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Connective Tissue Disorder Next Generation Sequencing (NGS) Panels: Information for Ordering Providers

Background

Heritable connective tissue disorders are a group of conditions caused by genetic variants that impact the development and maintenance of the extracellular matrix, which provides support and structure throughout the body. Connective tissue represents the most abundant tissue type in the body, and is comprised of proteins such as collagen and elastin. Due to the widespread role of connective tissue in most organs and body systems, connective tissue disorders can present with a diverse array of cutaneous, ocular, skeletal, cardiovascular, and craniofacial features.[1]

The panels listed below include genes related to aortopathies and other groups of heritable connective tissue disorders. Associated clinical features or genetic conditions are listed for each gene and the inheritance pattern for each condition (AD – autosomal dominant, AR – autosomal recessive, XL – X-linked).

***Please be advised that order restrictions apply for the following panels. Carrier testing/presymptomatic testing is currently restricted to Clinical Genetics. Testing for symptomatic patients is restricted based on clinical specialty. Please refer to the APL Test Directory for specific ordering restrictions for each panel*.**

Aortopathy Panels (Core and Extended)

Aortopathies are a group of disorders that affect the structure of the aorta, conferring an increased susceptibility to aortic dilation, aneurysm, and/or dissection. An aortic aneurysm is defined as localized dilation of the aorta to a diameter that is 50% greater than normal, while an aortic dissection refers to a tear in the inner layer of the aorta, which can lead to aortic rupture and sudden cardiac death.[2] Aortic aneurysms and dissections can occur in the thoracic aorta or in the abdominal aorta. Abdominal aortic aneurysms are more common in the general population, and typically have a multifactorial etiology related to factors such as age and hypertension. In contrast, approximately 20% of thoracic aortic aneurysms and dissections have a genetic etiology, including both syndromic and non-syndromic conditions.[2] Marfan syndrome is the most common syndromic aortopathy, and is associated with an increased risk for aortic aneurysm and dissection, as well as variable skeletal, cutaneous, ocular, and craniofacial features.[3] Other genetic syndromes associated with aortic disease include vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, and Shprintzen-Goldberg syndrome. Familial thoracic aortic aneurysms and dissections (FTAAD) represents a group of non-syndromic inherited aortopathies, in which aortic disease is the primary feature.[2,3]

Aortopathy Panel, Core

Genes	Associated clinical features or genetic conditions[4]	Inheritance
ACTA2	Aortic aneurysm, familial thoracic 6; Moyamoya disease 5; Multisystemic smooth muscle dysfunction syndrome	AD
BGN	Meester-Loeys syndrome; Spondyloepimetaphyseal dysplasia, x-linked	XL
COL3A1	Ehlers-Danlos syndrome, vascular type; Polymicrogyria with or without vascular-type EDS	AD/AR
EFEMP2	Cutis laxa, autosomal recessive, type 1B	AR
FBN1	Acromicric dysplasia; Ectopia lentis, familial; Geleophysic dysplasia 2; Marfan lipodystrophy syndrome; Marfan syndrome; MASS syndrome; Stiff skin syndrome; Weill-Marchesani syndrome 2	AD
FBN2	Contractural arachnodactyly, congenital; Macular degeneration, early-onset	AD
FLNA	Cardiac valvular dysplasia, x-linked; Congenital short bowel syndrome; Frontometaphyseal dysplasia 1; Heterotopia, periventricular, 1; Intestinal pseudoobstruction, neuronal; Melnick-Needles syndrome; Otopalatodigital syndrome, type 1; Otopalatodigital syndrome, type 2; Terminal osseous dysplasia	XL
FOXE3	Anterior segment dysgenesis 2, multiple subtypes; Cataract 34, multiple types	AD/AR

Genes	Associated clinical features or genetic conditions[4]	Inheritance
LOX	Aortic aneurysm, familial thoracic 10	AD
MAT2A	Thoracic aortic aneurysms, Complement system	AD/AR
MFAP5	Aortic aneurysm, familial thoracic 9	AD
MYH11	Aortic aneurysm, familial thoracic 4	AD
MYLK	Aortic aneurysm, familial thoracic 7; Megacystic-microcolon-intestinal hypoperistalsis syndrome	AD/AR
NOTCH1	Adams-Oliver syndrome 5; Aortic valve disease 1	AD
PRKG1	Aortic aneurysm, familial thoracic 8	AD
SKI	Shprintzen-Goldberg syndrome	AD
SLC2A10	Arterial tortuosity syndrome	AR
SMAD2	Loeys-Dietz syndrome; Congenital heart defects, nonsyndromic	AD
SMAD3	Loeys-Dietz syndrome	AD
SMAD4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; Myhre syndrome; Polyposis, juvenile intestinal	AD
TGFB2	Loeys-Dietz syndrome	AD
TGFB3	Arrhythmogenic right ventricular dysplasia 1; Loeys-Dietz syndrome	AD
TGFBR1	Loeys-Dietz syndrome	AD
TGFBR2	Loeys-Dietz syndrome	AD

