Identification and reclassification of genetic variants in X-linked intellectual disability

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Upcoming Master 2 internship

CNRS UMR 7104 - Inserm U 1258

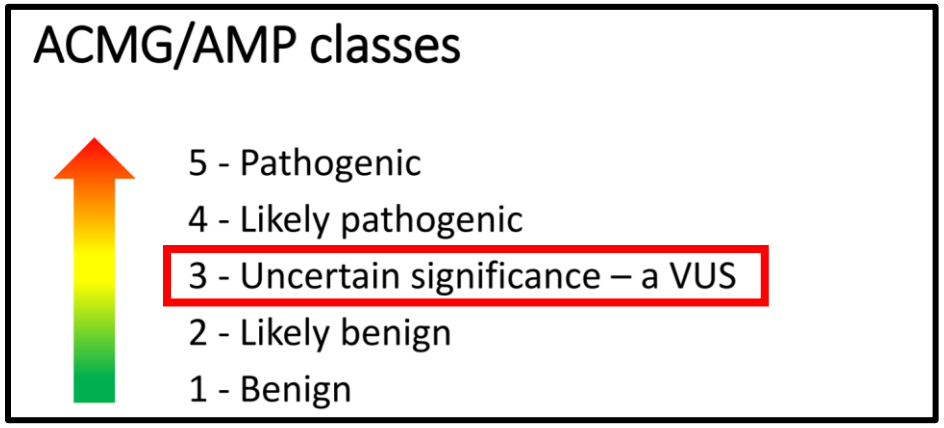
Génétique et physiopathologie des maladies neurodéveloppementales et épileptogènes

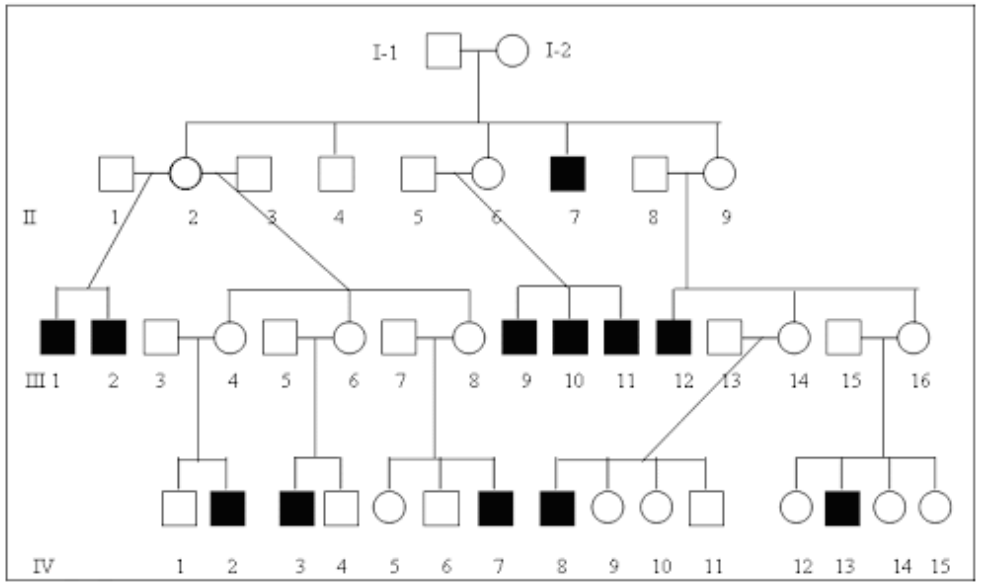
Dr Amélie Piton

Roma ERASMUS week
December 14th – December 18th 2020

Intellectual disability

- Significant limitation in intellectual capacity and adaptative functioning
  - IQ < 70
- 2% of the population
- 50% : monogenic cause > 1000 genes (AR, AD, XL)
  - 122 genes X-linked +/- 50 candidates



