Standardized behavioral characterization of mouse models of genetic diseases with intellectual disabilities

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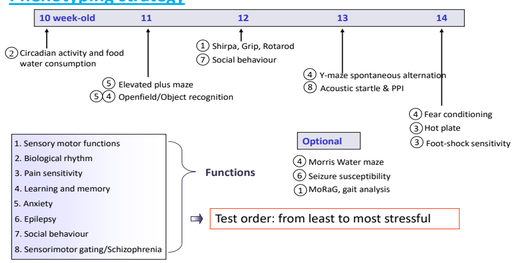
INTRODUCTION

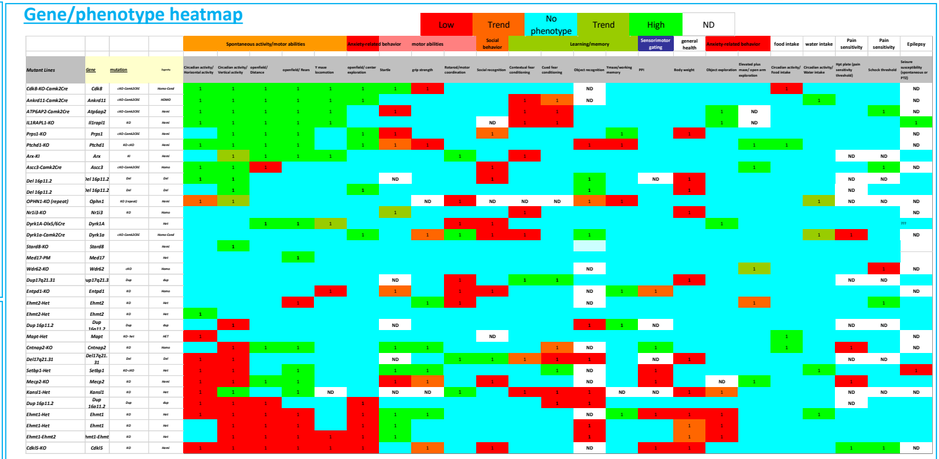
Intellectual disability (ID) is a major medical and socio-economical problem owing to their high incidence in the population. To elucidate the molecular mechanisms underlying cognitive deficits and to screen for potential therapeutics, PHENOMIN-iCS generated and characterized more than 40 mouse mutant lines within the frame of the GENCODYS project, a European translational program (http://www.gencodys.eu/). Standardized behavioral screens were carried out, including several tests allowing to evaluate a wide range of functions or their pathologies covering circadian activity, neurological reflexes and specific motor abilities, anxiety-related behavior, sensorimotor gating and learning and memory processes. Additional analyses were performed in some mutant lines to further characterize the observed abnormalities or to extend phenotypic traits related to the individual genes. Furthermore, pharmacological treatments were carried out on some relevant lines to screen for therapeutic candidates and potentially reverse the behavioral changes.

Phenotyping strategy



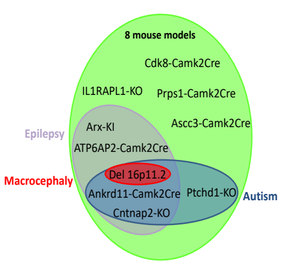
- 8-12 WT, 8-12 mutant males
- At the end of behavioural phenotyping
  - ✓ Brain structures dissection: hippocampus, cortex, cerebellum, Striatum, remaining brain), for molecular analysis
  - ✓ Cranio-facial abnormalities

