Universität Basel

Research Project

Behavioral genetics approach to the role of KRAB/KAP1 for human memory and emotional traits in health and disease: Genetic studies

Third-party funded project

Project title Behavioral genetics approach to the role of KRAB/KAP1 for human memory and emotional traits in health and disease: Genetic studies
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This proposal aims at exploring the molecular and genetic bases of vulnerability to behavioral stress and stress-

related disorders, taking as a starting point the role of epigenetics in this process. The four participating groups

have all recently contributed to this topic by i) discovering that transcriptional modulation by the KRAB/KAP1

epigenetic regulatory system in the hippocampus conditions vulnerability to behavioral stress and stress-

induced cognitive defects in the mouse (DT & CS), and ii) identifying genetic factors related to non-emotional

and emotional memory through behavioral and genetic studies in humans, including patients suffering from

traumatic memories and post-traumatic stress disorder (DdQ & AP). The four groups will pool efforts to tackle

this as yet largely unexplored problematic through a combination of molecular biology, mouse genetics, mouse

and human behavioral neurobiology, human genetics and neuroimaging. The specific aims of this project are:

1. To characterize molecularly the stress vulnerability of KAP1 KO mice by asking:

a) Is the phenotype of KAP1 knockout mice restricted to a particular neuro-developmental stage?

b) Is the increased stress vulnerability of KAP1 KO mice reversible?

c) What KAP1 molecular determinants are essential for normal vulnerability to stress?

d) What KRAB-ZFPs control KAP1-dependent vulnerability to behavioral stress?

e) What are the downstream effectors of abnormal stress responses in KAP1 KO mice?

f) Which are dysregulated at baseline and after stressful challenges?

g) What are their roles in increasing stress vulnerability? How do they act?

h) What is the mechanism of their epigenetic regulation and dysregulation in the absence of KAP1?

2. To further the behavioral and neurobiological characterization of KAP1 KO mice, by:

a) Expanding the behavioral characterization of KAP1 forebrain KO mice to obtain a precise picture of the

emotional and cognitive consequences of this mutation.

b) Exploring potential alterations of KAP1 forebrain deletion on other relevant behavioral domains, by

studying the implications of this genotype on social behaviors.

c) Investigating the nature of the vulnerability to stress in KAP1 KO mice, by exploring potential alterations

(neuroendocrine, behavioral, neurobiological) to acute, subchronic and chronic stressors of varying intensity

and nature (in interaction with objective d).

d) Investigating the involvement of KRAB/KAP1-related genes in several rodent models of psychopathology

(PTSD, depression, pathological aggression), by studying alterations in those genes in wild-type animals

submitted to such models and by studying the behavioral consequences in KAP1 mutant mice submitted to

these models.

e) Defining better the contribution of KRAB/KAP1-related genes by studying the responses of newly

developed genetically modified mice (i.e., late knockout, overexpression of unregulated genes, re-introduction

of KAP1, etc.) on those situations providing major results under objectives a-d.

3. To test the influence of genetic polymorphism on stress-related behaviors and cognitive functions in

humans

A high-density genetic mapping effort will be directed towards the identification of putative polymorphisms in

KAP1, KRAB-ZFP genes, and human orthologues of genes found to be dysregulated in the brain of KAP1

knockout mice.ă Populations under study will include:

a)ă 450 healthy Swiss subjects previously investigated for episodic memory, emotional memory, working

memory, and attention.

b)ă 200 subjects who experienced highly emotional, stressful events (survivors of the 1994 Rwandan genocide,

about 60% of whom suffer from post-traumatic stress syndrome), already investigated for traumatic memory,

anxiety, and depression, to whom 200 new subjects will be added.

c) ă 500 healthy Swiss subjects tested for episodic and emotional memory along with stress- and anxiety status,

symptoms of depression and cortisol levels (to control for the actual stress status).

4. To explore the value of neuroimaging (fMRI) for the analysis of stress-related molecular parameters.

In the context of another project, fMRI scans and DNA are currently acquired from about 100 healthy human

subjects during emotional memory tasks. These data will be available for the analysis of genotype-dependent

differences in brain activations of genetic variants identified in the present project.

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