Aortopathy Panel, Extended

Genes	Associated clinical features or genetic conditions[4]	Inheritance
ACTA2	Aortic aneurysm, familial thoracic 6; Moyamoya disease 5; Multisystemic smooth muscle dysfunction syndrome	AD
ARIH1	Aortic aneurysm, familial thoracic	AD
BGN	Meester-Loeys syndrome; Spondyloepimetaphyseal dysplasia, x-linked	XL
CBS	Homocystinuria, B6-responsive and nonresponsive types; Thrombosis, hyperhomocysteinemic	AR
COL3A1	Ehlers-Danlos syndrome, vascular type; Polymicrogyria with or without vascular-type EDS	AD/AR
COL5A1	Ehlers-Danlos syndrome, classic type, 1	AD
COL5A2	Ehlers-Danlos syndrome, classic type, 2	AD
EFEMP2	Cutis laxa, autosomal recessive, type 1B	AR
FBLN5	Cutis laxa, autosomal recessive, type 1A; Macular degeneration, age-related, 3; Neuropathy, hereditary, with or without age-related macular degeneration	AD/AR
FBN1	Acromicric dysplasia; Ectopia lentis, familial; Geleophysic dysplasia 2; Marfan lipodystrophy syndrome; Marfan syndrome; MASS syndrome; Stiff skin syndrome; Weill-Marchesani syndrome 2	AD
FBN2	Contractural arachnodactyly, congenital; Macular degeneration, early-onset	AD
FLNA	Cardiac valvular dysplasia, x-linked; Congenital short bowel syndrome; Frontometaphyseal dysplasia 1; Heterotopia, periventricular, 1; Intestinal pseudoobstruction, neuronal; Melnick-Needles syndrome; Otopalatodigital syndrome, type 1; Otopalatodigital syndrome, type 2; Terminal osseous dysplasia	XL
FOXE3	Anterior segment dysgenesis 2, multiple subtypes; Cataract 34, multiple types	AD/AR
LOX	Aortic aneurysm, familial thoracic 10	AD
MAT2A	Thoracic aortic aneurysms, Complement system	AD/AR
MED12	Lujan-Fryns syndrome; Ohdo syndrome, x-linked; Opitz-Kaveggia syndrome	XL

Genes	Associated clinical features or genetic conditions[4]	Inheritance
MFAP5	Aortic aneurysm, familial thoracic 9	AD
MYH11	Aortic aneurysm, familial thoracic 4	AD
MYLK	Aortic aneurysm, familial thoracic 7; Megacystic-microcolon-intestinal hypoperistalsis syndrome	AD/AR
NOTCH1	Adams-Oliver syndrome 5; Aortic valve disease 1	AD
PLOD1	Ehlers-Danlos syndrome, kyphoscoliotic type, 1	AR
PRKG1	Aortic aneurysm, familial thoracic 8	AD
SKI	Shprintzen-Goldberg syndrome	AD
SLC2A10	Arterial tortuosity syndrome	AR
SMAD2	Loeys-Dietz syndrome; Congenital heart defects, nonsyndromic	AD
SMAD3	Loeys-Dietz syndrome	AD
SMAD4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; Myhre syndrome; Polyposis, juvenile intestinal	AD
TGFB2	Loeys-Dietz syndrome	AD
TGFB3	Arrhythmogenic right ventricular dysplasia 1; Loeys-Dietz syndrome	AD
TGFBR1	Loeys-Dietz syndrome	AD
TGFBR2	Loeys-Dietz syndrome	AD

