Novel *In Vivo* Models of Pediatric Diseases

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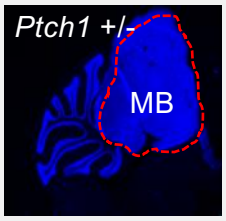
Mouse models have extensively been used to provide insight into mechanisms underlying many diseases, to explore the efficacy of innovative therapeutic methods of disease cure as well as testing candidate drugs to predict patient responses. Our laboratory has a long-standing experience in generation and functional characterization of novel mouse mutant models of human diseases. In particular, we have recently developed two models that can be used as innovative tools for better understanding the biological processes leading to and allowing progression of severe pediatric disorders, like e.g. medulloblastoma (MB) and primary ciliary dyskinesia (PCD).

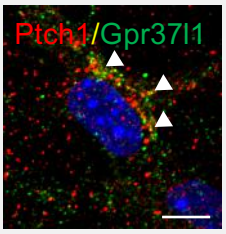
MEDULLOBLASTOMA

Medulloblastomas (MBs) have the highest incidence among malignant brain tumors of childhood (maximal occurrence between 4 and 7 years of age).

Loss-of-function mutations of the human patched 1 (PTCH1) orthologue gene are a major risk factor for the sonic hedgehog (Shh) subgroup of cerebellar MBs.

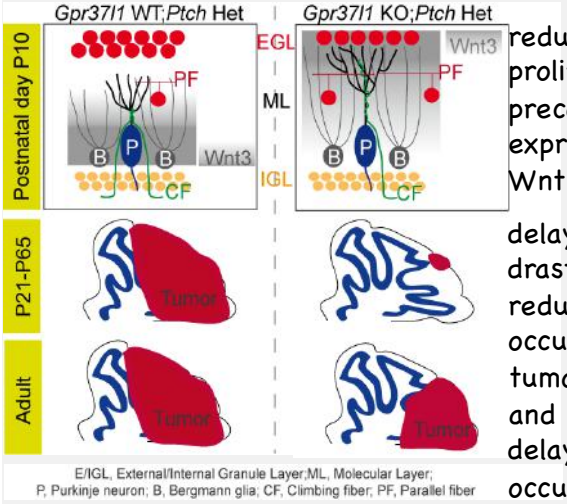


- Mice heterozygous for *Ptch1* gene mutations are important models for MB
- *Ptch1* heterozygous mice survive to adulthood and 14-20% develop MB.



- Gpr37l1 is an orphan G-protein coupled receptor, expressed in the cerebellum.
- Gpr37l1 specifically interacts with Ptch1.
- Gpr37l1 KO mice exhibit precocious postnatal cerebellar development.

Novel Gpr37l1$^{-/-}$;Ptch1$^{+/-}$ mouse line exhibits:



reduction in GCP proliferation and precocious expression of Wnt3

delayed and drastically reduced occurrence of tumor lesions and delayed tumor occurrence

Marazziti *et al.*, PNAS 2013

Di Pietro *et al.*, Exp Neurol 2019

PRIMARY CILIARY DYSKINESIA (PCD)

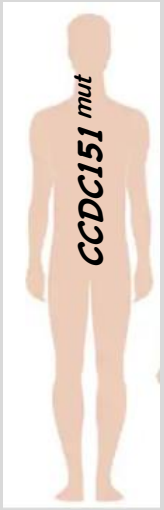
PCD (PCD; OMIM:244400) is a rare disease, with the first manifestation in childhood.

Mutations in genes critical for normal development of ciliated cells or protein components of motile cilia organelles have been associated with PCD.

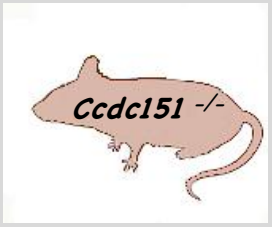
Autosomal recessive, nonsense mutations in *CCDC151* gene were identified in subsets of human patients with PCD disease.

Novel Ccdc151$^{-/-}$ mouse line models PCD

(Chiani *et al.*, Dis Model Mech 2019)

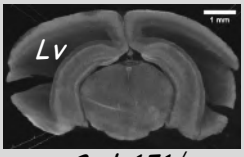


Hydrocephalus
Neurological defects

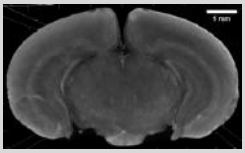


Situs abnormalities
Heart defects
Asplenia
Infertility

Hydrocephalus



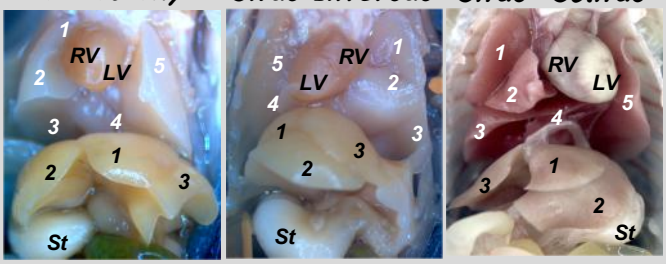
Ccdc151$^{-/-}$



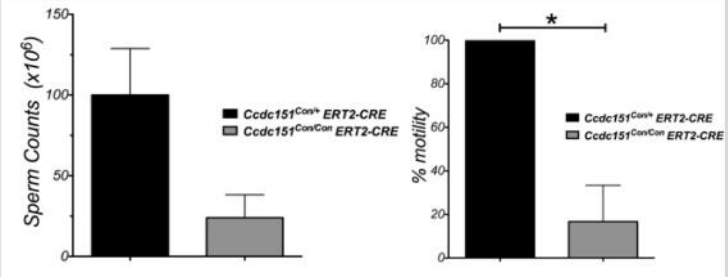
WT

Defects in left-right body asymmetry

Heterotaxy ***Situs Inversus*** ***Situs Solitus***



Congenital and Induced Male Infertility



MGI model: http://www.informatics.jax.org/allele/key/841313