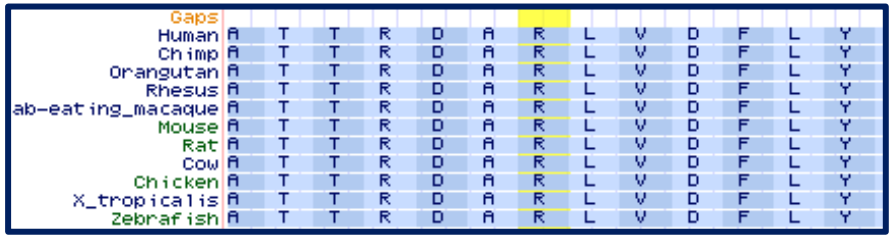


http://www.edu.upmc.fr/sdv/masselot_05001/cartographie/segregations.html

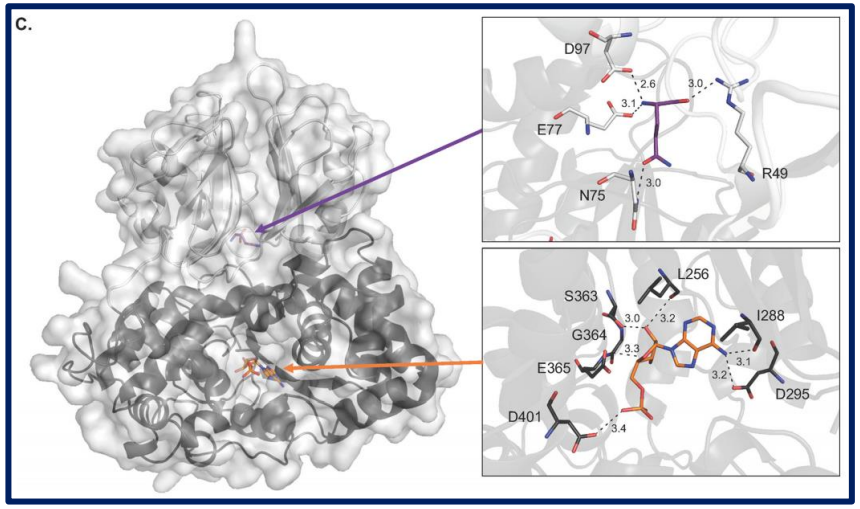
1) Analysis of reported missense variants in X-linked ID

CADD - Combined Annotation Dependent Depletion

Missense variants
(30 XLID genes
with VUS +++)