Ehlers-Danlos Syndrome Panel

Ehlers-Danlos syndrome (EDS) refers to a group of connective tissue disorders that result from defects in collagen proteins, which are an important component of skin, ligaments, blood vessels, and several other body systems. EDS is generally associated with joint laxity, skin hyperextensibility, poor wound healing, and variable cardiovascular, craniofacial, and skeletal features. EDS has been classified into several different subtypes based on clinical presentation and genetic etiology. Classic EDS is characterized by cutaneous features such as hyperextensible skin and poor wound healing, as well as generalized joint hypermobility and a susceptibility to dislocations. Vascular EDS is associated with an increased risk for arterial aneurysm and dissection, intestinal rupture, and uterine rupture during pregnancy. Other types of EDS include hypermobile EDS, kyphoscoliotic EDS, and arthrochalasia EDS.[5,6]

Genes	Associated clinical features or genetic conditions[4]	Inheritance
COL1A1	Caffey disease; Ehlers-Danlos syndrome, arthrochalasia type, 1; Osteogenesis Imperfecta (type I-IV)	AD
COL1A2	Ehlers-Danlos syndrome, arthrochalasia type, 2; Ehlers-Danlos syndrome, cardiac valvular type; Osteogenesis imperfecta (type II-IV)	AD/AR
COL3A1	Ehlers-Danlos syndrome, vascular type; Polymicrogyria with or without vascular-type EDS	AD/AR
COL5A1	Ehlers-Danlos syndrome, classic type, 1	AD
COL5A2	Ehlers-Danlos syndrome, classic type, 2	AD
PLOD1	Ehlers-Danlos syndrome, kyphoscoliotic type, 1	AR

Loeys-Dietz Syndrome Panel

Loeys-Dietz syndrome (LDS) is a connective tissue disorder caused by defects in the transforming growth factor beta (TGF-β) signaling pathway, which plays an important role in the production and maintenance of the extracellular matrix. LDS is generally characterized by cardiovascular, skeletal, craniofacial, and cutaneous features, and variability in clinical presentation can be seen both within and between families. Vascular complications in LDS can include dilation of the aortic root and increased risk for aortic aneurysm and dissection. Compared to other connective tissue disorders such as Marfan syndrome, individuals with LDS are prone to aortic dissections at smaller aortic diameters and at younger ages. In addition, arterial aneurysms and dissections are not limited to the thoracic aorta, but can occur throughout the aortic tree and may involve the cerebral and abdominal arteries. In addition to vascular features, individuals with LDS may have skeletal abnormalities including pectus excavatum or carinatum, scoliosis, joint laxity and hypermobility, and clubfoot. LDS can also be associated with characteristic craniofacial features, including widely-spaced eyes, bifid uvula, cleft palate, and craniosynostosis.[3,5]

Genes	Associated clinical features or genetic conditions[4]	Inheritance
FBN1	Acromicric dysplasia; Ectopia lentis, familial; Geleophysic dysplasia 2; Marfan lipodystrophy syndrome; Marfan syndrome; MASS syndrome; Stiff skin syndrome; Weill-Marchesani syndrome 2	AD
SMAD2	Loeys-Dietz syndrome; Congenital heart defects, nonsyndromic	AD
SMAD3	Loeys-Dietz syndrome	AD
TBFB2	Loeys-Dietz syndrome	AD
TGFB3	Arrhythmogenic right ventricular dysplasia 1; Loeys-Dietz syndrome	AD
TGFBR1	Loeys-Dietz syndrome	AD
TGFBR2	Loeys-Dietz syndrome	AD

Osteogenesis Imperfecta Panel

Osteogenesis imperfecta (OI) refers to a heterogeneous group of disorders that primarily affect connective tissue within the bones. OI is characterized by bone fragility and an increased susceptibility to fractures, and can also include features such as blue sclerae, hearing loss, and dentinogenesis imperfecta. Approximately 85% of all OI cases are caused by pathogenic variants in the *COL1A1* and *COL1A2* genes, which produce type I collagen.[7] *COL1A1/COL1A2*-related OI can vary greatly in severity and clinical presentation, and is generally classified into four main types: classic non-deforming OI with blue sclera (type I), perinatally lethal OI (type II), progressively deforming OI (type III), and common variable OI with normal sclerae (type IV). Classic non-deforming OI represents the mildest end of the spectrum, in which affected individuals are predisposed to fractures, but have near-normal height and lifespan. In contrast, more severe forms of OI can be associated with short stature, bone deformity, and perinatal death. In addition to *COL1A1* and *COL1A2*, pathogenic variants in several other genes involved in type I collagen processing, bone mineralization, and osteoblast differentiation can cause autosomal dominant or autosomal recessive OI of varying severity.[5,7] Other genetic disorders, such as perinatal hypophosphatasia (caused by pathogenic variants in the *ALPL* gene), have overlapping clinical features with OI including bone deformity and fracture.[5]

