

### OPPORTUNITIES FOR RESEARCH COLLABORATIONS AND RESEARCH TRAINING

The Algeria France and Morocco-France academic training and INSERM research programs in genetics 1998-2006

### A CLINICALLY- BASED NEONATAL SCREENING OF GENETIC DISEASES IN THE MAGHREB

- Western Europe and North America offer mass neonatal screening (NNS) for prevalent/treatable genetic diseases : PKU, CF, CAH and hypothyroidism
- In France, a regionally based, robust, efficient NNS with more than 20 millions neonates screened in the last 25yrs
- In the Maghreb, the truly prevalent/treatable genetic diseases remain unknown

### A CLINICALLY- BASED NEONATAL SCREENING OF GENETIC DISEASES IN THE MAGHREB

- In the Maghreb, the truly prevalent/treatable genetic diseases remain unknown
  - a major scientific issue for epidemiologists, clinical and molecular geneticists, prior to setting NNS
- Medical awareness, health organisation and good lab practices require continuous efforts
  - a training challenge for academics/decision makers

### A CLINICALLY- BASED NEONATAL SCREENING OF GENETIC DISEASES IN THE MAGHREB

- A long-term bi-national program (8yrs) aimed to the goals of:
- fostering partnership and joint research projects between Maghreb and France
  - promoting clinically based detection of genetic diseases
  - developing high-level training programs in clinical and molecular genetics

### TWO MAJOR REASONS FOR PARTNERSHIP BETWEEN MAGHREB AND FRANCE IN GENETICS

- With a rate of consanguinity averaging 25-50% and above, inbreeding is becoming a major issue in the Maghreb
  - genetic diseases turn out to be a burden for public health
- France harbours a community of 5-6 millions of Moslems, in majority from Maghreb, with similar genetic and socio cultural background
  - France is facing (in part) similar genetic diseases

### TWO MAJOR REASONS FOR PARTNERSHIP BETWEEN MAGHREB AND FRANCE IN GENETICS

- Most scientists from Maghreb have studied in France/french, they are more comfortable in french than in english-spoken meetings
  - extremely close, friendly and ancient relationship
- strong historical, geographical, intellectual, personal links and commitment
  - strong expectation of ongoing medical/scientific partnership with France, that decision makers tend to forget or ignore

### SUPPORTING PUBLIC INSTITUTIONS AND NATIONAL HEALTH CARE/RESEARCH AGENCIES

- France: Ministries of Foreign Affaires, Research and INSERM
- Algeria: Ministry of Health, Comité Médical National de Génétique
- Morocco: Ministry of Education and Research

A cooperation based on the principle of mutuality and reciprocity of fundings between Maghreb and France

### GENERAL GOALS OF THE BINATIONAL PROJECTS

- To ensure a high level of education, laboratory training and medical awareness in medical genetics, particularly regarding epidemiology and clinical presentation of diseases
- To promote clinically-oriented diagnosis, ie diagnosis based on early detection of presenting symptoms, rather than mass neonatal screening at this stage
- To identify hitherto unknown prevalent/treatable conditions, in the prospective of future mass neonatal screening programs
- To capitalize on the existing organisations, networks and links, built on respect and mutual confidence between partners

### TOOLS AND METHODS OF THE ALGERIA-FRANCE AND MOROCCO-FRANCE BINATIONAL PROJECTS

- The program offers access to the french pre-doctoral, doctoral and post-doctoral training programs, including the MD-PhD training programs (Ecole de l'INSERM)
- The program offers scholarships and post-doctoral fellowships to MDs, pharmacists and scientists from Maghreb in french university hospitals and INSERM laboratories

### TOOLS AND METHODS OF THE ALGERIA-FRANCE AND MOROCCO-FRANCE BINATIONAL TRAININGS

- long term trainings (12mths) in clinical, biochemical, molecular and cytogenetic units of major university hospitals
- INSERM Postes Verts positions for advanced scientists to achieve joint research projets in INSERM units
- short-term trainings (1 mths) for senior technicians/specialists to acquire specific skills
- short-term stays (2 wks) for program leaders
- long-term partnership between teams (Unité INSERM associée) open call, no dead line, fundings for scientists/consumables

