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Brain4Sight

Deconstructing gene regulatory networks for improving sight and brain disabilities

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Neuro-Developmental Visual Disorders (NDVD) are complex conditions caused by mutations in genes instructing cells on how to build an eye or other brain areas involved in vision. NDVD arise mostly during embryogenesis, are highly debilitating and variable disorders and often occur together with other neurodevelopmental disorders (NDD) such as intellectual disability, autism or epilepsy. This phenotypic variability severely hampers clinical diagnosis, disease management and delays possible alleviating therapies, creating practical and emotional burden to clinicians, patients and their families. Unfortunately, to date, there is only poor understanding of how mutations in a single gene can cause such a bewildering variability of clinical manifestations, as well as why the same mutation can have unique effects in different patients. The Brain4Sight consortium, composed of clinicians and basic researchers, seeks to unravel the reasons behind this understudied variability, focusing on the SOX2 and NR2F1 genes. These genes are, respectively, responsible for syndromic anophthalmia/microphthalmia and Bosch-Boonstra-Schaaf Optic Atrophy syndrome (BBSOA). To reach its goal, Brain4Sight will employ state-of-the-art genomic and sequencing technologies, human retinal and brain organoids derived from patients´ blood cells, which should closely mimic the processes that fail during individual human organ formation, as well as mouse models that reproduce human pathologies to address the complex issue of how such mutations make brain assembly go awry. Brain4Sight will thereafter use this new knowledge to restore genetic programs and reprogram brain cells to regenerate the cells most severely affected by the mutations, with the long-term goal to restore vision. Brain4Sight will thus provide fundamental knowledge towards improving diagnosis, management, prognosis and therapeutics for NDVD, in particular, and for NDD in general.

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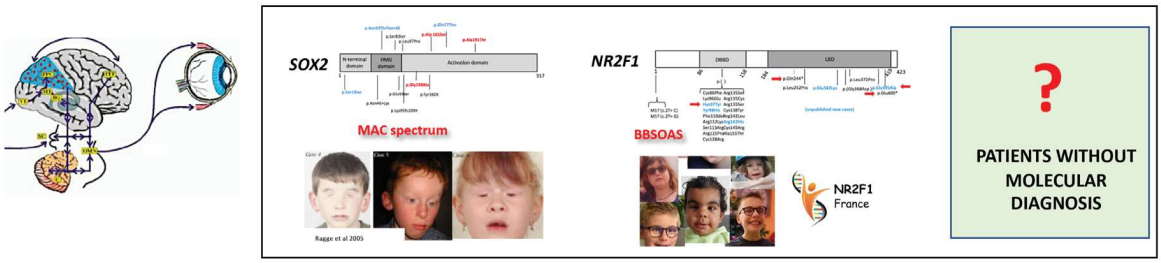

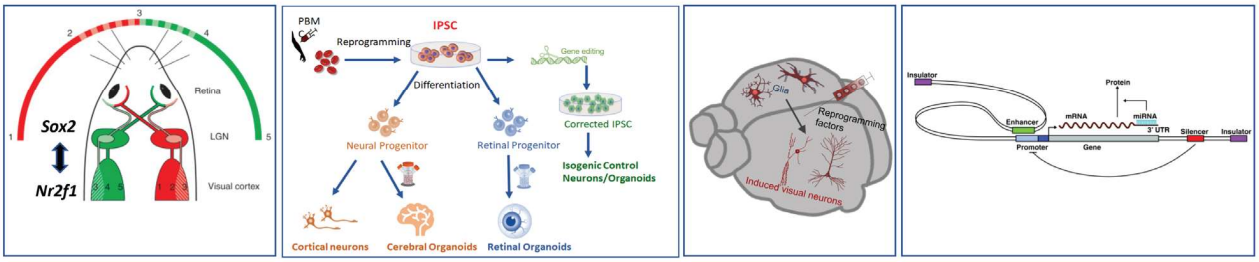

***Aim 1**: Sox2 and Nr2f1 tissue specific interaction and function in the mouse VS*

Aim 3: *Challenging SOX2 and NR2F1 mutations using human organoids*

***Aim 4**: Generation of visual neurons by cell reprogramming*

***Aim 2**: Discovering new variants in regulatory elements linked to the SOX2 gene*