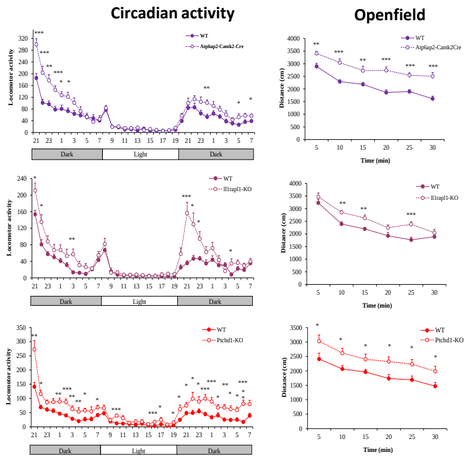
Gene/phenotype heatmap



Over the 37 mutants lines, more than 200 behavioural phenotypes
Activity driven classification: Three main groups of mutant lines
Mutants with hyperactivity : substantial increase in spontaneous activity in several situations
Mutants with no specific activity phenotypes
Mutants with hypoactivity : decreased spontaneous exploration in several situations

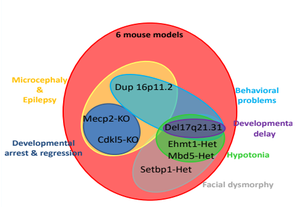
Hyperactivity group

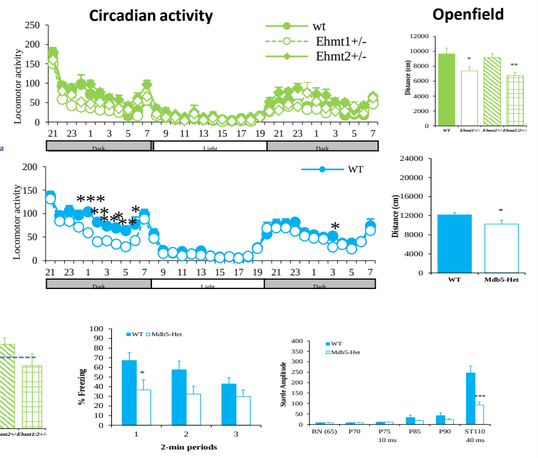




Il1Rapll1-KO, Ptchd1-KO and Atp6ap2-camk2Cre-KO males showed increased locomotor activity (and rears) in different situations

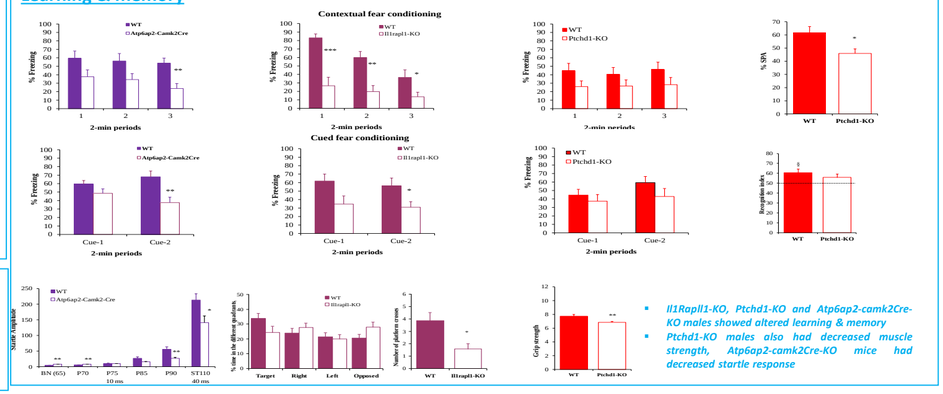
Hypoactivity group





Ehmt1+/- and Mbd5+/- mutants showed decreased activity and altered memory performance.
Mbd5+/- mutants also had decreased startle response

Learning & memory



CONCLUSION

These data show heterogeneity of phenotypes between mutation types. Nevertheless, three main classes were identified based on activity phenotypes, together with other motor abilities or cognitive deficits, recapitulating some of the human features, and suggesting the relevance of these mutants for better understanding the complexity of human ID syndromes, and to build appropriate therapeutic strategies.

- *Il1Rapll1-KO, Ptchd1-KO and Atp6ap2-camk2Cre-KO males showed altered learning & memory*
- *Ptchd1-KO males also had decreased muscle strength, Atp6ap2-camk2Cre-KO mice had decreased startle response*

EXCELLENCE IN MOUSE PHENOGENOMICS