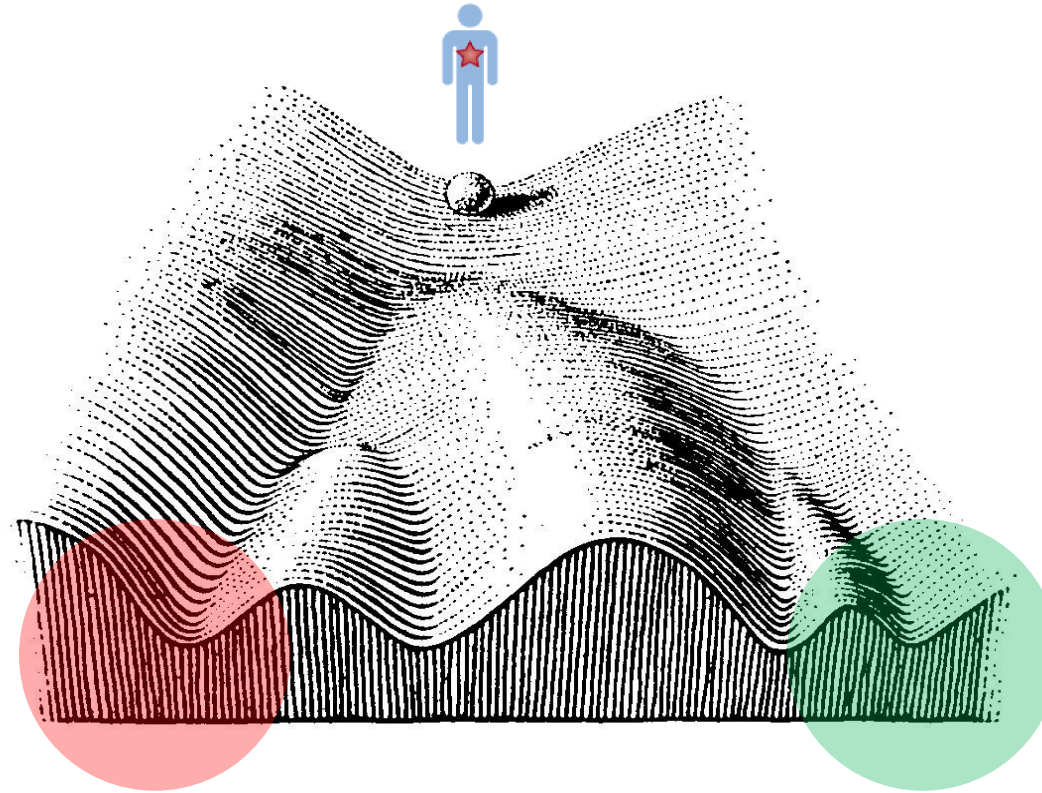
Phelan McDermid Syndrome

Thomas Bourgeron,
Institut Pasteur, France
(thomasb@pasteur.fr)



INSTITUT PASTEUR

Université de Paris

AUTISME & TROUBLES DU NEURO-DÉVELOPPEMENT GIS

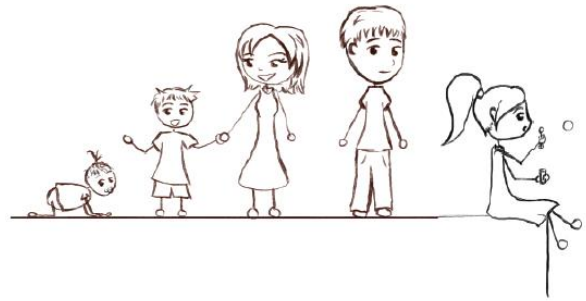
cnrs

INOVAND

Clinical team, Robert Debré Hospital

R. Delorme, Head of unit
A. Ayrolles, A. Maruani, Psychiatrists
M. Rachid, AC. Tabet, Cytogeneticists
R. Bonicel, Engineer

Autistic individuals, their families and non-autistic individuals



Assistant

B. Devauchelle

Head of unit

T. Bourgeron

Project/data managers

S. Dauzet

C. Lehoucq

A. Batut

Mouse models

S. Coquerant, Technician

F. de Chaumont, Engineer

B. Forget, Postdoc

E. Verpy, Scientist

Genetics and brain imaging

E. Barthome, PhD student

F. Cliquet, Engineer

M. Fleury, Postdoc

C. Leblond, Scientist

N. Lemière, Technician

A. Mathieu, Engineer

T. Rolland, Scientist

A. Vitrac, Postdoc

Phelan-McDermid Syndrome INTERNATIONAL REGISTRY

the SHANK2 foundation

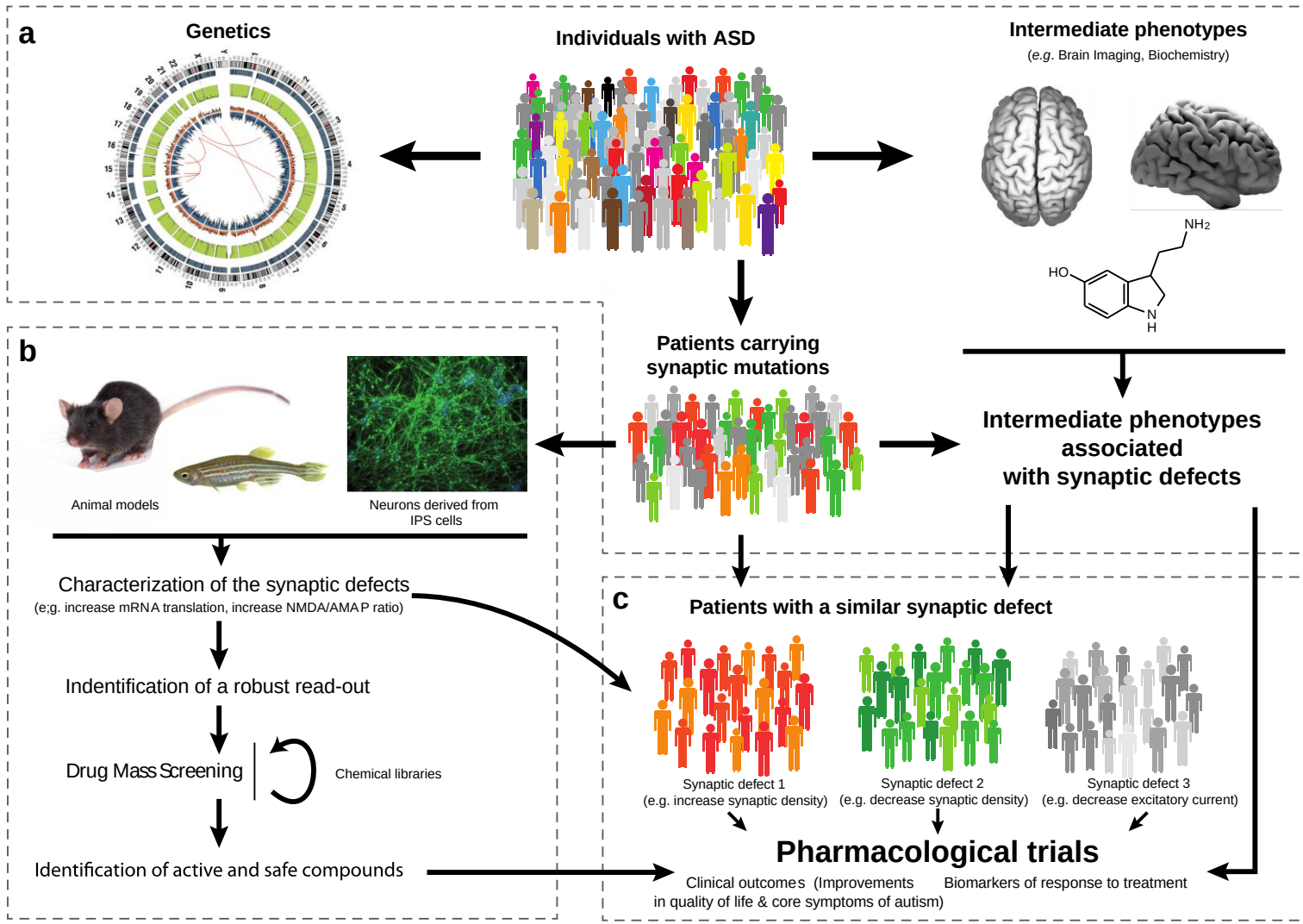
AIMS•2•TRIALS AUTISM RESEARCH FOR EUROPE

