGFB3
COL1A1	COL5A2	FBN2	MYLK	SMAD3	TGFBR1
COL1A2	EFEMP2	FLNA	NOTCH1	SMAD4	TGFBR2
COL3A1	ELN	MED12	SKI	TGFB2	

Recommended Clinical Referral Criteria

- Patients with relevant symptoms
- Family history of condition

Molecular Analysis

Mutation screen:
Next Generation Sequencing (NGS) –
target genes are enriched using an Illumina TruSight One assay and sequenced on an Illumina HiSeq

Family follow-up: Testing for known familial mutations in any of the genes in the panel

Test (Price available on request)	TAT
Aortopathy disorders panel screen	84 CD
Testing for known familial mutations (per gene listed above)	42 CD

** This TAT may be exceeded if primers have to be ordered; if a 20-day TAT is important for your case please give prior notification to the laboratory

Contact Details
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Accredited to ISO 15189:2012
(8988)

Sample Requirements
Blood – 5ml in EDTA (1ml neonates/infants);
please contact lab prior to sending a prenatal sample.
Please label samples with three identifiers and date of collection

All samples must be accompanied by request form

Consent for testing & DNA storage is assumed when request for test received

Links

Orphanet
http://www.orpha.net/
EDDNAL
http://www.eddnal.com/
OMIM
http://www.omim.org/
Genetic Test Registry
http://www.ncbi.nlm.nih.gov/gtr/
Support
Marfan Association UK
http://www.marfan-association.org.uk

This NGS assay aims to cover the coding sequence and 5bp of flanking intron to a minimum vertical depth of 20X. Where this is not achieved (i.e. % horizontal coverage is less than 100%) due to design or patient-specific gaps then Sanger sequencing is available for some genes on request. The selection of gaps to be filled is guided by the patient's phenotype and by interaction with the referring clinician.

Gene	OMIM No	Condition/s (OMIM/s)	Mode of inheritance
ACTA2	102620	Aortic aneurysm, familial thoracic 6; AAT6 (611788); Multisystemic smooth muscle dysfunction syndrome (613834); Moyamoya disease 5; MYMY5 (614042)	AD
COL1A1	120150	Osteogenesis imperfect, type I; OI1 (166200); Osteogenesis imperfect, type II; OI2 (166210)	AD
COL1A2	120160	Osteogenesis imperfect, type II; OI2 (166210)	AD
COL3A1	120180	Ehlers-Danlos syndrome, type IV; EDS IV (130050)	AD
COL5A1	120215	Ehlers-Danlos syndrome, classic type; EDS (130000)	AD
COL5A2	120190	Ehlers-Danlos syndrome, classic type; EDS (130000)	AD
EFEMP2	604633	Cutis laxa, autosomal recessive, type IB; ARCL1B (614437)	AR
ELN	130160	Cutis laxa, AD; ADCL1 (123700); Supravalvar aortic stenosis; SVAS (185500)	AD
FBN1	134797	Marfan syndrome; MFS (154700); MASS syndrome (604308)	AD
FBN2	612570	Contractural arachnodactyly, congenital; CCA (121050)	AD
FLNA	300017	Cardiac valvular dysplasia, X-linked; CVD1 (314400); Frontometaphyseal dysplasia 1; FMD1 (305620); Heterotopia, periventricular (300049)	XLR/D
MED12	300188	Lujan-Fryns syndrome (309520)	XLR
MYH11	160745	Aortic aneurysm, familial thoracic 4; AAT4 (132900)	AD

MYLK	600922	Aortic aneurysm, familial thoracic 7; AAT7 (613780)	AD
NOTCH1	190198	Adams-Oliver syndrome 5; AOS5 (616028); Aortic valve disease 1; AOVD1 (109730)	AD
SKI	164780	Shprintzen-Goldberg syndrome; SGS (182212)	AD
SLC2A10	606145	Arterial tortuosity syndrome; ATS (208050)	AR
SMAD3	603109	Loeys-Dietz syndrome 3; LDS3 (613795)	AD
SMAD4	600993	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; JPHT (175050); Myhre syndrome; MYHRS (139210)	AD
TGFB2	190220	Loeys-Dietz syndrome 4; LDS4 (614816)	AD
TGFB3	190230	Loeys-Dietz syndrome 5; LDS5 (615582); Arrhythmogenic right ventricular dysplasia 1; ARVD1 (107970)	AD
TGFBR1	190181	Loeys-Dietz syndrome 1; LDS1 (609192)	AD
TGFBR2	190182	Loeys-Dietz syndrome 2; LDS2 (610168)	AD