(CMT2K) and demyelinating recessive (CMT4A) forms of Charcot-Marie-Tooth (CMT) neuropathy. Loss of function recessive mutations in GDAP1 are associated with decreased mitochondrial fission activity, while dominant mutations result in impairment of mitochondrial fusion with increased production of reactive oxygen species and susceptibility to apoptotic stimuli.
Knockout Gdap1 mice show abnormal motor behaviour at early stage. Electrophysiological and biochemical studies confirmed the axonal nature of the neuropathy whereas histopathological studies showed progressive loss of motor neurons (MNs) in the anterior horn of the spinal cord and defects in neuromuscular junctions. Cultured embryonic MNs neurons showed large and defective mitochondria, changes in the endoplasmic reticulum (ER) cisternae and increased autophagy vesicles. We observed defects in cytoskeletal α-tubulin acetylation and in the axonal mitochondria transport. MNs showed reduced Ca^{2+} influx through store-operated Ca^{2+} entry (SOCE) upon mobilization of ER-Ca^{2+}, in association with an abnormal distribution of the mitochondrial network when treated with the ER stress inducer thapsigargin.
The phenotypic and functional study of the Gdap1 KO mice revealed the presence of an axonal neuropathy. We propose that lack of GDAP1 induces changes in the mitochondrial network biology and mitochondria-endoplasmic reticulum interaction leading to abnormalities in calcium homeostasis, which may represent part of the GDAP1-related CMT pathophysiology.

C06.5
Junctophilin-1 expression levels could modify the effects of GDAP1 mutations in Charcot-Marie-Tooth disease

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Charcot-Marie-Tooth (CMT) disease is a hereditary sensory and motor neuropathy with more than 60 genes associated. CMT type 2K (CMT2K) is caused by mutations in the GDAP1 gene and is characterized by incomplete penetrance and intrafamilial clinical variability. We have recently described the junctophilin1 (JPH1) as a genetic modifier of GDAP1. We characterized the combination of the JPH1 p.R213P and the GDAP1 p.R120W mutation in one patient with a more severe clinical picture. Through cellular studies we established that the combination of these two mutations significant increases the basal cytosolic Ca2+ and reduces SOCE activity, and therefore, JPH1 contribute to the phenotypical consequences of GDAP1 mutations.
Junctophilin genes are characterized by having a long 3'UTR (from 1861 nt of JP in Drosophila melanogaster to 2347 nt of JPH1 in humans) and that is conserved in the case of JPH1. We searched for variants in the 3'UTR of JPH1 in CMT2K families with the GDAP1 p.R120W mutation. We have identified the ENST00000342232.4:c.*1962G>A (rs57375187) variant in two brothers with an unusual early onset and severe clinical picture. We have demonstrated that the c.*1962G>A increase the transcript levels by a luciferase assay. Moreover, with the aim to gain insight into the disease mechanisms, we have used a Drosophila models in order to investigate how altered junctophilin expression levels could modify the effects of the Gdap1 related neural degeneration. Moreover, the Drosophila model has allowed us to discover new pathways related to junctophilin.
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C06.6
CCDC174 mutation underlies a syndrome of hypotonia and psychomotor developmental delay with abducens nerve palsy

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Two siblings of non-consanguineous Ethiopian Jewish ancestry presented with congenital axial hypotonia, weakness of the abducens nerve, psychoning of corpus callosum, cardiac septal defects and undescended testes. Homozygosity mapping identified a single disease-associated locus of 3.5Mb on chromosome 3. Studies of a Bedouin consanguineous kindred with 4 individuals affected with a similar recessive phenotype identified a single disease-associated 18Mb homozygosity locus containing the entire 3.5Mb locus of the Ethiopian family. Whole exome sequencing demonstrated one homozygous mutation in CCDC174 (c.1404A>G, p.[*468Trpext*6]) within a shared identical haplotype of 0.6Mb, common to both Bedouin and Ethiopian affected individuals, suggesting an ancient common founder effect. The mutation segregated as expected in both kindreds and was not found in 400 Bedouin and 100 Jewish Ethiopian controls. Knockdown of the CCDC174 ortholog in Xenopus laevis embryos resulted in poor neural fold closure at the neurula stage with later embryonic lethality. Knockdown embryos exhibited a sharp reduction in expression of n-tubulin, a marker for differentiating primary neurons, and of hindbrain markers krox20 and hoxb. The Xenopus phenotype could be rescued by the human normal, yet not the mutant CCDC174 transcripts. CCDC174 is ubiquitously expressed and was previously shown to interact with EIF4a3 which is crucial for RYR1 formation in frogs. In accordance, while maintaining normal mRNA level, RYR1 proteins in skeletal muscle of our patients were not detectable by immunohistochemistry. Also, in-vitro model showed co-localization of CCDC174 and EIF4a3 in the nucleus while overexpression of mutant but not wild-type CCDC174 caused rapid cell death.

C07.1
Does paternal imprinting of FOXF1 on 16q24.1 explain maternal UPD(16) phenotype?

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Trisomy 16 in humans, typically resulting from maternal meiosis I nondisjunction, is the most common prenatal trisomy and lethal unless rescued early embryonically. In one-third of such cases, children with maternal UPD(16) manifest IUGR (attributed to trisomic placenta) and multiple congenital malformations, including heart defects, pulmonary hypoplasia, tracheosophageal fistula, gut malrotation, absent gall bladder, renal agenesis, hydronephrosis, imperforate anus, and single umbilical artery. In contrast, relatively normal phenotype was reported in few patients with paternal UPD(16), and imprinted gene(s) on chromosome 16 were suggested as causative for maternal UPD(16) phenotype. All the above clinical features, except IUGR, are observed in the vast majority of children with a neonatally lethal lung developmental disorder Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins (ACDMPV). ACDMPV is caused by heterozygous point mutations or genomic deletions involving FOXF1 on 16q24.1, previously shown to be paternally imprinted, incompletely and in a tissue-specific manner. Most recently, genomic duplications involving FOXF1 were associated with pyloric stenosis, mesenterium commune, and aplasia of the appendix [PMID: 25472632]. We knocked-in a Cre-inducible Foxf1 allele at the ROSA26 locus and activated it with Tie2-cre to specifically overexpress Foxf1 in endothelial and hematopoietic cells. Using timed-matings, microCT, and plethysmography analyses, we found that these mice exhibit hypoplastic lungs, abnormal breathing, gastrointestinal abnormalities, edema, skin hemorrhages, and die perinatally. We propose that Foxf1 overexpression in mice corroborates the clinical observations seen in patients with maternal UPD(16) and conclude that paternal imprinting of FOXF1 may be responsible for the key phenotypic features of maternal UPD(16).

C07.2
Next-gen cytogenetics in prenatal diagnosis: lessons learned with balanced de novo rearrangements

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Specific identification of disrupted and dysregulated genomic regions is critical in precision diagnosis and in management of some individuals with constitutional and acquired rearrangements, especially considering the accelerated increase in annotation of the human genome. Rapidly defining structural chromosome abnormalities that underlie these genomic regi-