CANDY

ITHACA

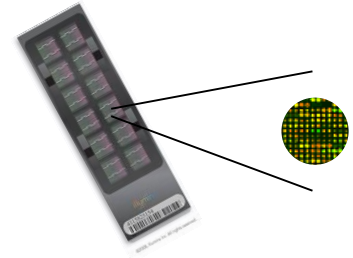
R2D2 Mental Health

Strategy

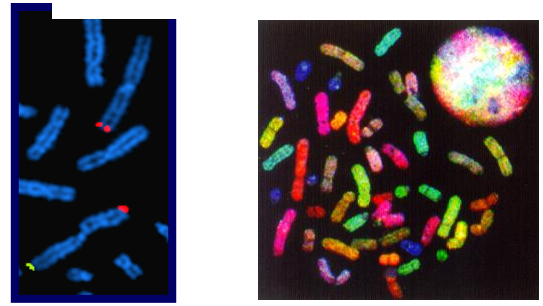


Delorme *et al.* *Nature Medicine* 2013

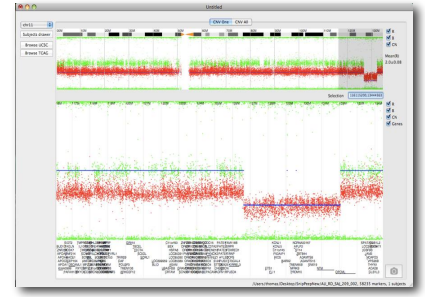
Human genome



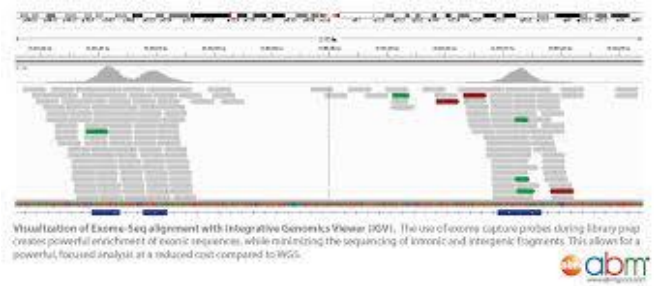
1980



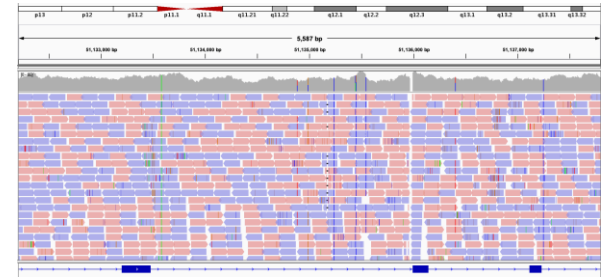
1990



2000



2010



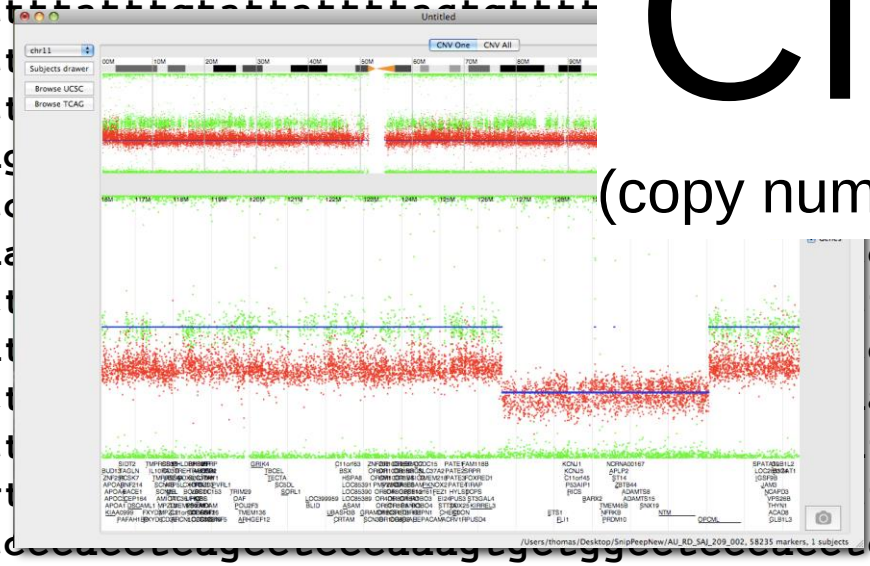
Genetic variations

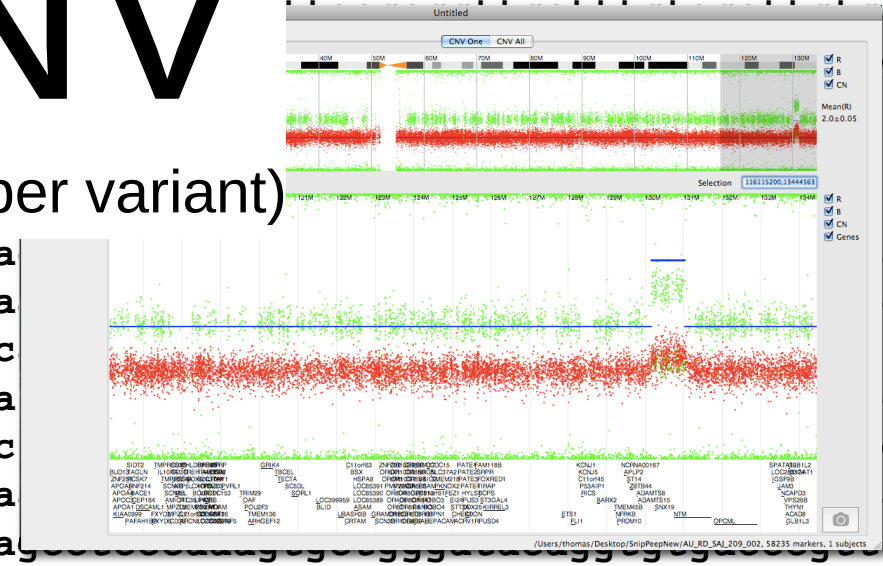
SNP

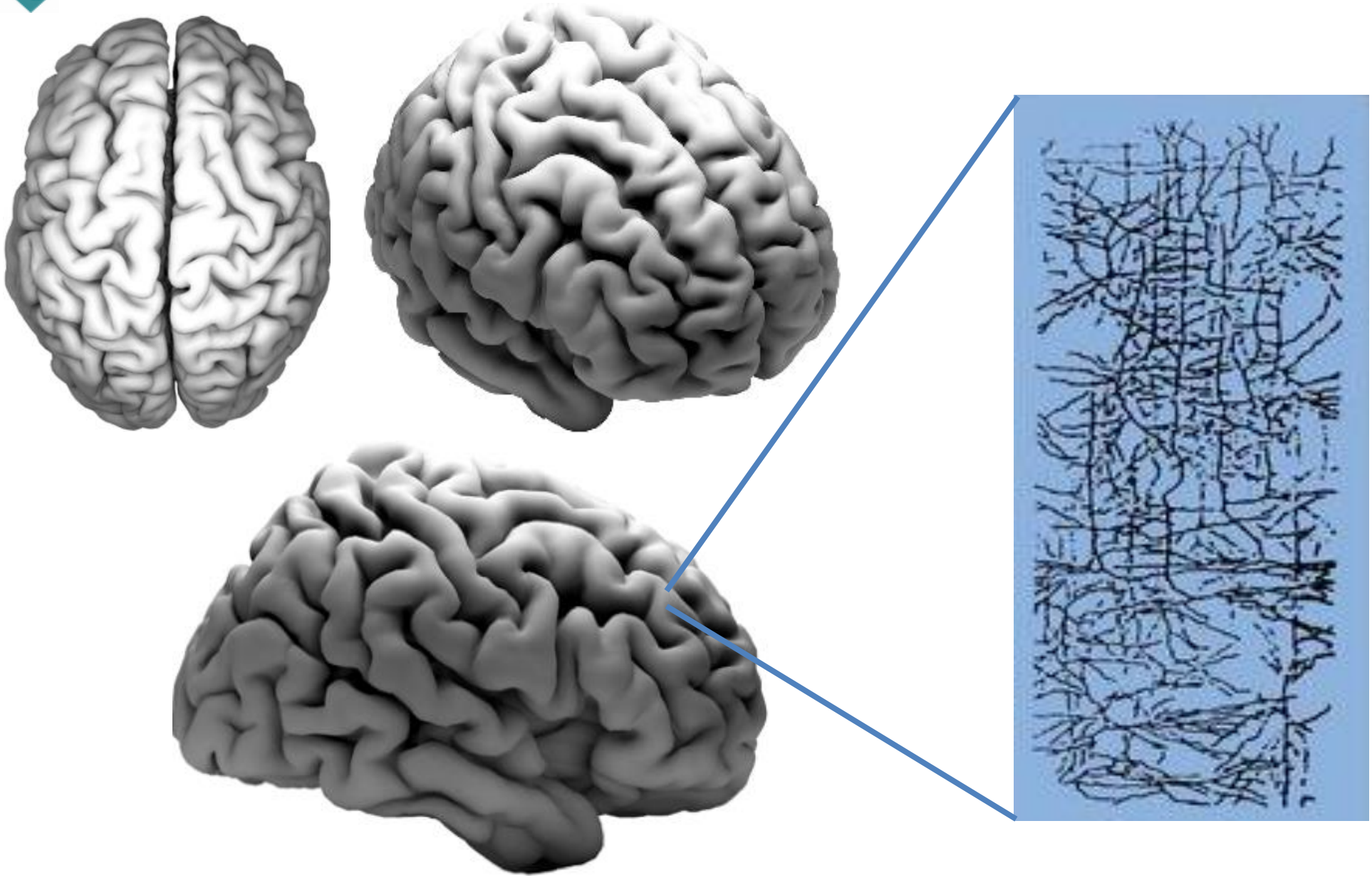
(single nucleotide polymorphism)

CNV

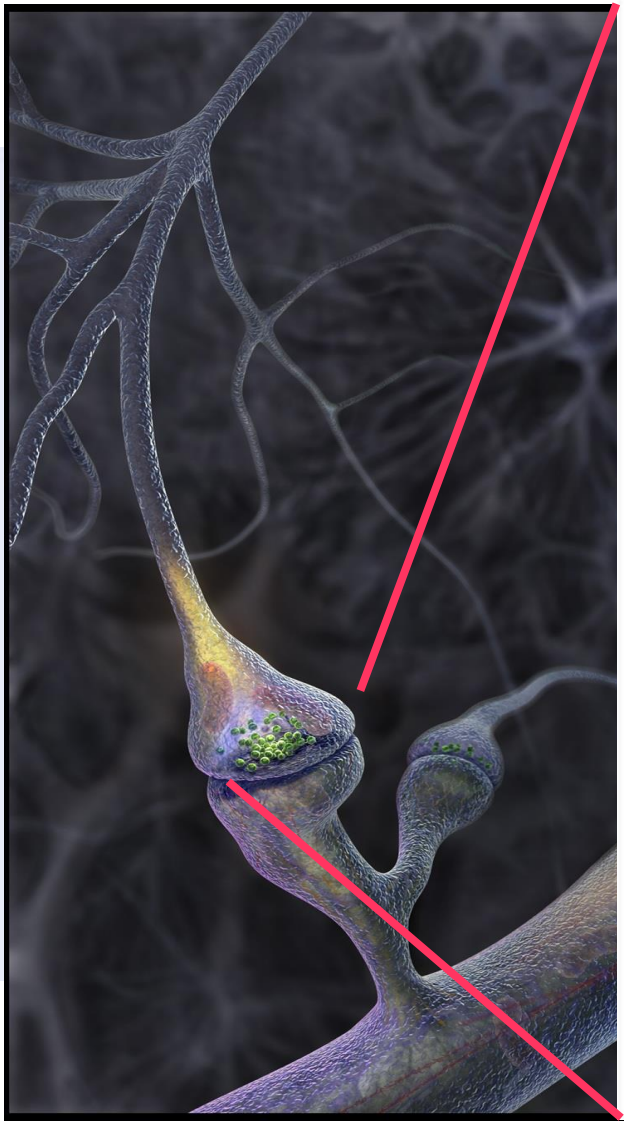
(copy number variant)

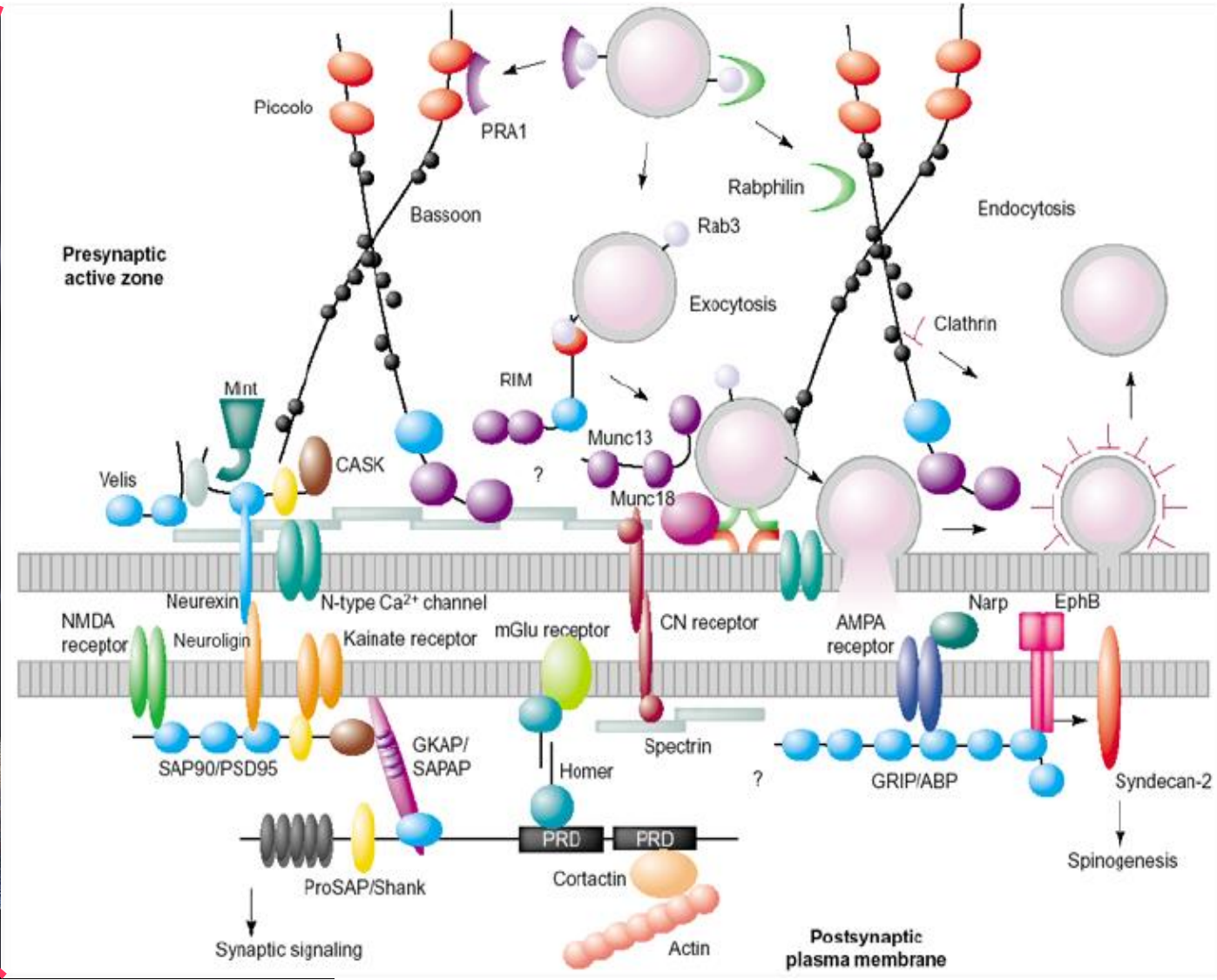




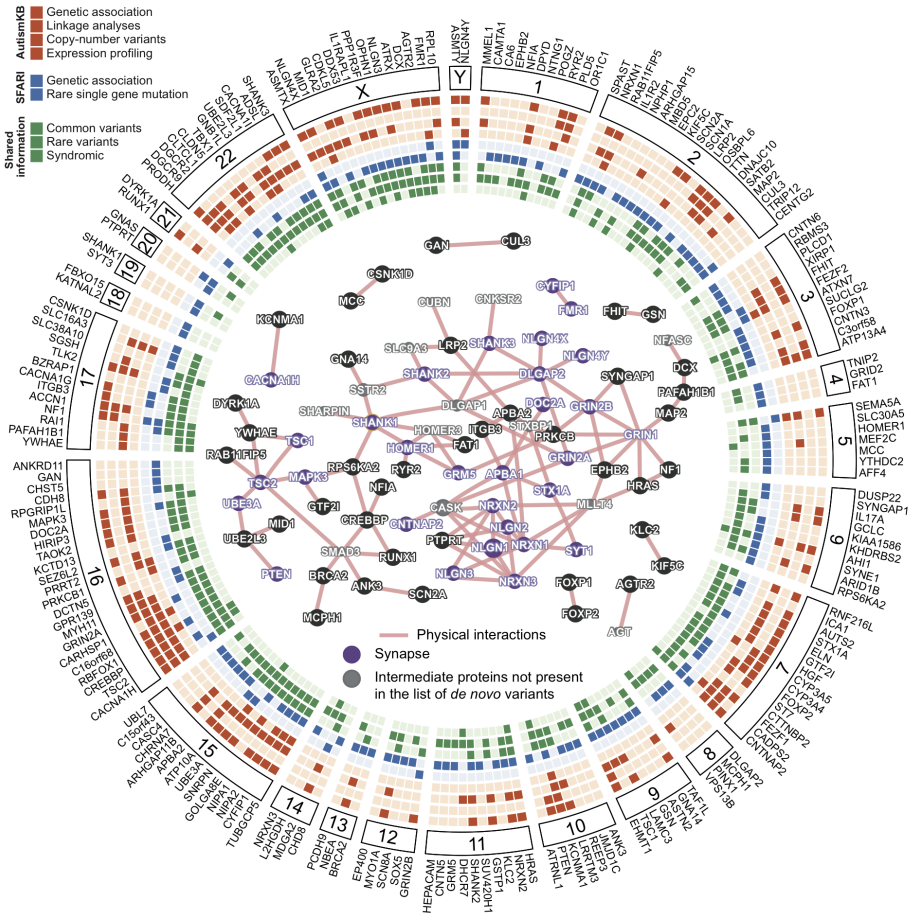


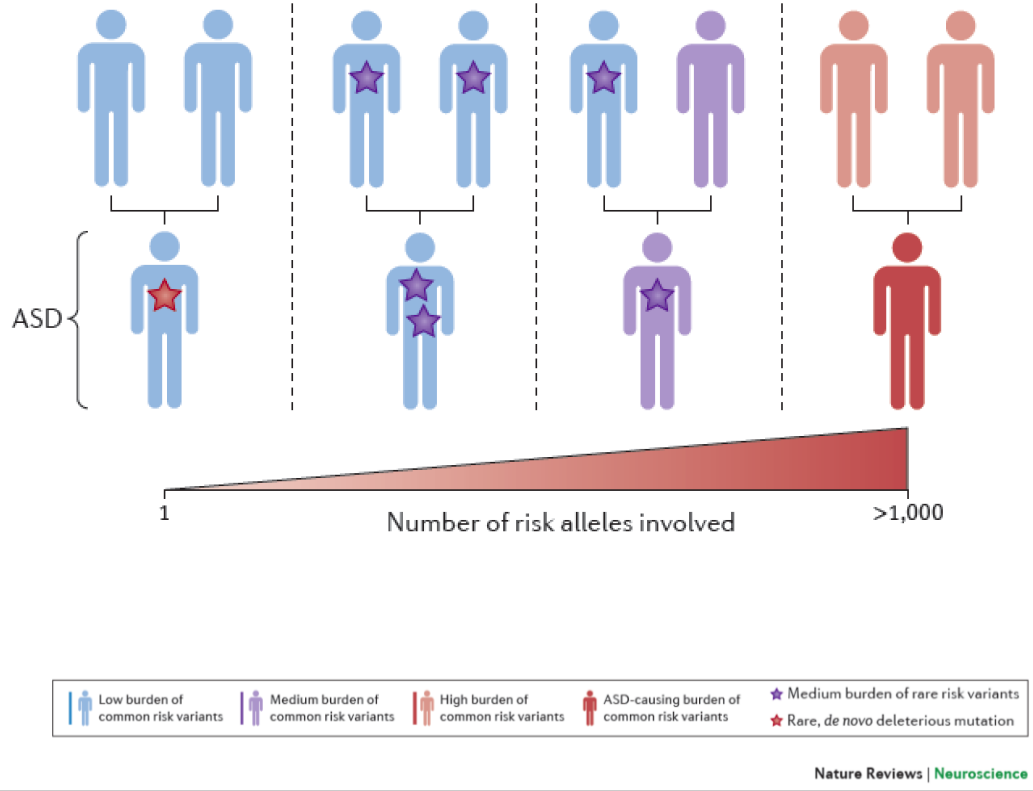
Synapses




Piccolo
PRA1
Bassoon
Rabphilin
Rab3
Endocytosis
Presynaptic
active zone
Exocytosis
Clathrin
RIM
Mint
Munc13
CASK
Velis
?
Munc18
Neurexin
N-type Ca2+ channel
NMDA
receptor
Neuroligin
Kainate receptor
mGlu receptor
CN receptor
AMPA
receptor
Narp
EphB
SAP90/PSD95
GKAP/
SAPAP
Homer
Spectrin
?
GRIP/ABP
Syndecan-2
PRD
PRD
ProSAP/Shank
Cortactin
Spinogenesis
Synaptic signaling
Actin
Postsynaptic
plasma membrane