### TOOLS AND METHODS OF THE ALGERIA-FRANCE AND MOROCCO-FRANCE BINATIONAL TRAININGS

French academics/scientists play an active/continuous role

- conferences, workshops and didactic consultations in Rabat, Casablanca, Constantine, Algier (Parnet, Ben Aknoun, Bab el Oued and Mustapha-CPMC)
- technical courses (karyotyping, PCR, D-HPLC, sequencing)
- initiation to good medical/lab practices and procedures, DNA/ tissue banking technology, record of relevant informations
- devise of joint research projects (epidemiology, gene mapping and identification, mutation search, translational research)

### MAJOR HEALTH ISSUES COVERED BY THE BI-NATIONAL TRAINING AND RESEARCH PROGRAMS 1998-2006

- neuromuscular diseases
- neurogenetics and epilepsy
- metabolic diseases
- infectious diseases
- mental retardation
- dysmorphology
- genodermatoses
- retinal dystrophies
- bone dysplasias
- cancer genetics (breast, thyroid, retina)

**RESULTS OF THE BI-NATIONAL TRAINING AND RESEARCH PROGRAM IN MEDICAL GENETICS  
1998-2006**

In Algeria,

- a total of 19 algerian senior residents have received a 1yr clinical/laboratory training fellowship in leading french medical genetic and INSERM research centers
- a total of 40 algerian specialists/senior technicians have received a 1-6 mth fellowship to acquire specific expertise
- a total of 6 PhD theses defended or in preparation, joint publications, training programs for algerian GPs in Algier
- upgrading of platforms and biochemical/molecular core facilities

**RESULTS OF THE BI-NATIONAL TRAINING AND RESEARCH PROGRAM IN MEDICAL GENETICS  
1998-2006**

In Morocco, under the impulsion of former Director of INSERM, Claude Griscelli:

- a total of 10 twinning research projects have been funded in the field of neurogenetics, epidemiology, infectious diseases (1yr fellowship for young scientists + 10.000 euros/project)
- numerous leading scientists trained/graduated in France In this period
- a total of 125 pediatricians, nurses and managerial staffs from Rabat and Casablanca received in France for 1mth-1yr periods of special training in Necker and R.Debré hospitals

**STRENGTHS AND WEAKNESSES OF THE BI-NATIONAL PROGRAMS**

- The major strengths/assets are:
  - the quality and true motivation of the trainees from Maghreb
  - eager to learn, intelligent, inventive, dedicated, grateful
- The major weaknesses are:
  - the uneven degree of motivation of the french partners
  - the lack of ambition/self confidence of the counterpart,
  - the lack of confidence in their ability to collectively overcome the obstacles (bureaucracy, slowness, disorganisation)
  - the uneven expertise of biologists, relative to physicians

**CONCLUSION AND PERSPECTIVES**

There are real needs in term of health care and huge expectations in ongoing cooperations in genetics  
→ it is important to pursue, secure, amplify the programs

Future bi national training programs aimed to nurses, midwives, genetic counsellors, managerial staffs should contribute to promote and improve the notions of:

- pediatric nursing
- hygiene and dietetics
- prevention of infections
- genetic counselling and prenatal diagnosis
- family planning

THANK YOU !!!!

**OPPORTUNITIES FOR RESEARCH COLLABORATIONS AND RESEARCH TRAINING**

A collaboration between Algeria and France in clinical, molecular and population genetics of mental retardation

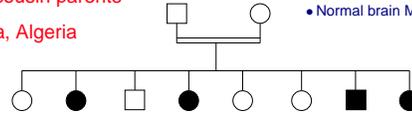
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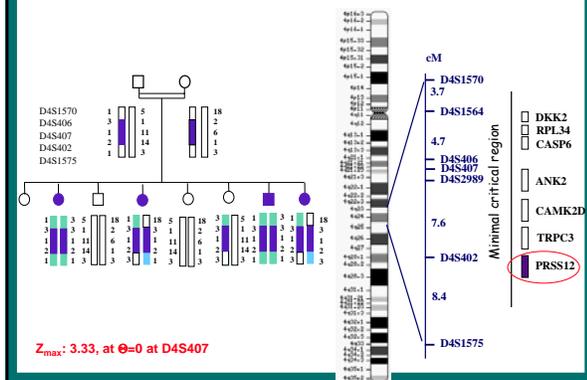
## Family Mel.