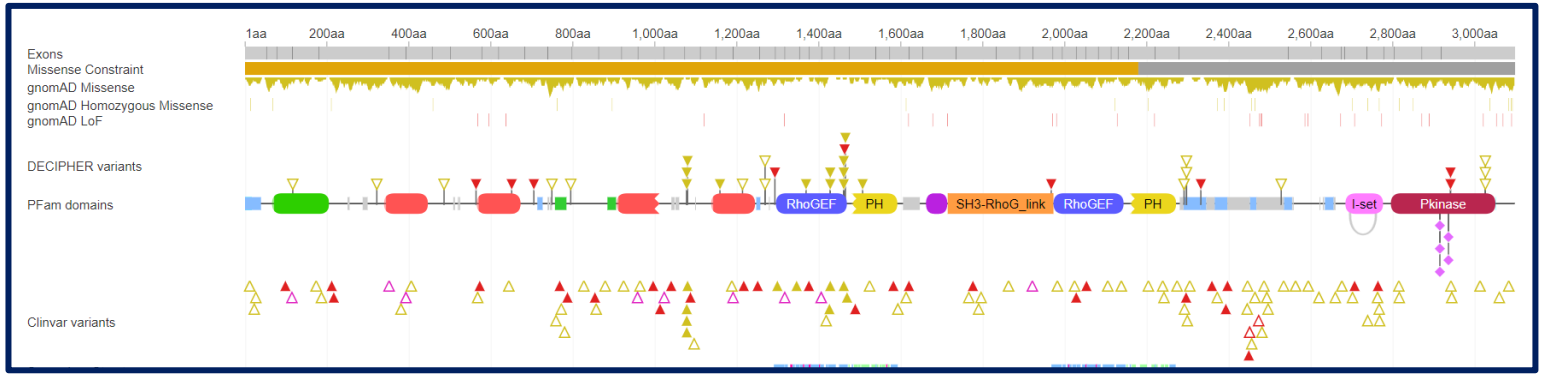


https://genome.ucsc.edu/



Lomelino et al, 2017

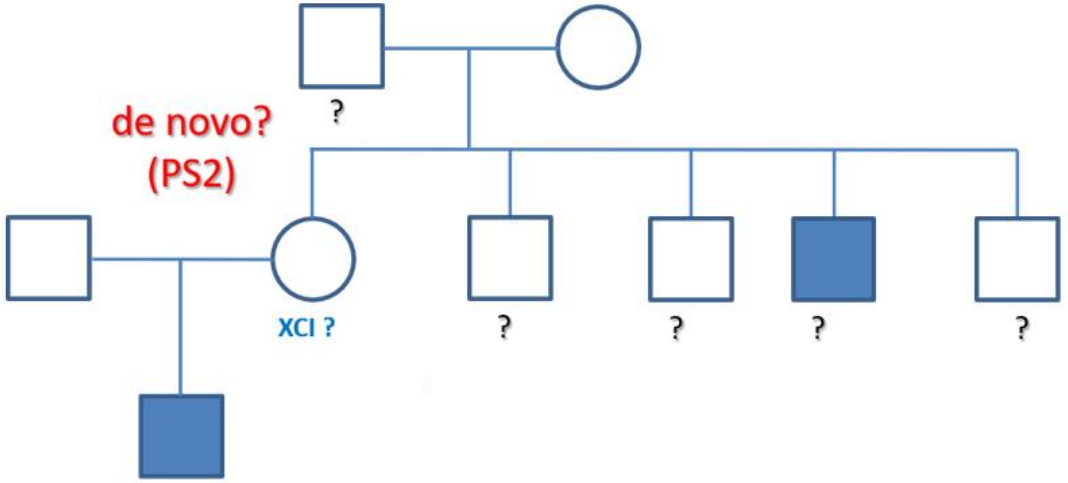
gnomAD



https://decipher.sanger.ac.uk/gene/TRIO/overview/protein-info

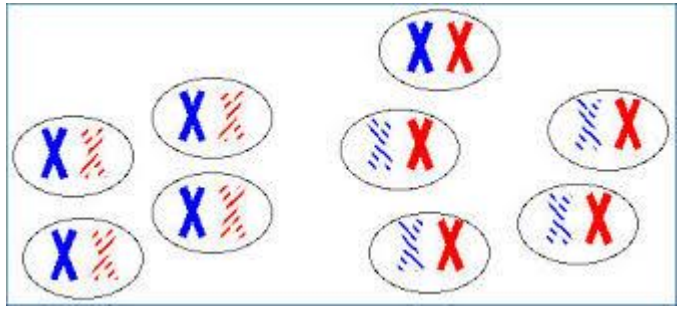
2) Genetic follow-up testing

Segregation analysis



Recurrence?

Inactivation bias?



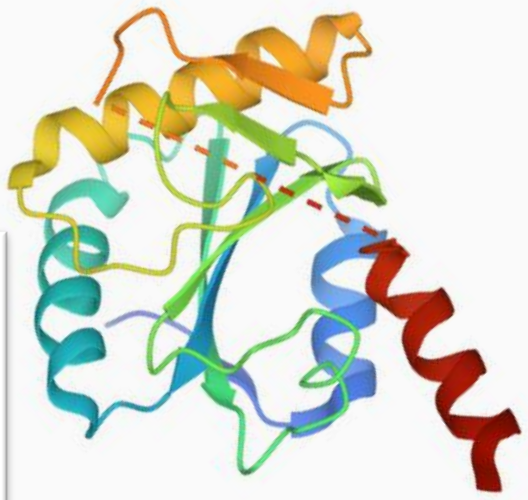
Dr H.Karmous-Benailly

Genetic studies + in silico predictions

→ Solve individual cases (VUS)

→ Establish specific recommendations for each gene

3) Functional studies



PQBP1 : regulation of transcription and splicing

hSNCS

Inactivation of *PQBP1* (siRNA)

Non-transfected cells

Cells transfected with siRNA scramble

Sequencing

Analysis of differentially expressed genes (DESeq)

Genes with significantly affected expression

mRNA testing of patients with pathogenic variants (multiplex RT-qPCR)

mRNA testing of controls

Confirmation of a significant difference **" transcriptomic signature"**

Normal expression level of *PQBP1*

Specificity ? (mRNA from patients with FXS)

Analysis of mRNAs from patients with VUS in *PQBP1*

Patients with VUS in *PQBP1*

➔ Establish the transcriptomic signature of *PQBP1* (5 to 10 genes)

4) And for the patients with no pathogenic variation?

- Data reanalysis

  → identification of potential new genes

- Genome sequencing

https://www.integragen.com/fr/services/sequencage-dadn

Thank you for your attention