Genetics and autismS+

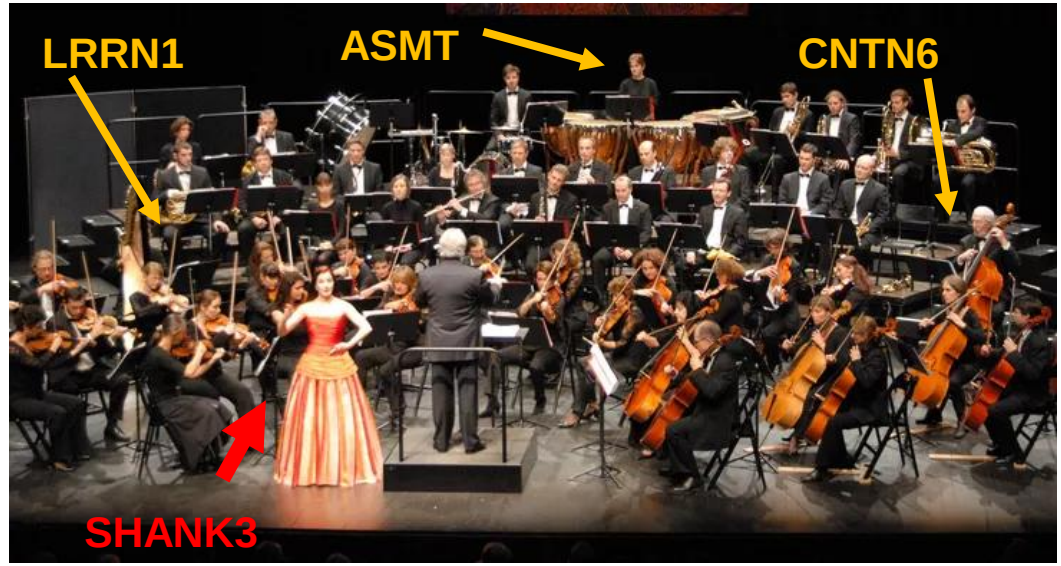


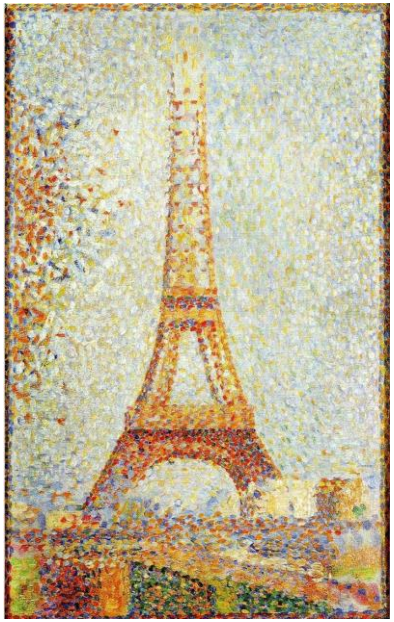


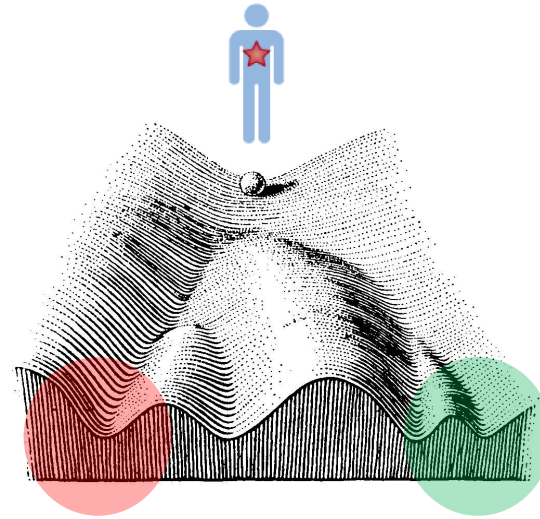
Huguet *et al. Annu Rev Genomics Hum Genet.* 2013

Bourgeron *Nature Reviews Neuroscience* 2015

Genetic cocktail/orchestra







Phelan-McDermid Syndrome

Phelan-McDermid Syndrome

Katy Phelan

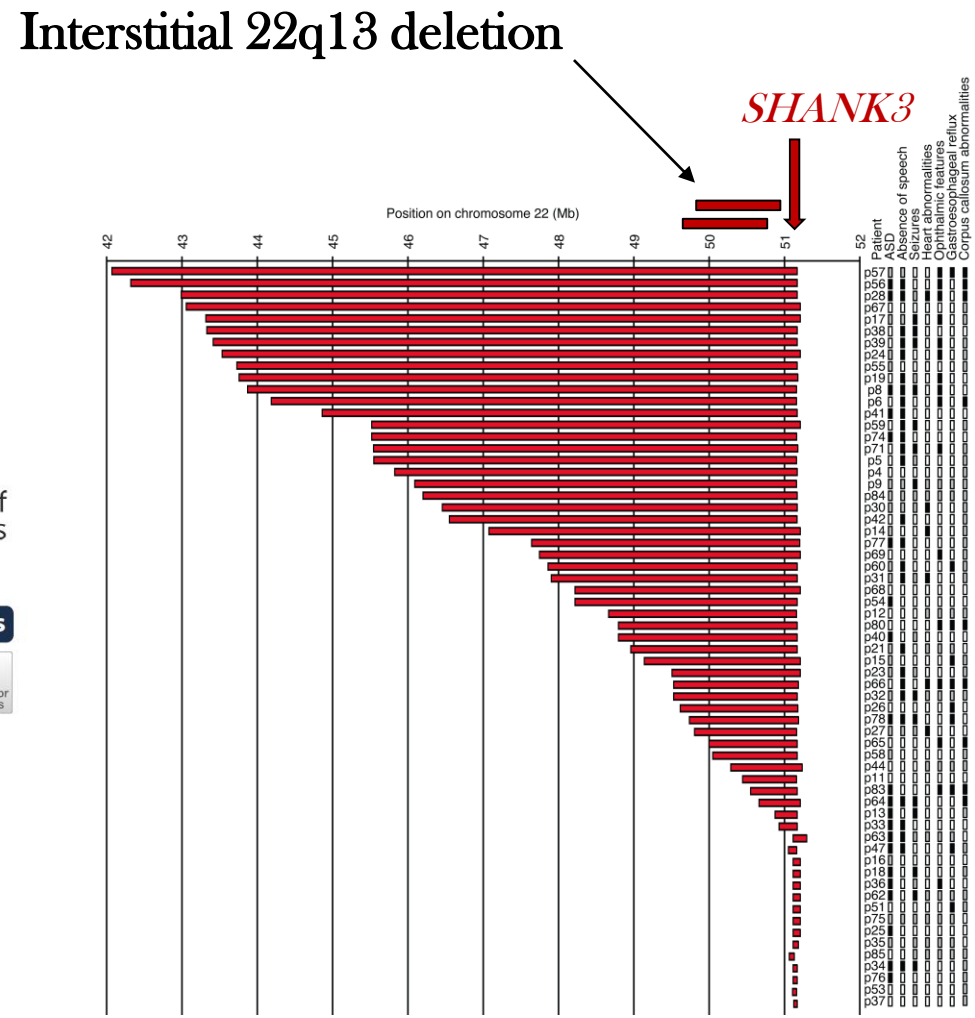
Phelan *et al.*
Orphanet Journal of Rare Diseases (2022) 17:27
https://doi.org/10.1186/s13023-022-02180-5

Orphanet Journal of Rare Diseases

LETTER TO THE EDITOR Open Access

Phelan-McDermid syndrome: a classification system after 30 years of experience

Katy Phelan[1*], Luigi Boccuto[2], Craig M. Powell[3], Tobias M. Boeckers[4], Conny van Ravenswaaij-Arts[5], R. Curtis Rogers[6], Carlo Sala[7], Chiara Verpelli[7], Audrey Thurm[8], William E. Bennett Jr.[9], Christopher J. Winrow[10], Sheldon R. Garrison[11], Roberto Toro[12] and Thomas Bourgeron[12*]

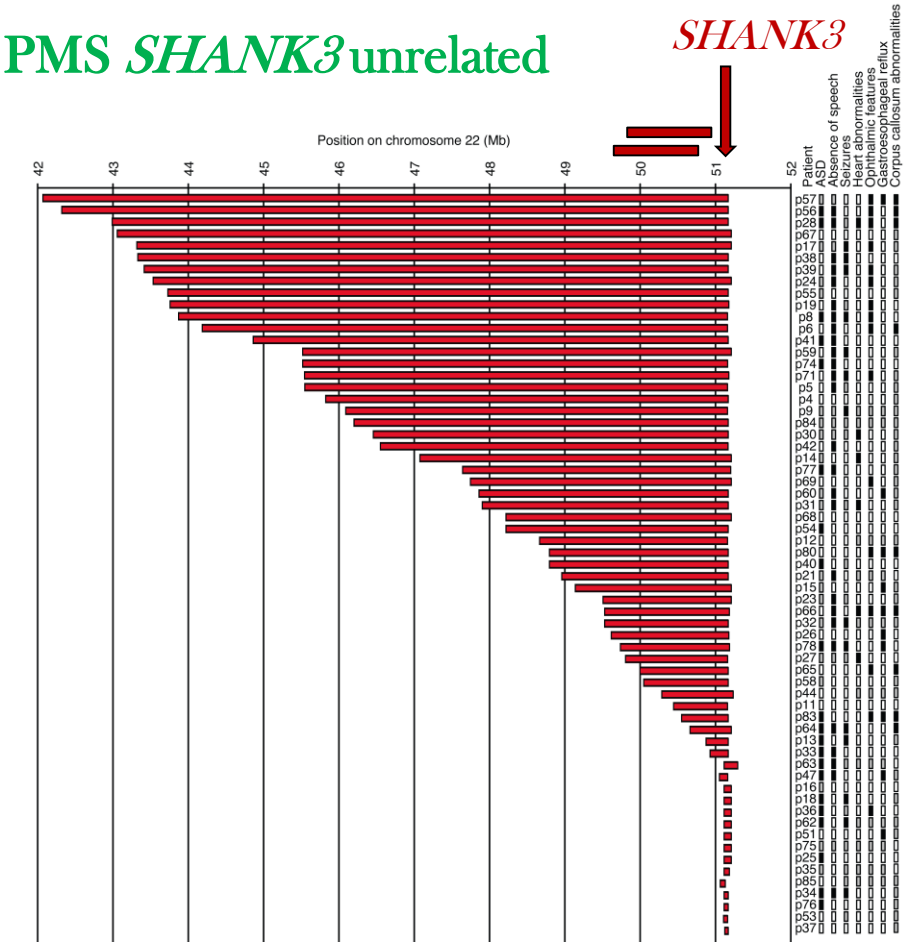


Phelan-McDermid Syndrome

Katy Phelan

Classification :

- PMS *SHANK3* related
- PMS *SHANK3* unrelated



Phelan *et al.*
Orphanet Journal of Rare Diseases (2022) 17:27
https://doi.org/10.1186/s13023-022-02180-5

