From mouse to human: deciphering neurodevelopmental anomalies

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INTRODUCTION

According to SysID (https://sysid.cmbi.umcn.nl/), neuro-anatomy is an endophenotype of 45% of intellectual disability (ID) cases (**Figure 1**). In collaboration with the International Mouse Phenotyping Consortium (IMPC), we measured 161 neuroanatomical parameters in 1,566 mutant mouse lines. This work allowed us to identify 164 genes newly implicated in mammalian brain morphology (scan the link below for more information).

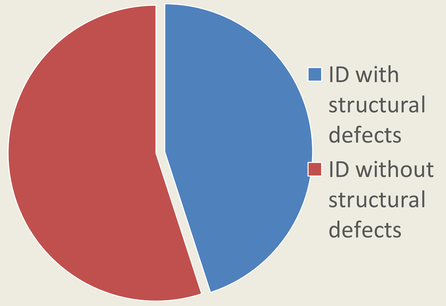

Figure 1. Proportions of ID with or without brain structural anomalies

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PATIENTS AND METHODS

Data Sharing

Among 164 genes submitted to GeneMatcher (https://genematcher.org/), 18 genes were "matched" with one or more patients with similarities in brain phenotypes between the two species.

An example of a gene among these 18: *KDM4B* which codes for the specific Lysine Demethylase 4B and is strongly expressed in the brain.

Comparative study between *KDM4B* patients and *Kdm4b$^{+/-}$* mice

Brain MRI scans of seven patients presenting global (neuro)developmental delays with novel heterozygous LoF variants in the *KDM4B* gene were compared to a robust brain neuro-anatomical study of *Kdm4b+/-* mice using coronal sections (at position Bregma +0.98mm and Bregma -1.34mm). Furthermore, various pipelines including anapathological analysis of several systems, sensorimotor assessment, open arena behavior, dysmorphology and skeletal analysis analysis, blood biochemistry and a metabolic assessment were performed using *Kdm4b+/-* mice.

RESULTS AND DISCUSSION

List of 18 genes associated with similar phenotypes between patients and mutant mice

ARID4A, CAND2, CATIP, CSNK1G3, DDX23, DLGAP4, GTPBP3, ***KDM4B****, MAGEE2, PDZD8, PIK3CB, POLR2F, PTPRD, PPP1CC, SFPQ, TRAPPC10, USP15, WDR47.*

Proof of concept: *KDM4B* patient

Patient with a *de novo* mutation (His768Arg), showing neuro-developmental delays, post shunt hydrocephalus, agenesis of the corpus callosum, and subcortical heterotopia (**Figure 2**).

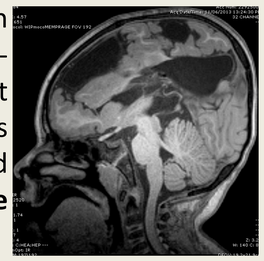

Figure 2. Brain MRI image of patient 1159-01. Courtesy of Pankaj Agrawal and Anna Duncan.

Characterization of the mouse *Kdm4b+/-*

Kdm4b+/- mice show decrease in brain area of 13.8% (P=0.0005) at Bregma +0.98mm, reduced dentate gyrus size of -25.3% (P=7.0E10-5), and a lower height of the corpus callosum of -24.7% (P=0.01) compared to matched controls. The area of the lateral ventricles is increased by 92% (P=0.009) (**Figure 3**). With the exception of skeletal parameters and facial dysmorphism, most of the other tests do not show a phenotype (**Table 1**).

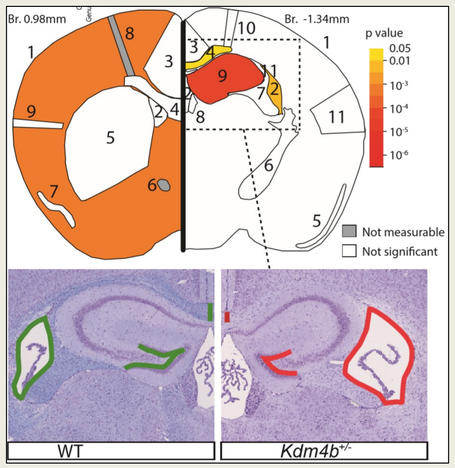

Figure 3. Neuro-anatomical analysis of the mouse *Kdm4b$^{+/-}$*

TEST	Phenotype
Hair follicle	Normal
Open field arena	Normal
SHIRPA modified	Normal
Grip test	Normal
Hot plate	Normal
Dysmorphological features	Abnormal
Blood glucose	Normal
Hearing	Normal
X-rays, skeleton	Abnormal
Body composition	Normal
Body temperature	Normal
Blood biochemsitry	Normal
Collaboration Valerie Vancollie and Christopher Lelliott	

Table1. Phenotypic study of the *Kdm4b$^{+/-}$* mouse

CONCLUSION AND PERSPECTIVES

These preliminary results demonstrate the value of our high-throughput brain neuro-anatomical analyses and the relevance of the mouse model to provide a solution to diagnostic wandering, especially in complex and ultra-rare cases.

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