This study shows that truncating mutations in TTN induce a DCM that is less severe at presentation and more amenable to standard therapy than either LMNA mutation induced DCM or TTN/LMNAneg DCM.

PS05.37

Assessment of the mechanical stability of the aorta in a mouse model of Ehlers-Danlos syndrome vascular type (EDS IV)

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Introduction: EDS IV is an autosomal dominant connective tissue disorder caused by mutations in the COL3A1 gene and associated with an increased risk for aortic rupture. So far, only disease management and treatment of symptoms are available. Haploinsufficient mice of a recently described novel mouse model of Col3a1 show reduced mechanical stability of the aorta and spontaneous death (~28% of cases) due to aortic rupture similar to the human EDS IV phenotype. Our goal was to characterize the mechanical stability of the aorta in this mouse model compared to wild-type mice.
Methods: 1.5-mm-long sections of aortic arch as well as ascending and descending aorta from Col3a1 mice were mounted on two 200-µm diameter stainless steel wires on a TissuePuller (Danish Myo Technology) and stretched radially until tissue damage, thereby continuously recording the stretching force (in mN).
Results: Maximum force at tissue damage was significantly lower in heterozygous Col3a1 mice compared to age- and gender-matched wild-type animals in both the ascending and descending parts of the aorta. For both genotypes, the mechanical stability of the aorta was decreasing, with increasing distance from the heart.
Conclusions: We developed a protocol for the assessment of the mechanical stability of mice aorta, which is suitable to detect significant differences between heterozygous and wild-type Col3a1 mice. Our results open the way to test pharmacological substances for their potential to increase the mechanical stability of the aorta with the goal to find a targeted therapy for patients with EDS IV and related aortic disorders.

PM05.38

The type of variants at the COL3A1 gene associates with the phenotype and severity of vascular Ehlers-Danlos syndrome

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Vascular Ehlers-Danlos syndrome (vEDS) is a rare and severe autosomal dominant disorder caused by COL3A1 gene variants, with little evidence of genotype-phenotype correlation. Clinical characteristics and course of disease of 215 molecularly-proven patients (146 index-cases and 69 relatives), were analysed. We found 126 distincts variants that were divided into five groups : 1) Glycine substitutions (71 variants in 127 patients), 2) splice-site and in-frame insertions-deletions (36 variants in 55 patients), 3) variants leading to haploinsufficiency (7 variants in 14 patients), 4) non glycine missense variants within the triple helix (4 variants in 7 patients), 5) non glycine missense variants or in-frame insertions-deletions, in the N- or C-terminal part of the protein (8 variants in 12 patients). Overall, our cohort confirmed the severity of the disease with a median age at first complication of 29 years [IQR 22 to 39], the most frequent being arterial (48%) and digestive (24%) ruptures. Groups 2 and 1 were significantly more severe than groups 3-5 with extreme median ages at first major complication of 23 to 47 years. Patients of groups 3-5 had a less typical phenotype and remarkably absence of digestive events. The glycine-replacing amino-acids were frequently destabilizing residues of the collagen assembly. Thus, the natural course of vEDS and the clinical phenotype of patients are influenced by the type of COL3A1 variant. This study also confirms that patients with variants located in the C- and N-termini or leading to haploinsufficiency have milder course of the disease, and less prevalent diagnostic criteria. These findings may help refine diagnostic strategy, genetic counselling and clinical care.

PS05.39

Differential DNA methylation in individuals with a history of cardiovascular diseases

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Cardiovascular disease (CVD) is among the leading causes of death worldwide. There are several known genetic and lifestyle risk factors, but association between epigenetics and CVD is poorly understood. In this study, we investigate the link between DNA methylation and CVD. We performed an epigenome-wide association study in a population-based cohort (N=730). Participants were not ascertained upon disease background, but some had a history of CVD (Table). DNA methylation was measured at 470789 autosomal CpG-sites. Differentially methylated sites were identified for a subset of diseases (Table). Some sites were located in genes previously associated to CVD, e.g. BNIP3 and GDF15. Enrichment analysis identified a number of molecular functions and biological processes, which are overrepresented among the differentially methylated genes. For example, participants with a history of myocardial infarction had an enrichment (FDR q-value=0.00142, Enrichment = 4.69) of differential methylation in genes associated with cardiac muscle tissue growth. The identified genes are good candidates for additional studies to further understand the genesis and progression of CVD, as well as for the development of therapies and treatments.

Table

CVD	No. affected individuals (%males)	No. significant CpG (FDR q-value < 0.05)
Cardiac Arrhythmia	5 (60%)	1
High Blood Pressure	147 (40%)	0
Myocardial Infarction	48 (58%)	211
Stroke	27 (56%)	0
Thrombosis	22 (59%)	0

PS05.41

Exome sequencing reveals novel functional mutation in APOB causing Familial Hypercholesterolaemia

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Introduction: APOB mutations are a rare cause of Familial Hypercholesterolaemia (FH) and routine genetic diagnosis only includes the study of two small APOB fragments (exon 26 and 29). Recently functional mutations have been described in APOB fragments not routinely studied and our group characterized 2/5 as causing FH.
The main aim of this project was to identify and characterize novel alterations in APOB in order to identify the genetic cause of the hypercholesterolemia in these patients.
Methods: we performed whole-exome sequencing of 5 Portuguese clinical FH patients apparently mutation negative. All results found in APOB were analysed. For functional studies LDL from index patients and relatives was separated and marked with FITC-LDL for studies by flow cytometry in HepG2 and U937 growth assays.
Results: We identified 2 alterations in exons 19 and 26 in 2 patients. In vitro analysis of exon 26 alteration (p.Thr3826Met) carrier showed a decrease in binding and internalization of LDL and in U937 growth assays, showing a similar effect as APO3527. As reported before, also in this family the penetrance is also reduced. Alteration in exon 19 had a neutral effect.
Conclusions: The spectrum of functional alterations in APOB outside the fragments routinely screened is growing. Screening of all 29 exons of APOB should be performed in routine diagnosis, now possible by NGS. It is expected that a further 10% of clinical FH patients can have FH due to a novel APOB mutation. On this basis we are currently sequencing a panel of 95 negative patients.

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LDLR functional in vitro assays: a step forward for the correct genetic diagnosis of familial hypercholesterolaemia

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