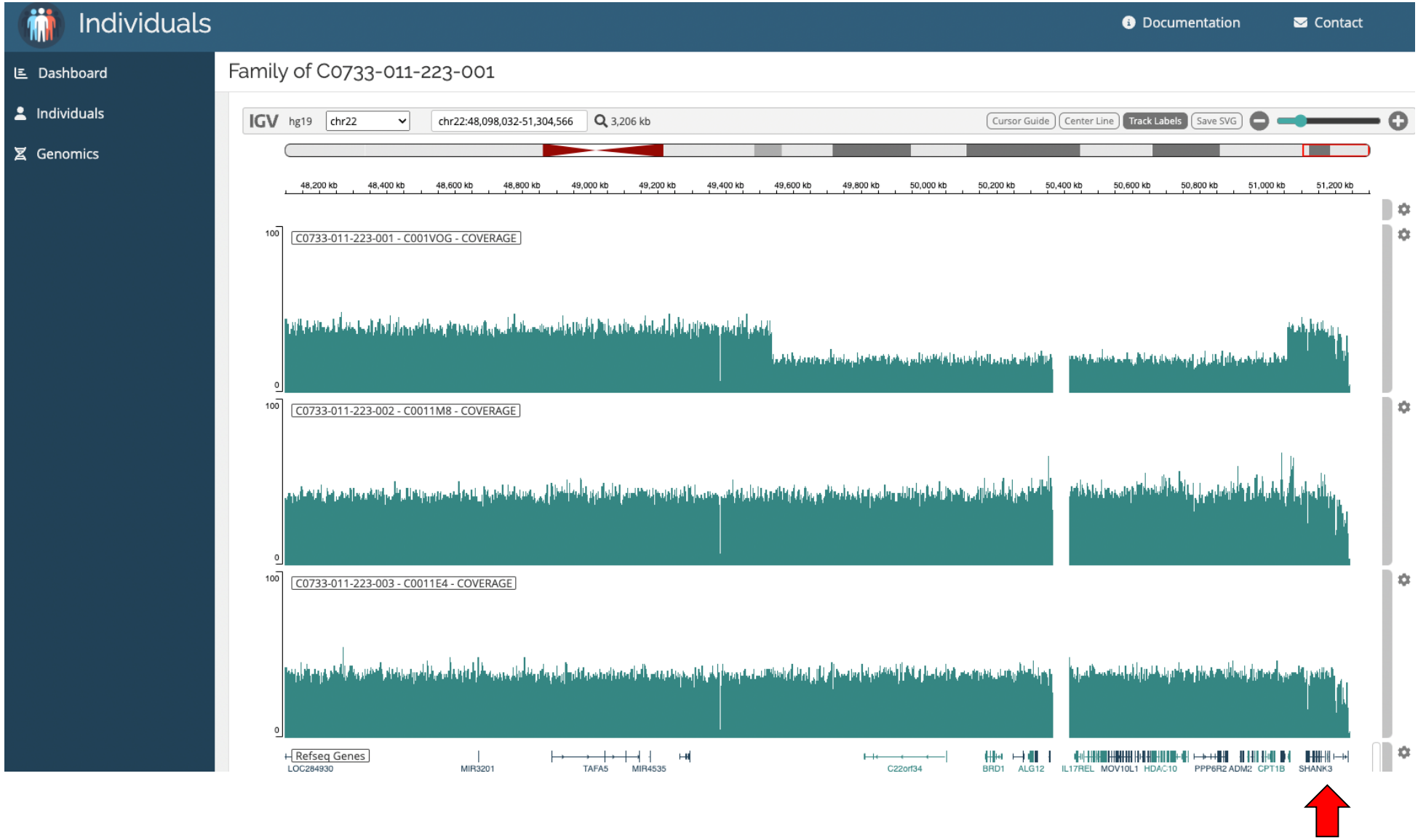
Orphanet Journal of Rare Diseases

LETTER TO THE EDITOR Open Access

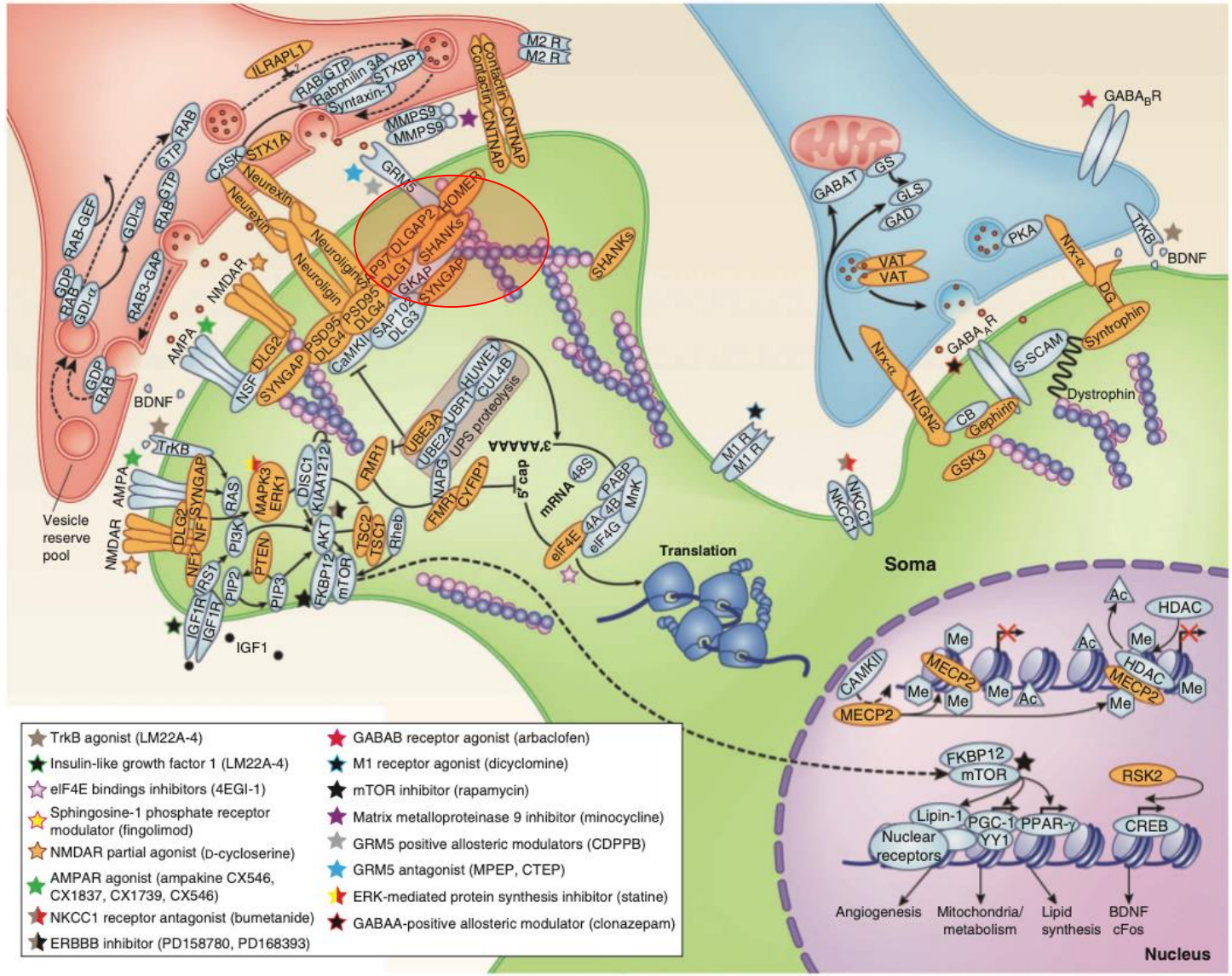
Phelan-McDermid syndrome: a classification system after 30 years of experience

Katy Phelan[1*], Luigi Boccuto[2], Craig M. Powell[3], Tobias M. Boeckers[4], Conny van Ravenswaaij-Arts[5], R. Curtis Rogers[6], Carlo Sala[7], Chiara Verpelli[7], Audrey Thurm[8], William E. Bennett Jr.[9], Christopher J. Winrow[10], Sheldon R. Garrison[11], Roberto Toro[12] and Thomas Bourgeron[12*]

Phelan-McDermid Syndrome



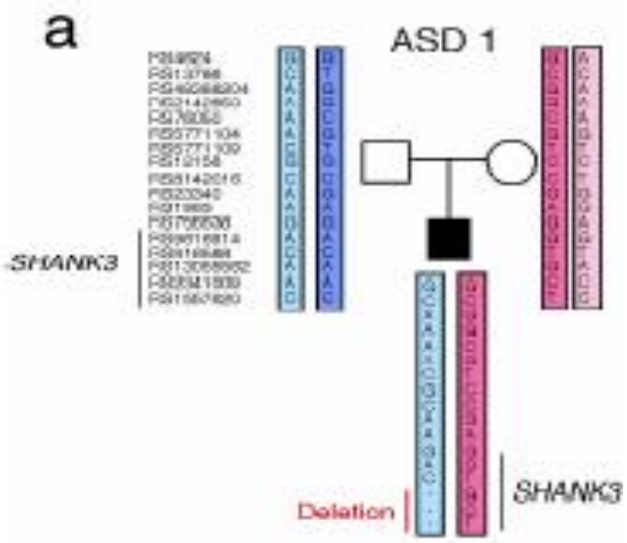
Why *SHANK3* is important for Phelan McDermid syndrome...

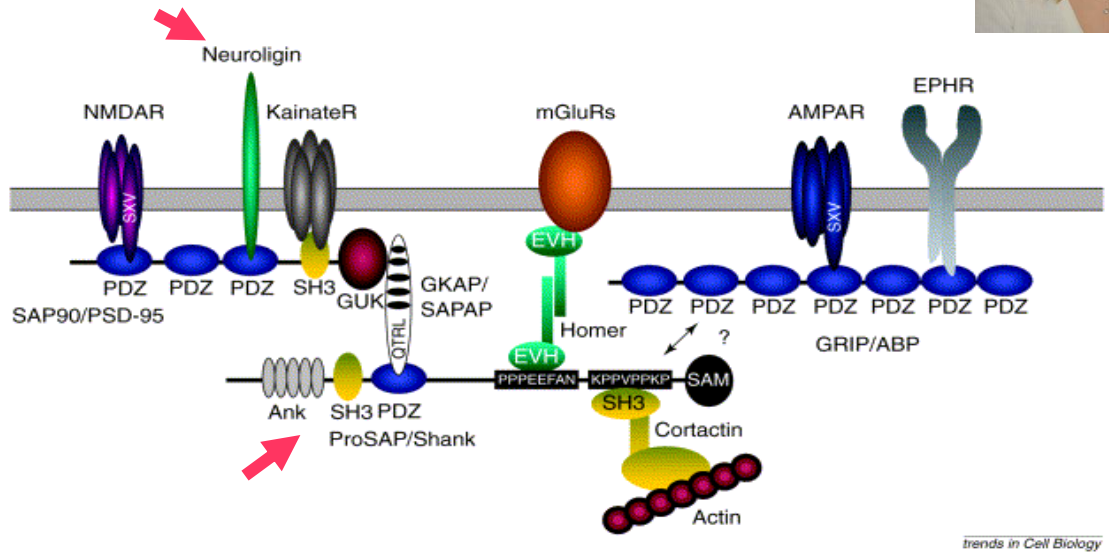


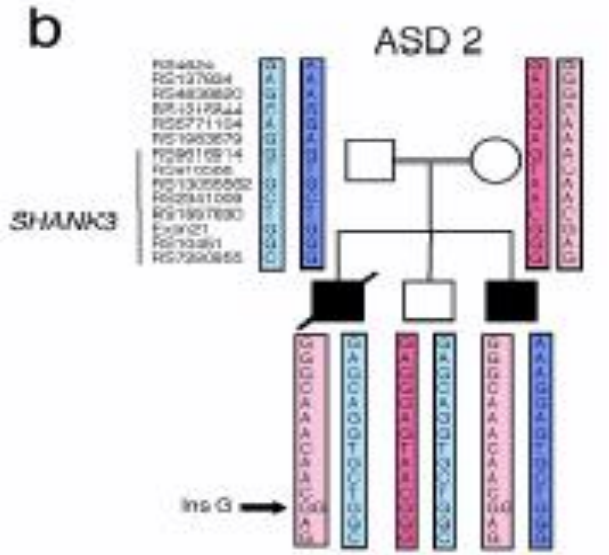
Delorme *et al.* *Nature Medicine* 2013

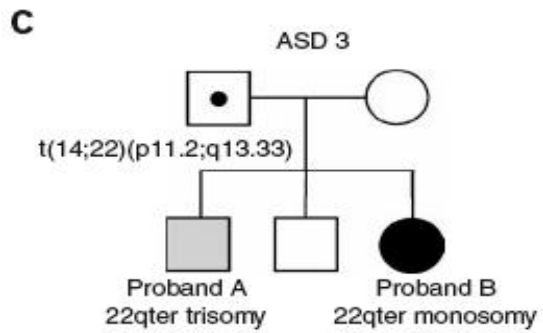
Mutations of the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders

