Human Neural Stem Cells derived from Induced Pluripotent Stem Cells to evaluate the effects of *RAI1* mutation and *CHRNA7* CNV

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The aim of this project is to use neural stem cells obtained from patient-derived Induced Pluripotent Stem Cells (iPS) as a cellular model, to evaluate the phenotype related to two genetic alterations.

The first mutation described is an alteration of the retinoic acid induced 1 (*RAI1*) gene, which causes Smith-Magenis Syndrome (SMS, OMIM # 18229, incidence 1:25000). About 90% of the cases present with a deletion of the chromosomal region 17p11.2 containing *RAI1* and another 10% of the patients have a heterozygosis mutation of *RAI1* gene. These alterations cause an haploinsufficiency of *RAI1* leading to many several consequences for SMS patients: intellectual disability, multiple congenital abnormalities, obesity, neurobehavioral anomalies and a disrupted circadian sleep-wake pattern.

The second genetic alteration is a CNV affecting the cytogenetic region 15q13.3 containing the α7 nicotinic receptor (*CHRNA7*). The α -7nAChR is a ligand-gated ion channel characterized by fast activation and desensitization by agonists, high Ca^{2+} permeability, and selective inhibitions by α-bungarotoxin (αBGT) and methyllycaconitine (MLA). It is a very peculiar receptor in physiology since it is present both pre- and post-synaptically and also in non-neural tissues. These very small CNV were considered sub-pathological, but recent studies have suggested a role in neuropsychiatric disorders, including Alzheimer's disease, schizophrenia, attention deficit hyperactivity disorder, addiction, pain and Parkinson disease. Furthermore, it has been suggested a role of the α -7nAChR in the regulation of the migration ability in mesenchymal stem cells.

Therefore, we compared *in vivo*, after transplantation into the brain of animal models, the integration, migration and differentiation properties of 4 hNSC lines: hNSCs derived from a Smith Magenis patient (SMS-hiNSCs) that presents with both the mutation and the CNV, a healthy fetal neural stem cell line (f-hiNSC), a fetal neural stem cell line with only CNV on the CHRNA7 gene (fCHRNA7 hNSCs), and a healthy human neural stem cells line generated upon neural differentiation of IPS. Our preliminary data, collected 6 months after the transplant, suggest that the CNV might influence the integration, migration and survival abilities of hNSCs into the brain Our data, points to the possibility that the CNV on CHRNA7 confers to SMS-hiNSC and fCHRNA7-hNSCs lines an extensive migration ability and an enhanced engraftment and survival capacity compared to the healthy fhNSC and hiNSC control.