Severe isolated MR  
First cousin parents  
Bejaia, Algeria

Unknown etiology:  
• Normal HR caryotype  
• Normal metabolic screening  
• Normal brain MRI

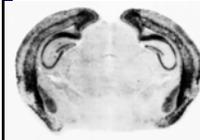
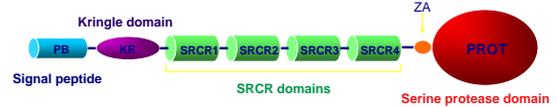


## Critical region: 13Mb on 4q24



## Neurotrypsin

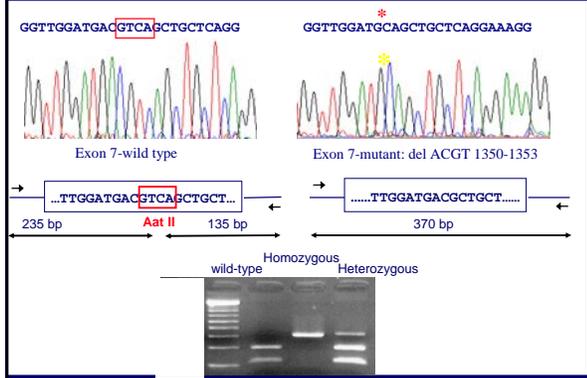
Trypsin-like serine protease, highly expressed in the brain



Expression in : Cerebral cortex  
amygdala  
hippocampus.

→ Likely involved in neuronal plasticity

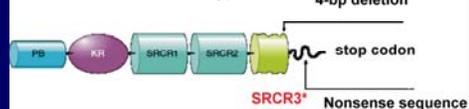
## Mutation in PRSS12 : del ACGT<sub>1350-1353</sub>

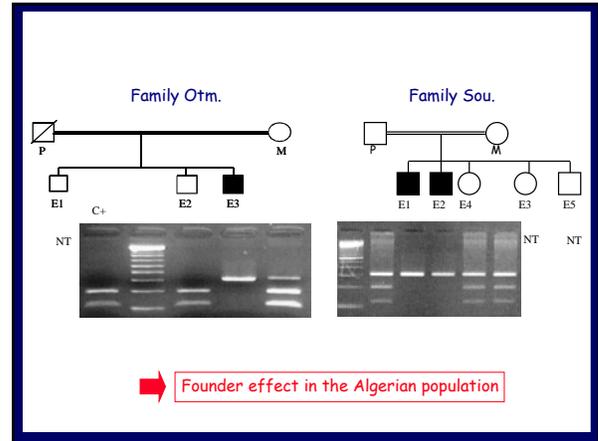
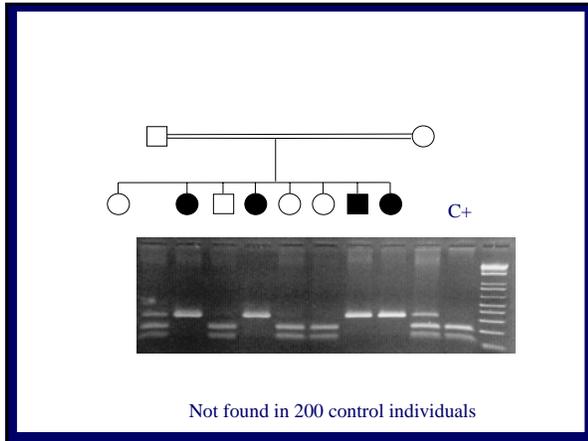