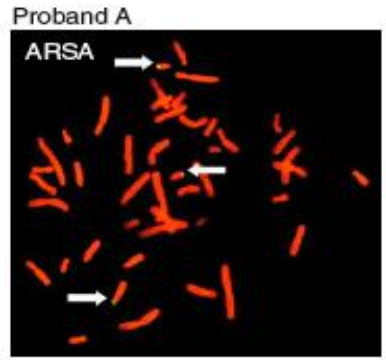
Durand *et al. Nature Genetics*, 2007

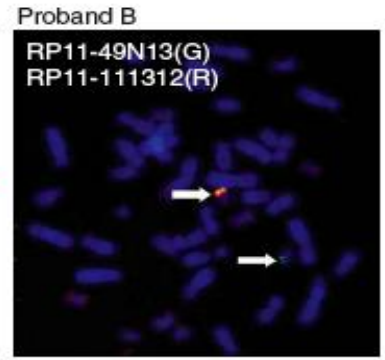












Phelan-McDermid Syndrome

npj | Genomic Medicine

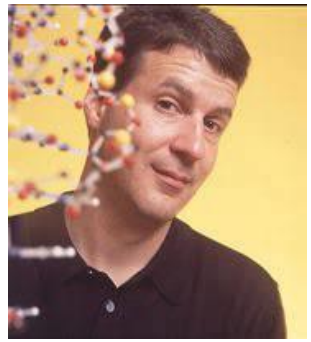
www.nature.com/npjgenmed

ARTICLE OPEN

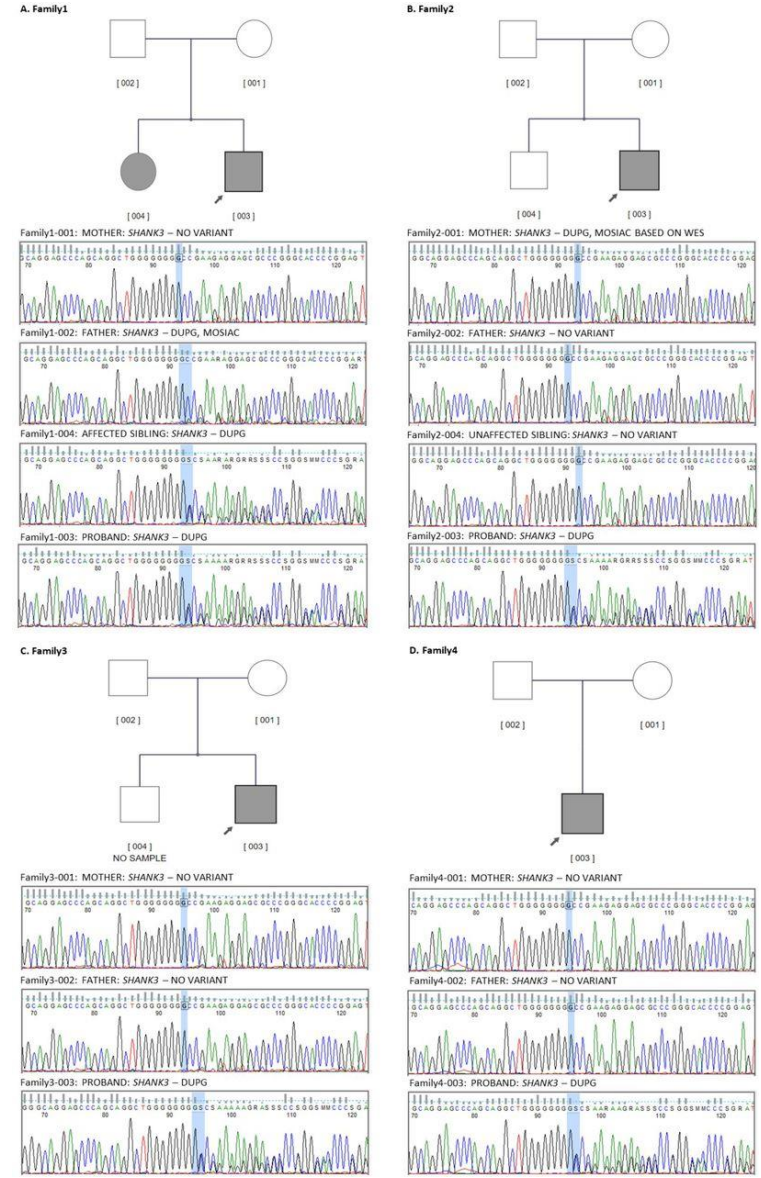
Check for updates

A recurrent *SHANK3* frameshift variant in Autism Spectrum Disorder

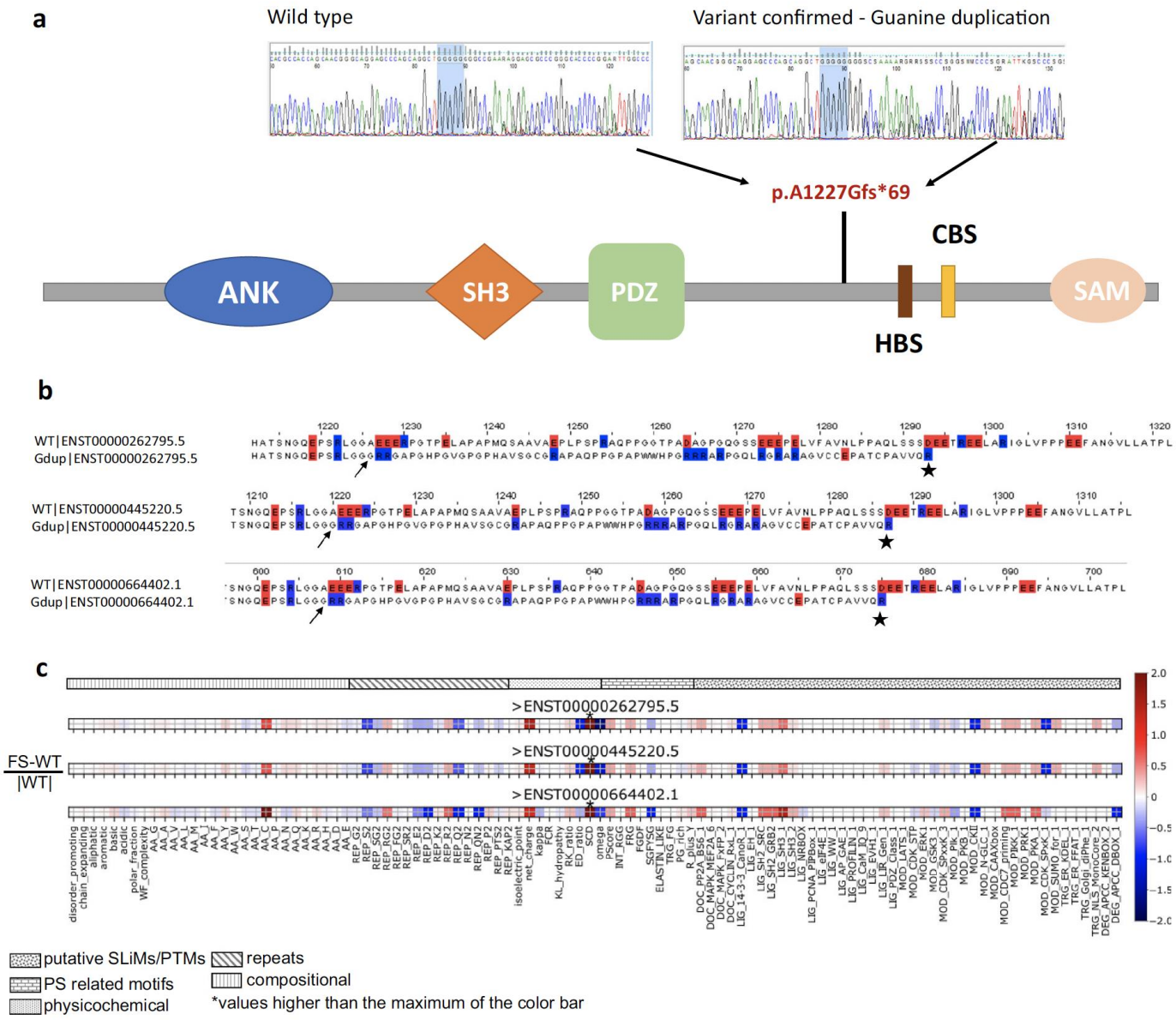
Livia O. Loureiro[1,27], Jennifer L. Howe[1,27], Miriam S. Reuter[2], Alana Iaboni[3], Kristina Calli[4], Delnaz Roshandel[1], Iva Pritišanac[5,6], Alan Moses[6], Julie D. Forman-Kay[5,7], Brett Trost[1], Mehdi Zarrei[1], Olivia Rennie[1], Lynette Y. S. Lau[8], Christian R. Marshall[8,9], Siddharth Srivastava[10], Brianna Godlewski[10], Elizabeth D. Buttermore[10], Mustafa Sahin[10], Dean Hartley[11], Thomas Frazier[12], Jacob Vorstman[13,14], Stelios Georgiades[15], Suzanne M. E. Lewis[4], Peter Szatmari[13,14,16], Clarrisa A. (Lisa) Bradley[1], Anne-Claude Tabet[17,18], Marjolaine Willems[19], Serge Lumbroso[20], Amélie Piton[21,22,23], James Lespinasse[19], Richard Delorme[17,24], Thomas Bourgeron[17], Evdokia Anagnostou[3,25] and Stephen W. Scherer[1,26]✉



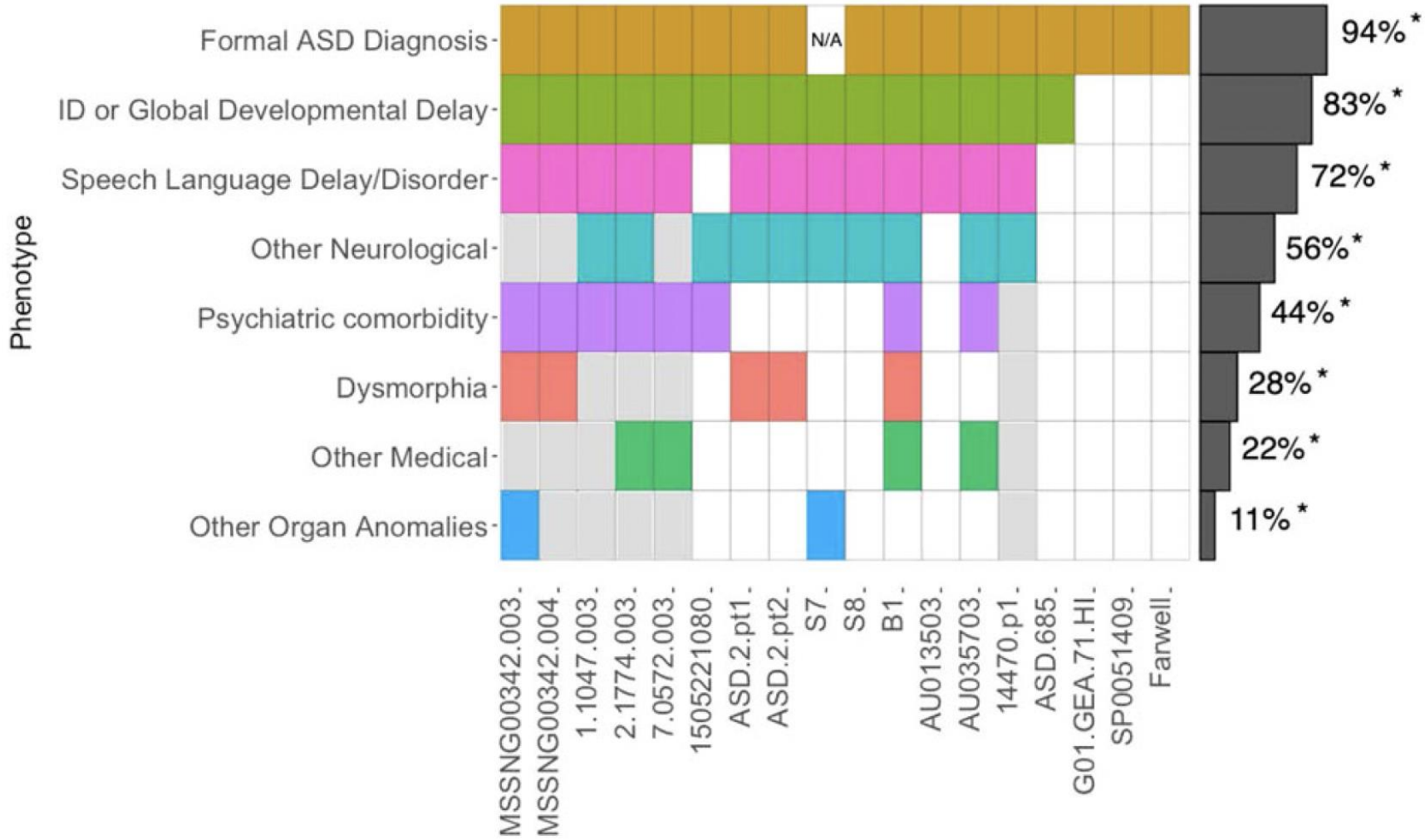
Steve Scherer



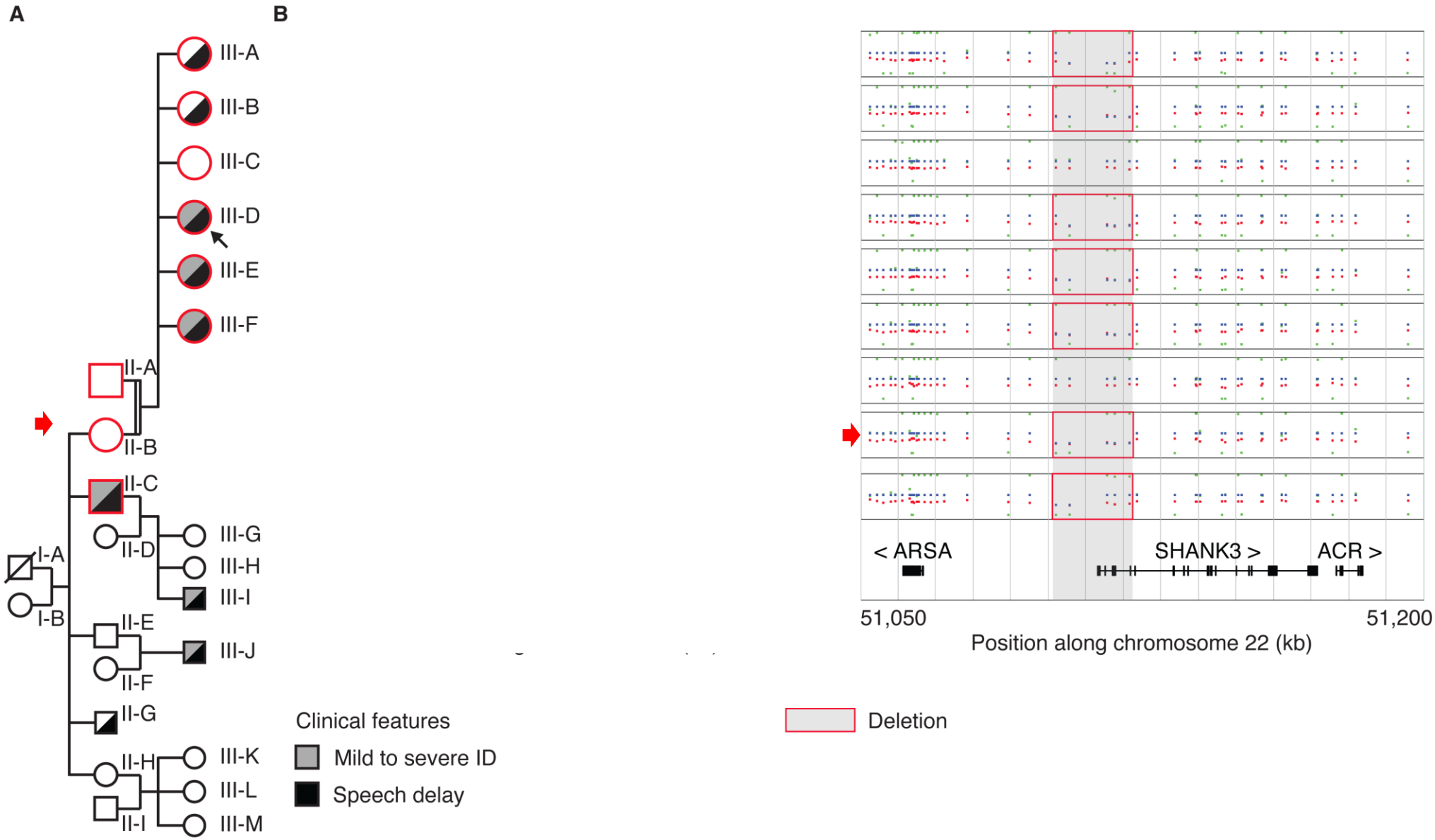
Phelan-McDermid Syndrome



Phelan-McDermid Syndrome



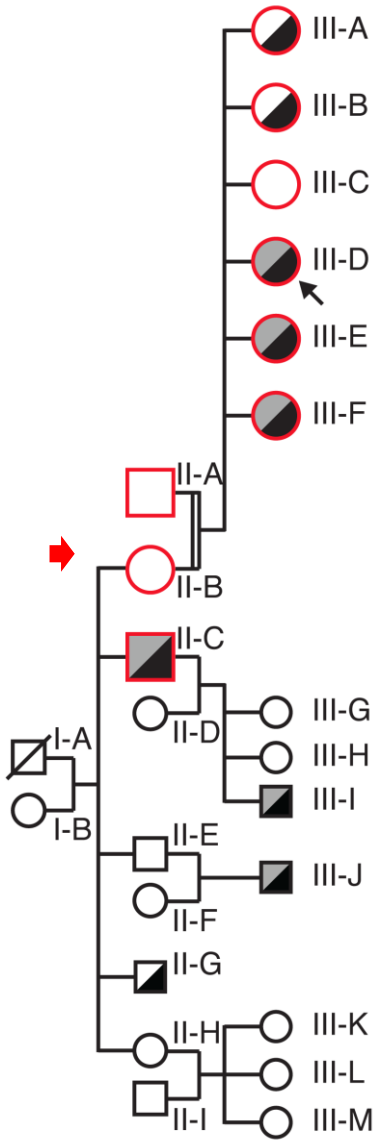
“Resilience” and *SHANK3*

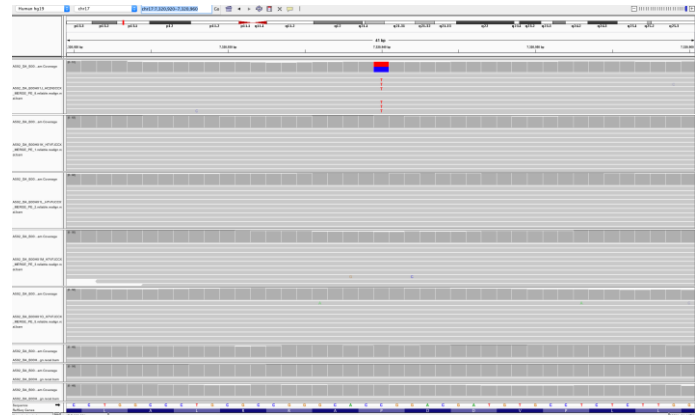


Tabet, Rolland *npj Genomic Medicine* 2017

a *de novo* NLGN2 p.P777L deleterious mutation

A





PolyPhen-2 report for Q8NFZ4 P777L

Query

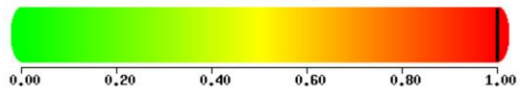
Protein Acc	Position	AA_1	AA_2	Description
Q8NFZ4	777	P	L	Canonical; RecName: Full=Neuroligin-2; Flags: Precursor; Length: 835

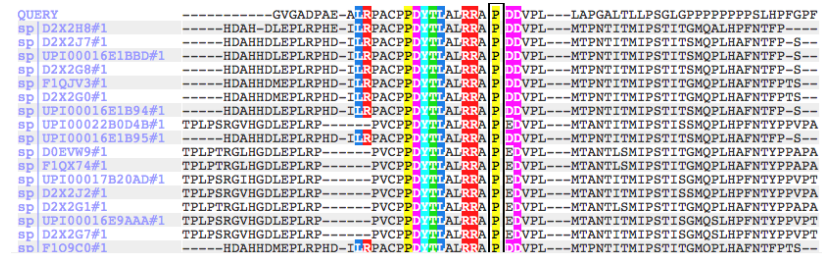
Results

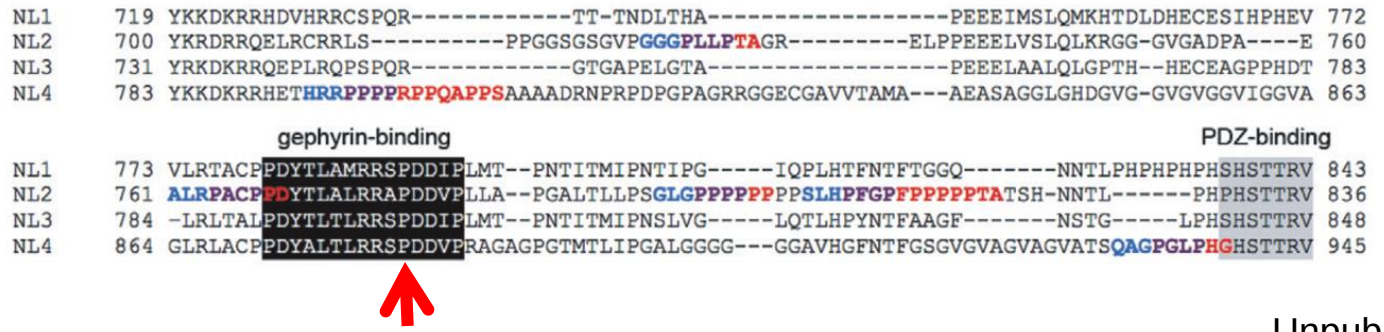
Prediction/Confidence — *PolyPhen-2 v2.2.2r398*