Genes	Associated clinical features or genetic conditions[4]	Inheritance
ALPL	Hypophosphatasia (adult, childhood, infantile); Odontohypophosphatasia	AD/AR
BMP1	Osteogenesis imperfecta, type XIII	AR
COL1A1	Caffey disease; Ehlers-Danlos syndrome, arthrochalasia type, 1; Osteogenesis Imperfecta (type I-IV)	AD
COL1A2	Ehlers-Danlos syndrome, arthrochalasia type, 2; Ehlers-Danlos syndrome, cardiac valvular type; Osteogenesis imperfecta (type II-IV)	AD/AR
CRTAP	Osteogenesis imperfecta, type VII	AR

Genes	Associated clinical features or genetic conditions[4]	Inheritance
FKBP10	Bruck syndrome 1; Osteogenesis imperfecta, type XI	AR
IFITM5	Osteogenesis imperfecta, type V	AD
LRP5	Exudative vitreoretinopathy 4; Hyperostosis, endosteal; Osteopetrosis, autosomal dominant 1; Osteoporosis-pseudoglioma syndrome; Osteosclerosis; Polycystic liver disease 4 with or without kidney cysts; van Buchem disease, type 2	AD/AR
P3H1	Osteogenesis imperfecta, type VIII	AR
PLOD2	Bruck syndrome 2	AR
PPIB	Osteogenesis imperfecta, type IX	AR
SERPINF1	Osteogenesis imperfecta, type VI	AR
SERPINH1	Osteogenesis imperfecta, type X	AR
TMEM38B	Osteogenesis imperfecta, type XIV	AR
WNT1	Osteogenesis imperfecta, type XV	AD/AR

Stickler Syndrome Panel

Stickler syndrome is a multisystem connective tissue disorder which can include variable auditory, ocular, orofacial, and skeletal features. Many individuals with Stickler syndrome have a characteristic facial appearance, which may include malar hypoplasia, a broad or flat nasal bridge, retrognathia or micrognathia, and cleft palate. Non-progressive high myopia is a common feature of Stickler syndrome, as well as vitreous abnormalities and an increased risk for retinal detachment. Stickler syndrome is also associated with both high frequency sensorineural hearing loss as well as conductive hearing loss, which may be progressive in some individuals. Affected individuals can also have skeletal and joint problems, including early onset arthritis, scoliosis, and spondylolisthesis. Joint laxity has been reported in younger individuals, but generally improves or resolves with age. Stickler syndrome can be classified into various types based on genetic etiology and clinical presentation, and most types of Stickler syndrome follow an autosomal dominant inheritance pattern.[5,6]

Genes	Associated clinical features or genetic conditions[4]	Inheritance
COL11A1	Fibrochondrogenesis 1; Marshall syndrome; Stickler syndrome, type II	AD/AR
COL11A2	Deafness, autosomal dominant 13; Deafness autosomal recessive 53; Fibrochondrogenesis 2; Otospondylomegaepiphyseal dysplasia, autosomal dominant; Otospondylomegaepiphyseal dysplasia, autosomal recessive	AD/AR
COL1A1	Caffey disease; Ehlers-Danlos syndrome, arthrochalasia type, 1; Osteogenesis Imperfecta (type I-IV)	AD
COL1A2	Ehlers-Danlos syndrome, arthrochalasia type, 2; Ehlers-Danlos syndrome, cardiac valvular type; Osteogenesis imperfecta (type II-IV)	AD/AR
COL2A1	Achondrogenesis, type II or hypochondrogenesis; Avascular necrosis of the femoral head; Czech dysplasia; Kniest dysplasia; Legg-Calve-Perthes disease; Osteoarthritis with mild chondrodysplasia; Platyspondylic skeletal dysplasia, Torrance type; SED congenital; SMED Strudwick type; Spondyloepiphyseal dysplasia, Stanescu type; Spondyloperipheral dysplasia; Stickler syndrome, type I; Vitreoretinopathy with phalangeal epiphyseal dysplasia	AD

Requisition forms, contact information and other resources can be found at Genetics and Genomics

Contact Information

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References

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