## A. Neurotrypsin



## B. Truncated Neurotrypsin





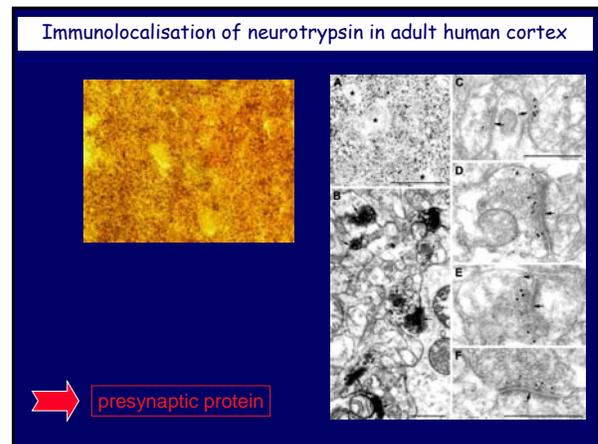
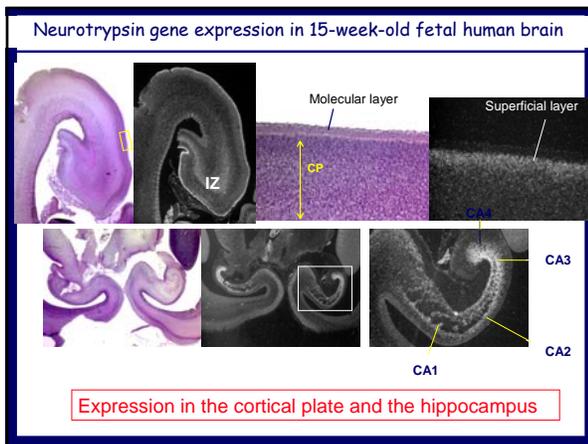
Family 1  
Photos have been removed for privacy and confidentiality purposes.

Family 2 Family 3  
Photos have been removed for privacy and confidentiality purposes.

- Isolated or syndromic MR
- Common facial dysmorphism ?
- Behaviour ? Course of the disease?

### Conclusions-1

- **Autozygosity mapping** is an efficient strategy to identify new autosomal recessive MR genes
- Neurotrypsin is the **first gene** involved in a **autosomal recessive non-syndromic MR**
- A prevalent cause of mental retardation in Algeria ?  
An epidemiology study and long-term clinical survey of this condition in Algeria is mandatory

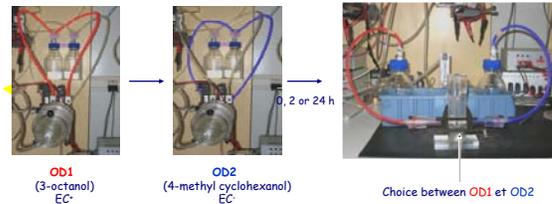


### Construction of a drosophila « knock-down » neurotrypsin model



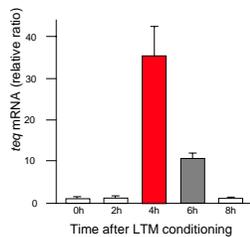
- Unequaled genetic, biochemical, molecular tools
- 87 % of MR genes with a drosophila ortholog
- efficient cognitive behavioral assays

### Measuring olfactory associative learning or memory

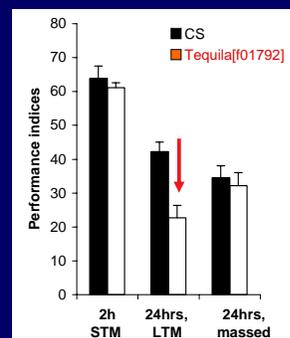


Performance index calculation

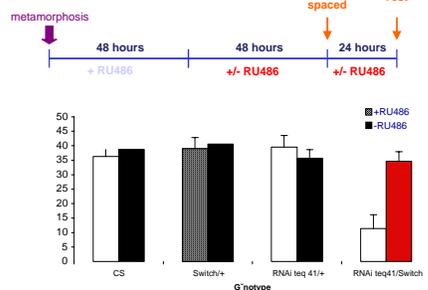
### Quantitative RT-PCR from Head RNAs



teq expression is up-regulated after LTM conditioning in the wild-type fly



tequila P mutant is a LTM mutant



LTM impairment in conditional teq mutant is reversible

### Conclusions-2

- Drosophila is a suitable model for studying the pathophysiology of neurotrypsin mutations
- Tequila may be a key player in the pathway underlying LTM formation
- Neurotrypsin mutations are prevalent in Algeria and possibly reversible/treatable
- CANDIDATE TO MASS NEONATAL SCREENING ?