HumDiv

This mutation is predicted to be **PROBABLY DAMAGING** with a score of **1.000** (sensitivity: **0.00**; specificity: **1.00**)







Unpublished

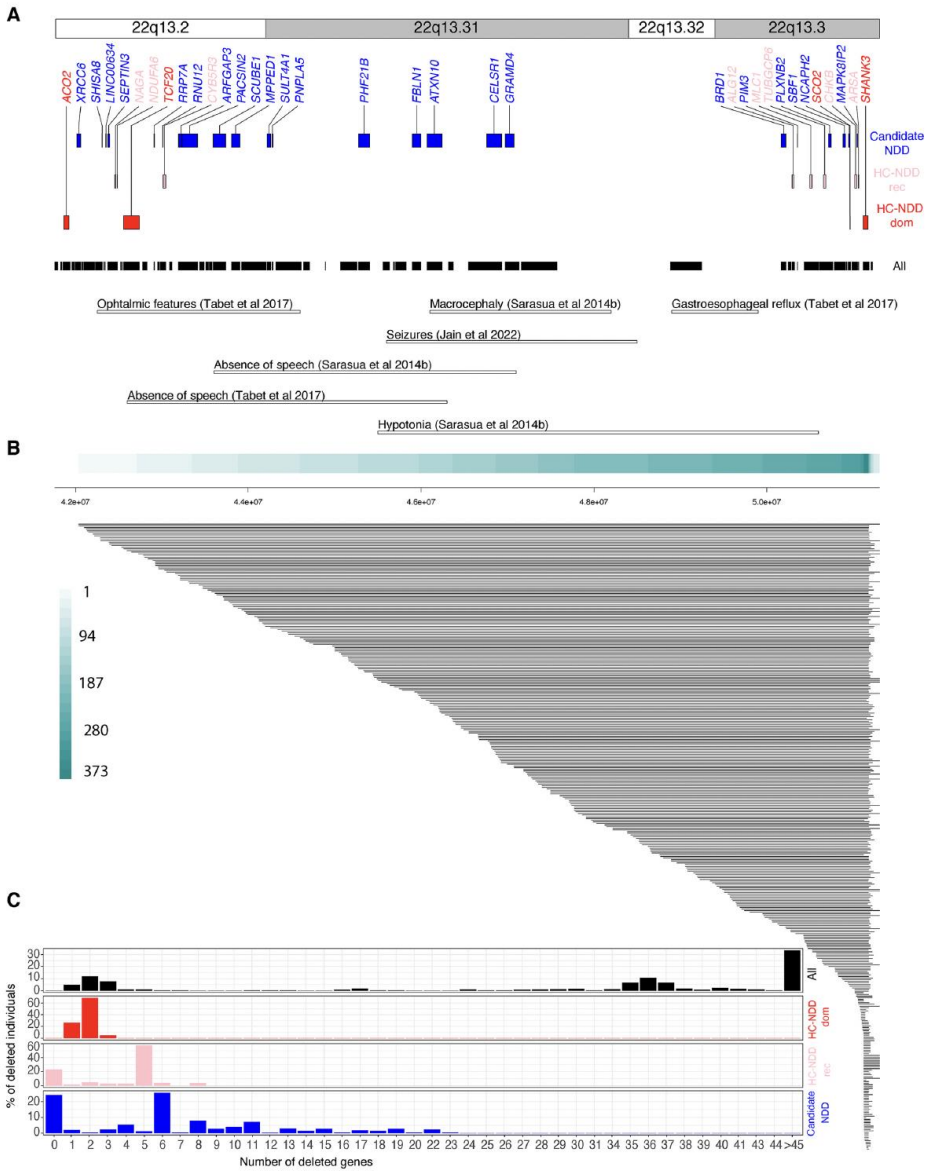
Phelan-McDermid Syndrome

Why *SHANK3* is important for Phelan McDermid syndrome ...

.... but, other genes are also important !

Phelan-McDermid Syndrome

Aline Vitrac



European Journal of Medical Genetics 66 (2023) 104732

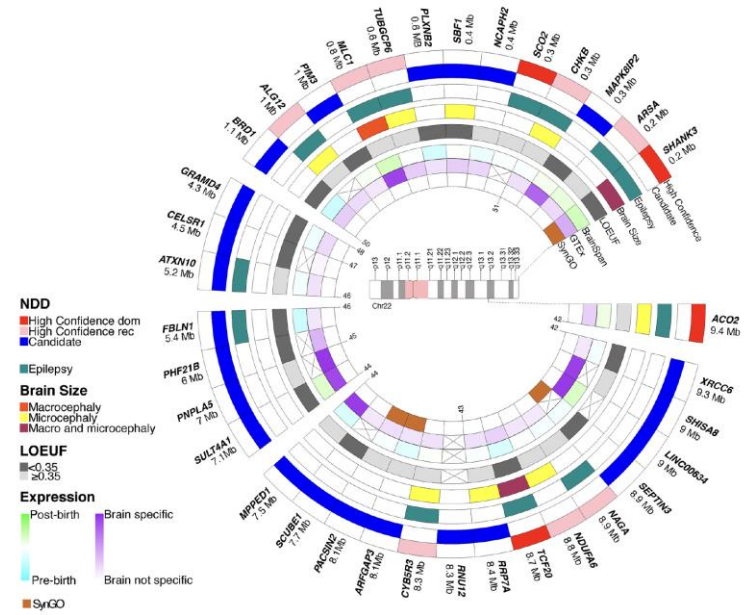
Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Dissecting the 22q13 region to explore the genetic and phenotypic diversity of patients with Phelan-McDermid syndrome

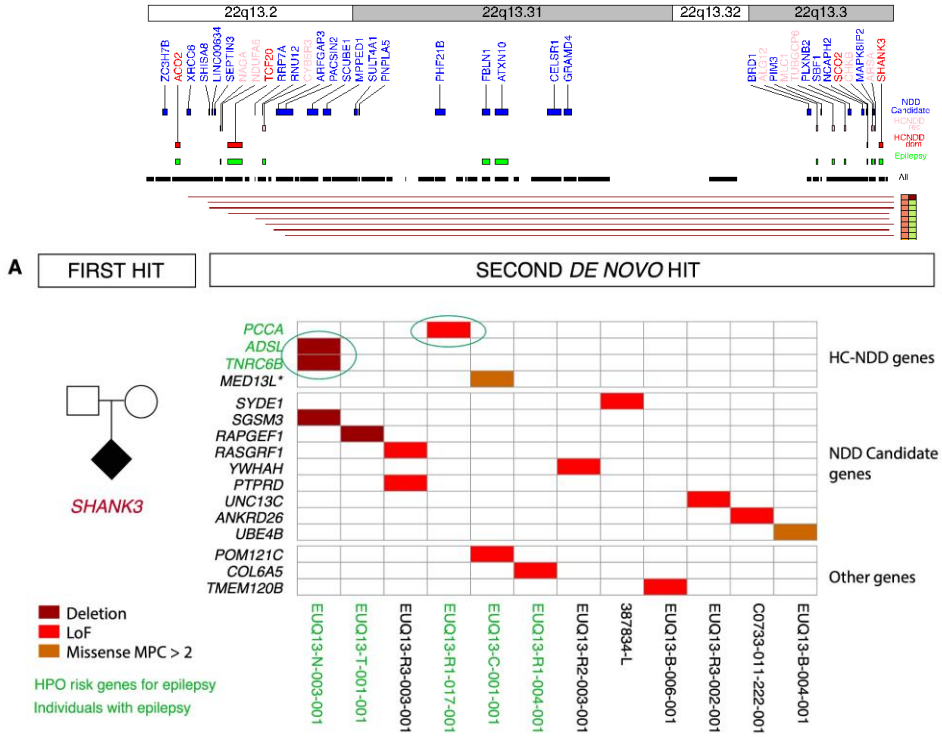
Aline Vitrac [a,**], Claire S. Leblond [a], Thomas Rolland [a], Freddy Cliquet [a], Alexandre Mathieu [a], Anna Maruani [b], Richard Delorme [b], Michael Schön [c], Andreas M. Grabrucker [d,e,f], Conny van Ravenswaaij-Arts [g], Katy Phelan [h], Anne-Claude Tabet [i], Thomas Bourgeron [a,*]



