(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 showed large and defective mitochondria, changes in the endoplasmic reticulum (ER) architecture and increased autophagy vesicles. We observed defects in cytoskeletal and tubulin acetylation and in the axonal mitochondrial transport. MNs showed reduced Ca\textsuperscript{2+} in low through store-operated Ca\textsuperscript{2+} entry (SOCE) upon mobilization of ER-Ca\textsuperscript{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.

**CD6.5**

**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 junctophilin 1 (JPH1) as a genetic modiﬁer of CMT1. 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 signiﬁcantly increases the basal cytosolic Ca\textsuperscript{2+} and reduces SOCE activity, and therefore, JPH1 contributes to the phenotypic consequences of GDAP1 mutations.

Junctophilin genes are characterized by having a long 3’UTR (from 1861 nt 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 ENST00000324232.4:*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 model 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.

Funds: IRDiRC & ISCIII (Grant no: IR11/TREATCMT)

**CD6.6**

**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 abdomen nerves, psychomotor developmental delay with abducens nerve palsy, reduced Ca\textsuperscript{2+}trophysiological 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 showed large and defective mitochondria, changes in the endoplasmic reticulum (ER) architecture and increased autophagy vesicles. We observed defects in cytoskeletal and tubulin acetylation and in the axonal mitochondrial transport. MNs showed reduced Ca\textsuperscript{2+} in low through store-operated Ca\textsuperscript{2+} entry (SOCE) upon mobilization of ER-Ca\textsuperscript{2+}, in association with an abnormal distribution of the mitochondrial network when treated with the ER stress inducer thapsigargin.

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