Vitrac et al. Eur. J. Med. Genet. 2023

Multiple hits in PMS

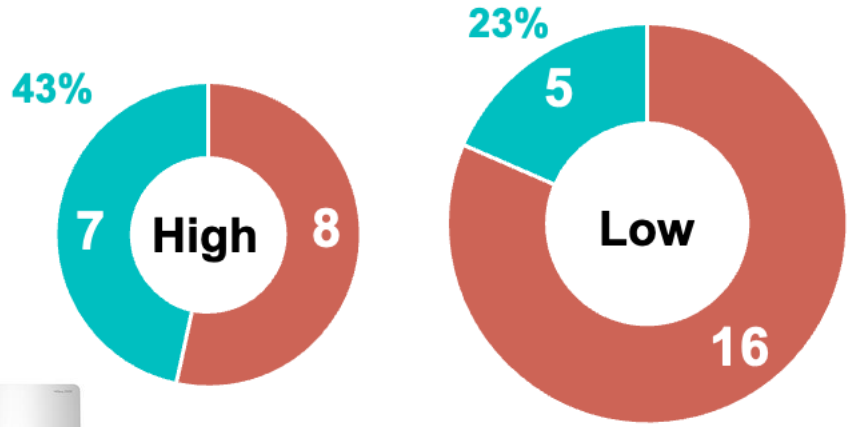
Aline Vitrac



N= 1,762 genes for epilepsy

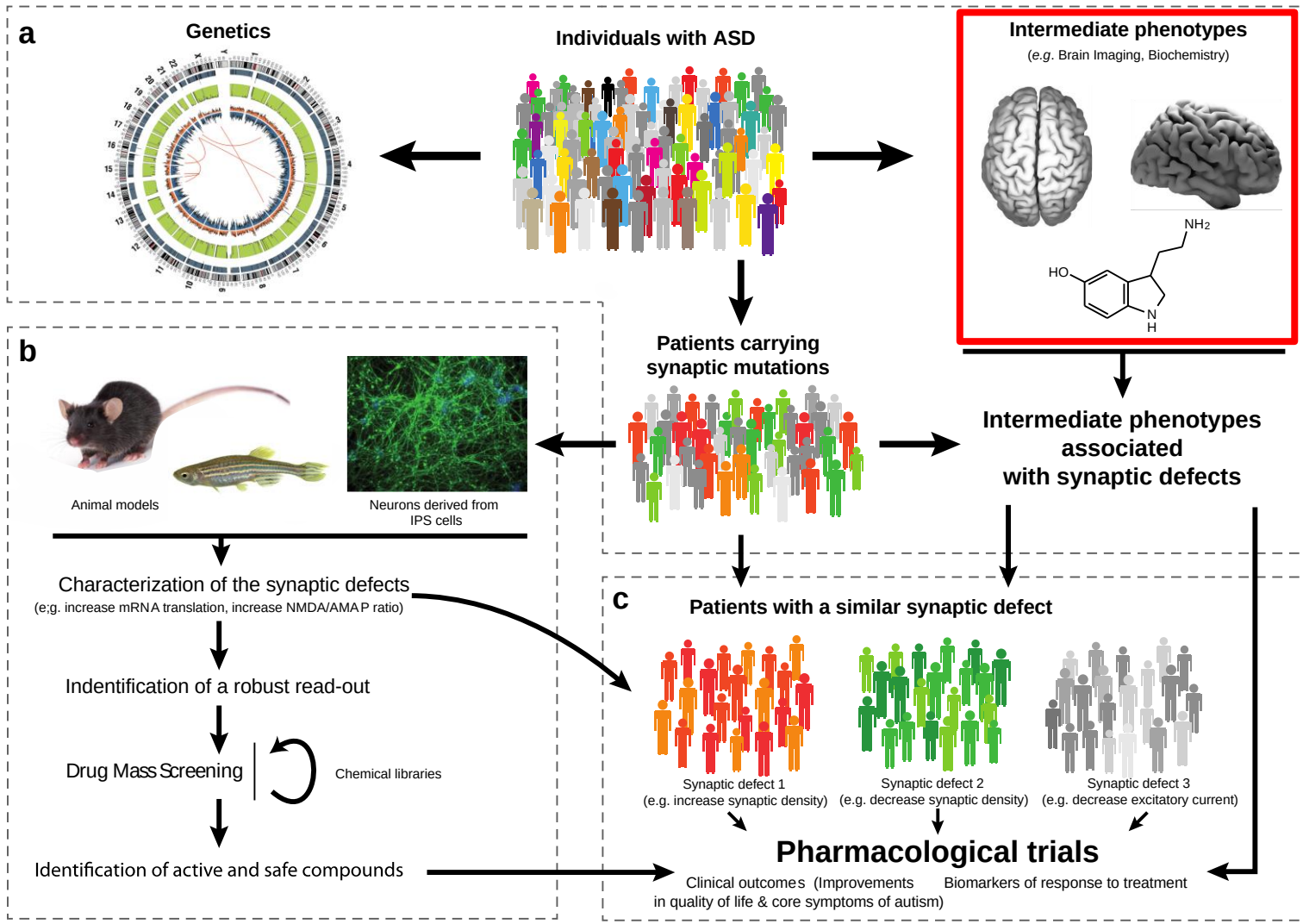
Median number of variants: 2.5

Individuals with epilepsy Yes No



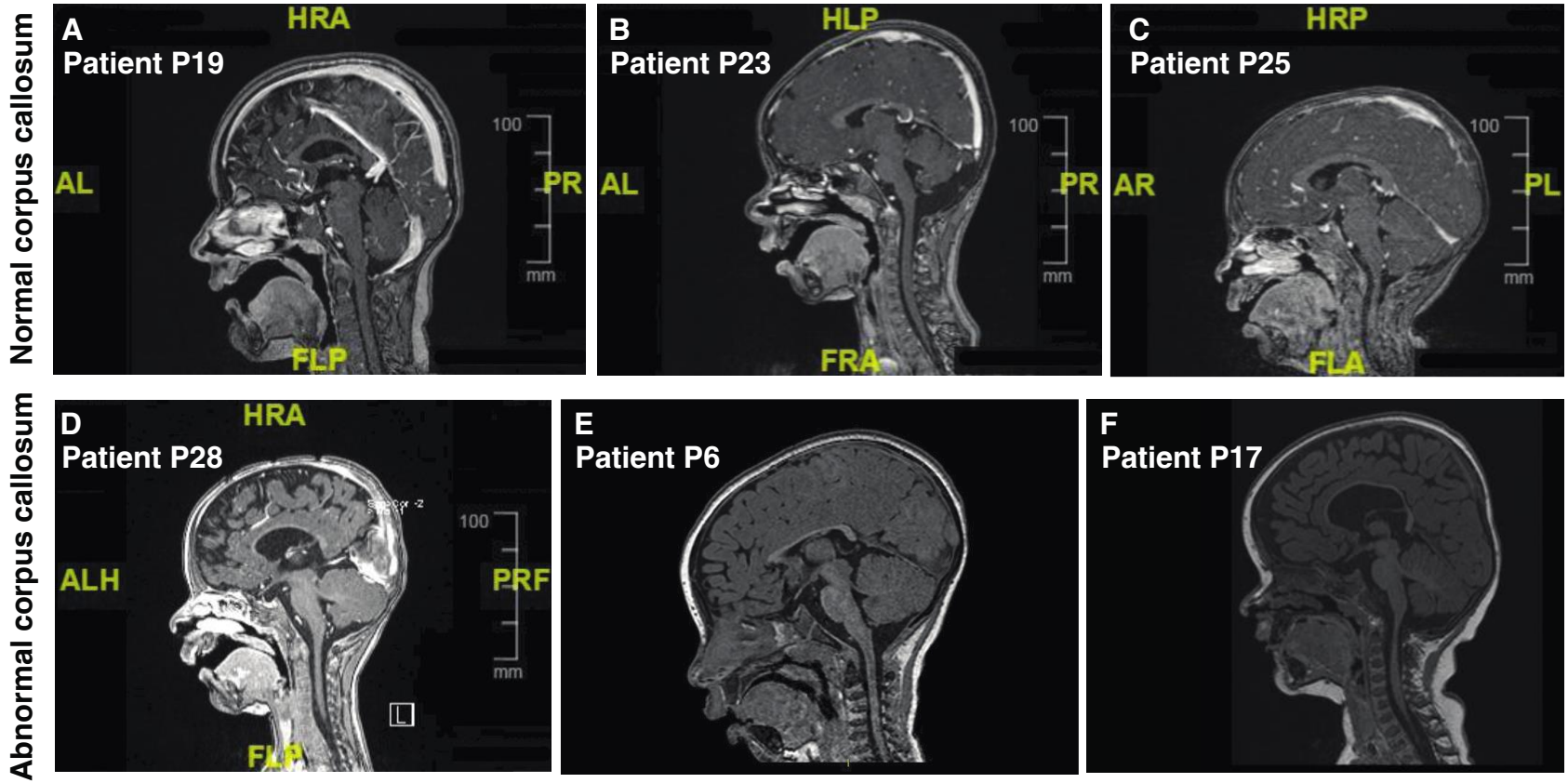
P=0.17

Strategy



Delorme *et al.* *Nature Medicine* 2013

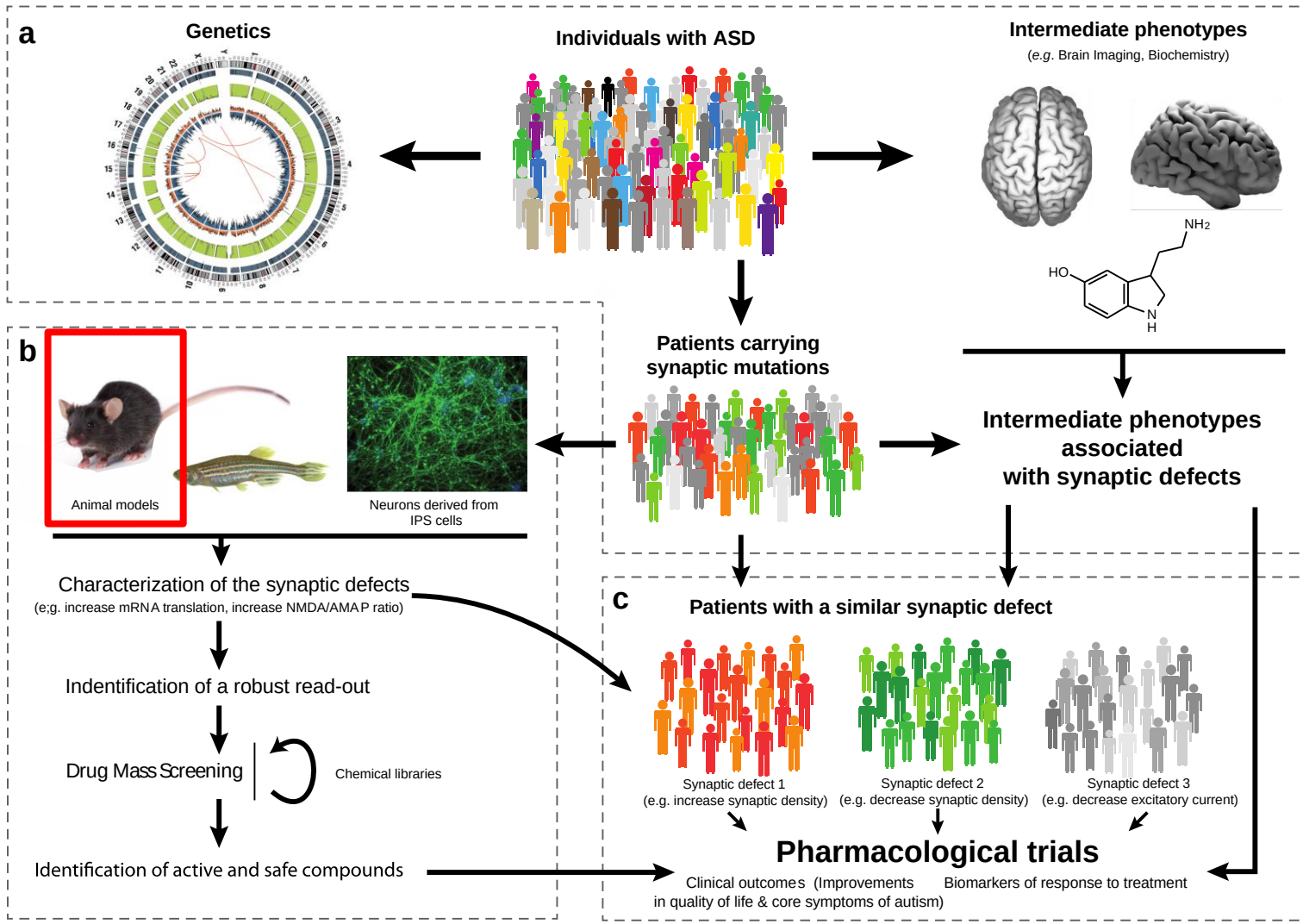
SHANK3/PMS



10/35 patients with corpus callosum (28%)

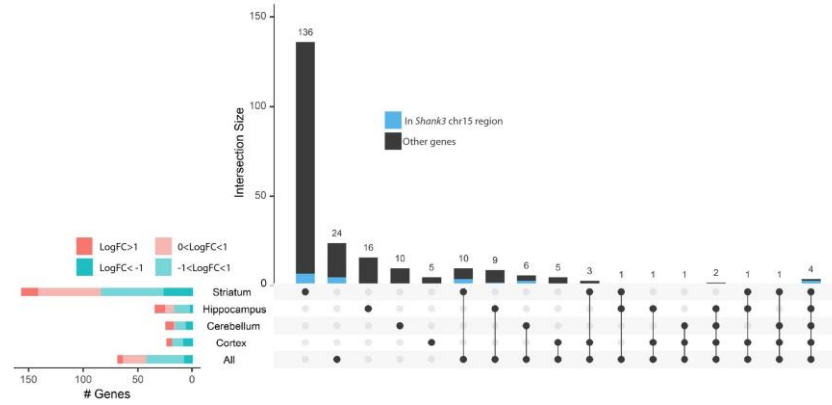
Tabet, Rolland Npj Genomic Medicine 2017

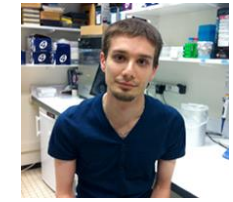
Strategy



Delorme *et al.* *Nature Medicine* 2013

Mouse models (SHANK3)



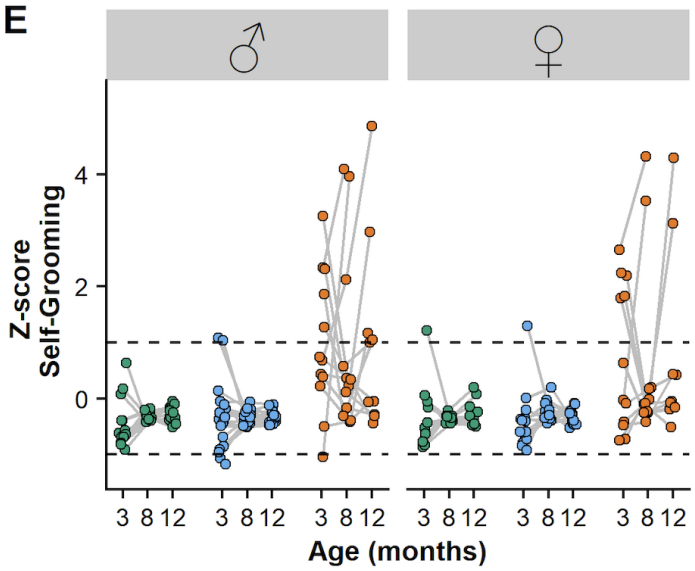


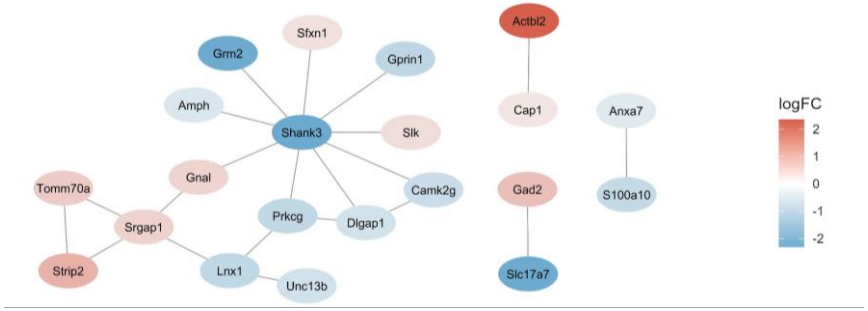
AT Ferhat

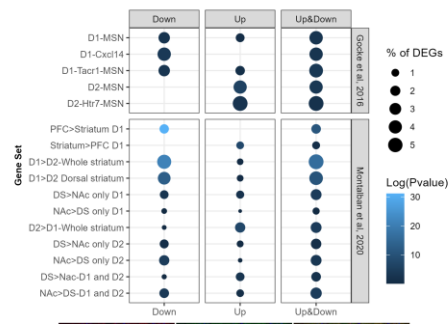
Sabrina Coquerant

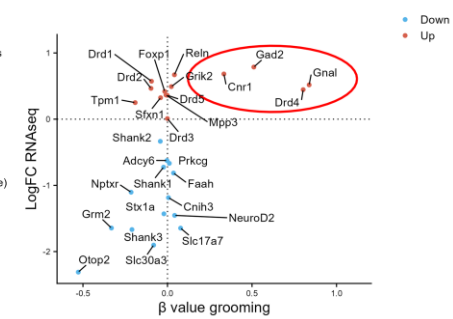
Benoit Forget

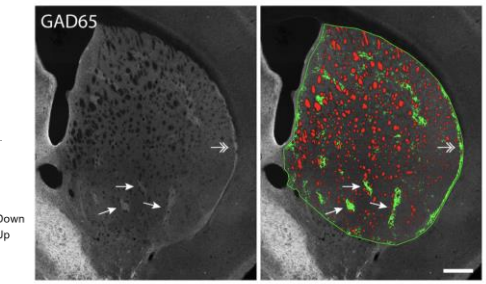
Lisa Verpy











Frontiers in Molecular Neuroscience

Live Mouse Tracker

Sharing tracking mouse databases

About Sign Up Login

nature biomedical engineering

Fabrice de Chaumont

Elodie Ey

De Chaumont, Ey *et al.*

Nature Medical Bioengineering, 2019

Live Mouse Tracker

Sharing tracking mouse databases

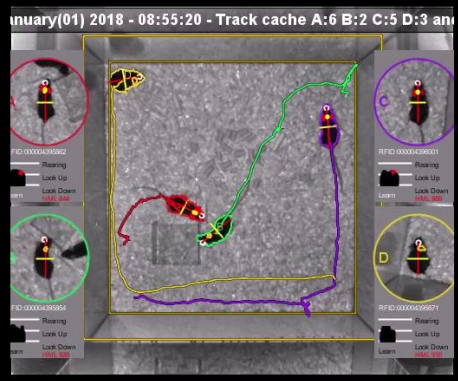
About Sign Up Login

nature biomedical engineering

Fabrice de Chaumont

Elodie Ey

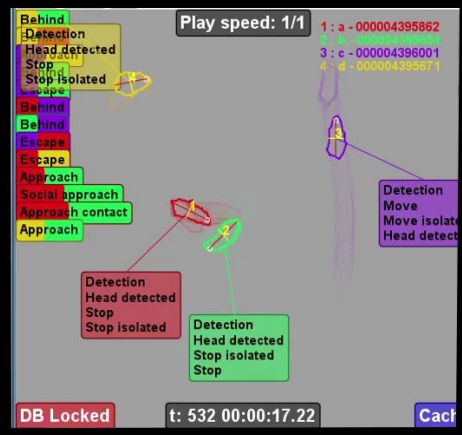
LMT - Live 3D rendering client demo



The tracking sends all tracking information in real-time to any third-party application

Here we present an example of application:

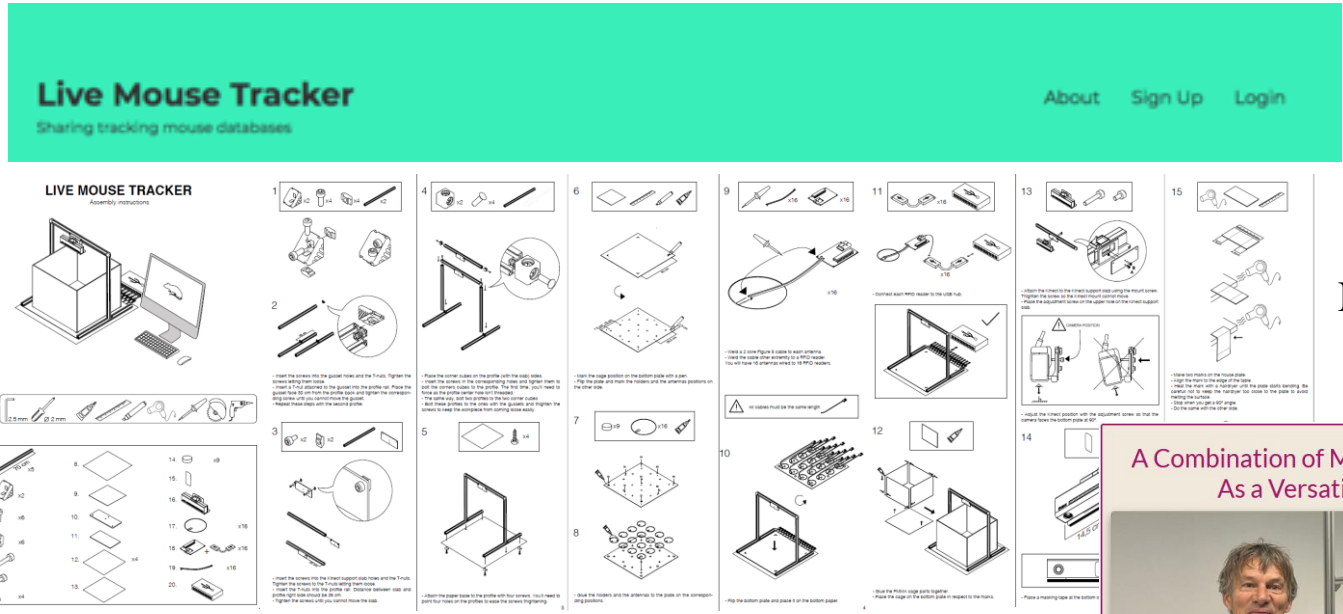
a live 3D rendering from the point of view of mice
(made with unreal engine)



The player also sends information to connected systems for test purposes

De Chaumont, Ey *et al.*
Nature Medical Bioengineering, 2019

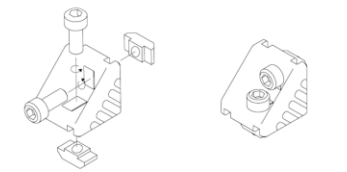
Live Mouse Tracker (LMT)

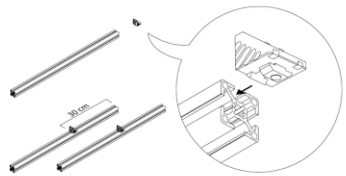


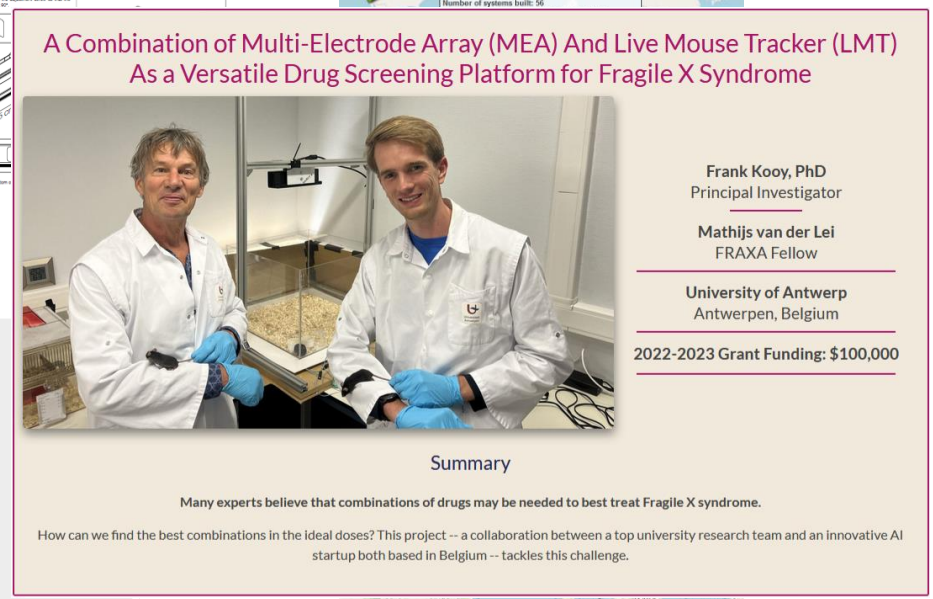
Fabrice de Chaumont

Elodie Ey

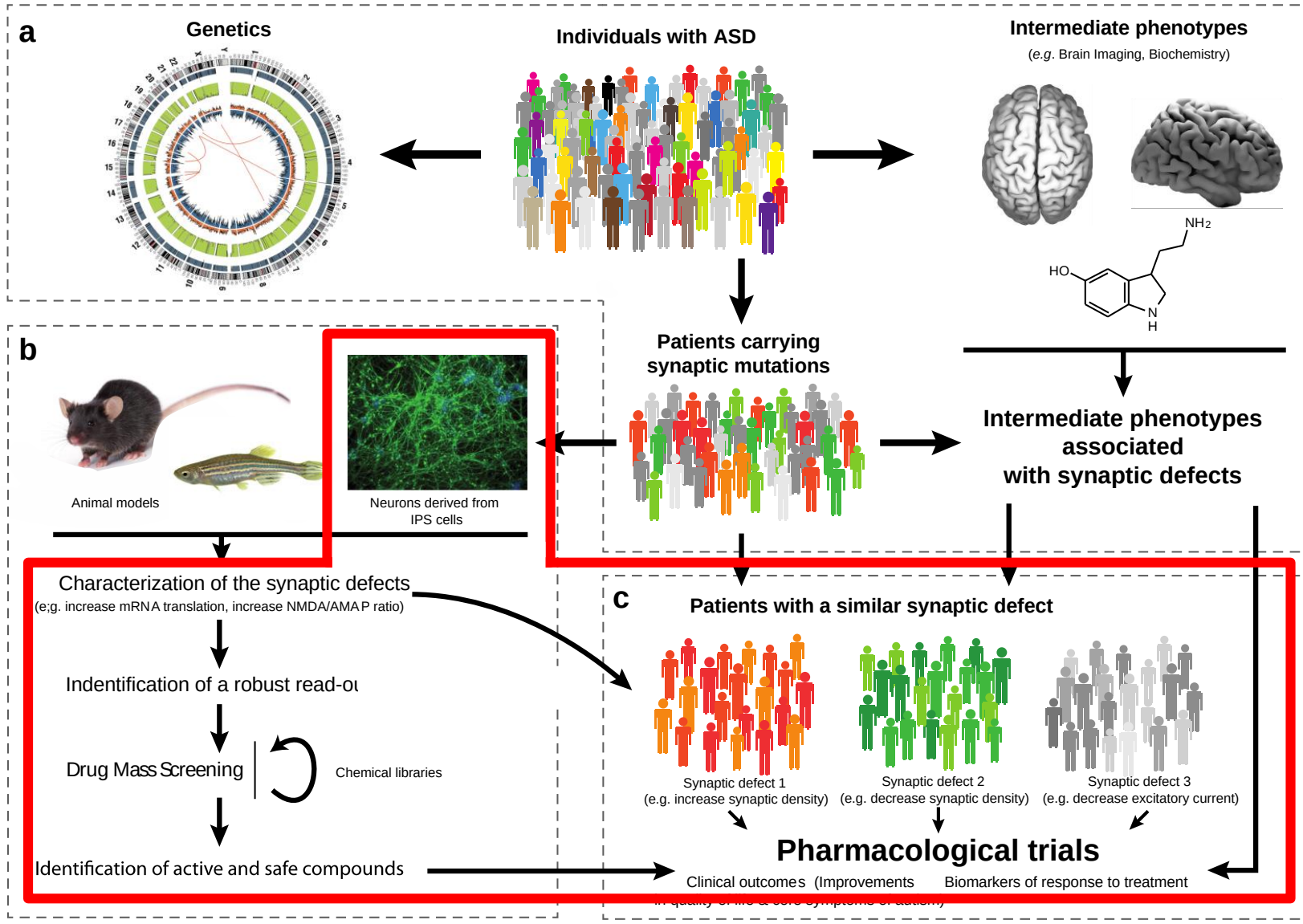
Albane Imbert







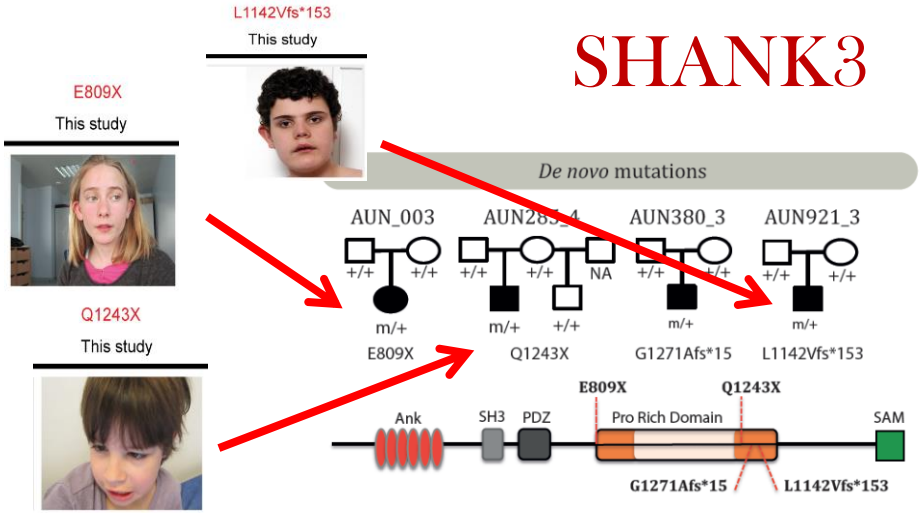
De Chaumont, Ey *et al.*
Nature Medical Bioengineering, 2019



Delorme *et al.* *Nature Medicine* 2013

Lithium and PMS

SHANK3



Gina G. Turrigiano

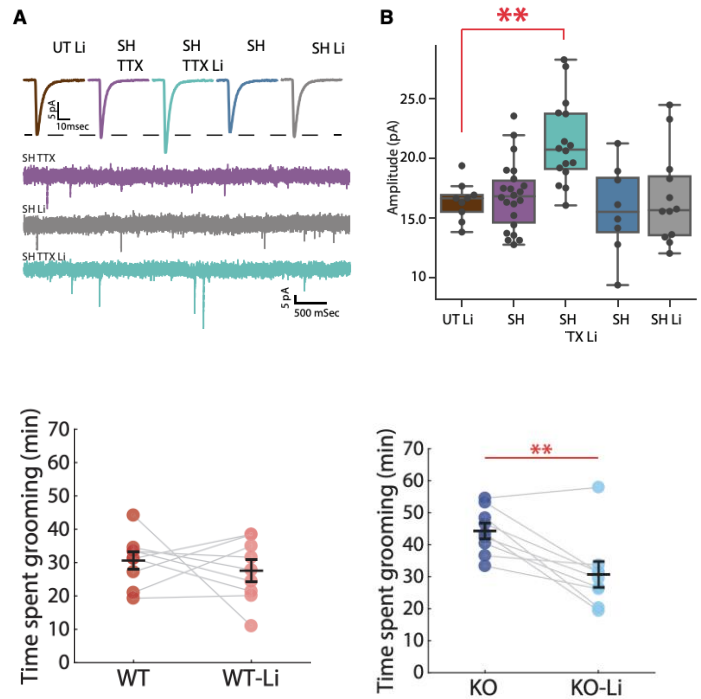
Neuron

CellPress

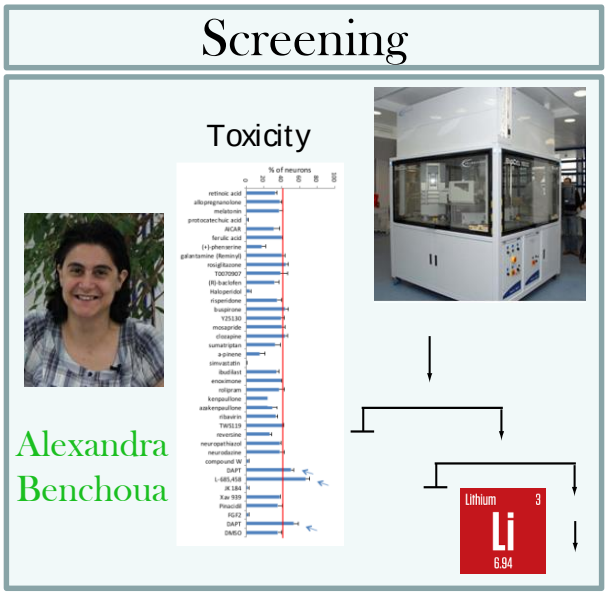
Report

Autism-Associated Shank3 Is Essential for Homeostatic Compensation in Rodent V1

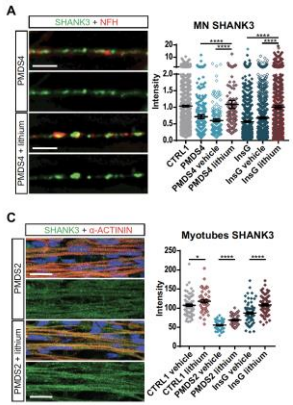
Vedakumar Tatavarty,[1,3] Alejandro Torrado Pacheco,[1] Chelsea Groves Kuhnle,[1] Heather Lin,[1,4] Priya Koundinya,[1] Nathaniel J. Miska,[1,5] Keith B. Hengen,[1,5] Florence F. Wagner,[2] Stephen D. Van Hooser,[1] and Gina G. Turrigiano[1,7,*]



Screening



Tobias Boeckers



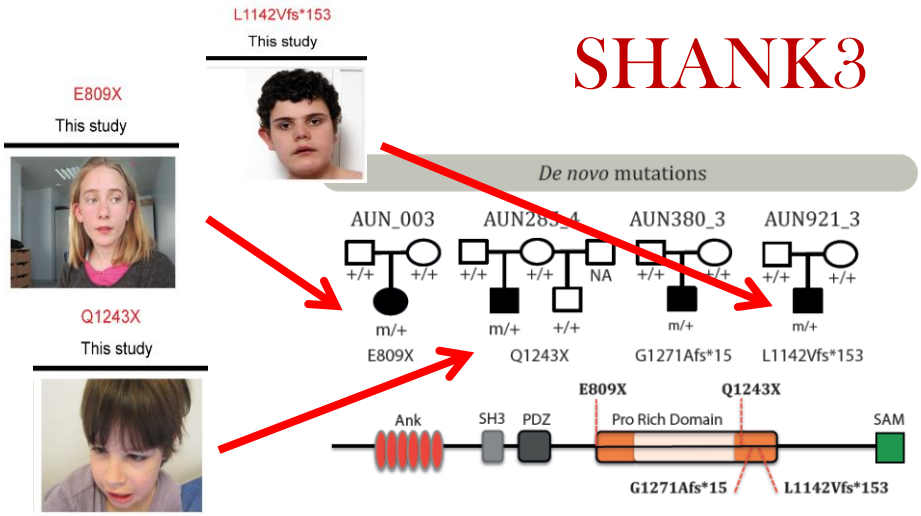
2016 EBioMedicine Published by THE LANCET

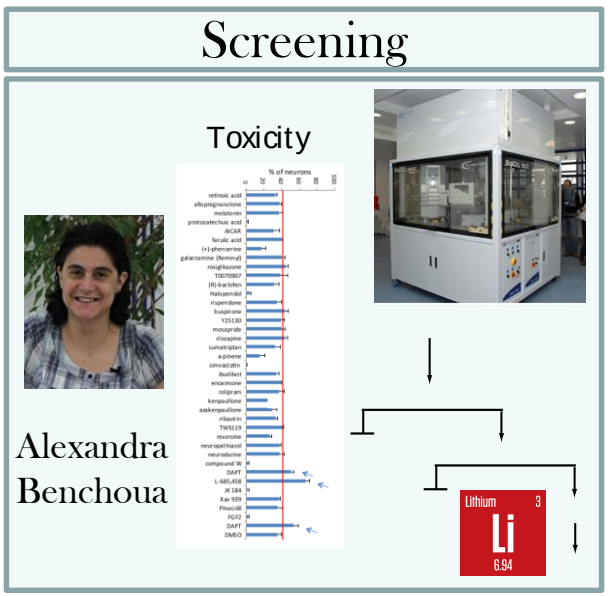
2020 Science Translational Medicine AAAS

2020

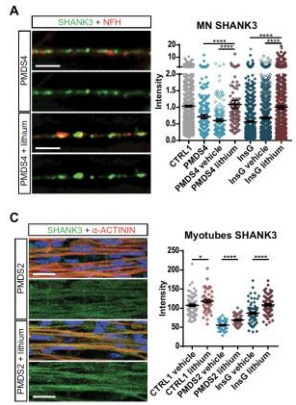
Lithium and PMS

SHANK3





Tobias Boeckers

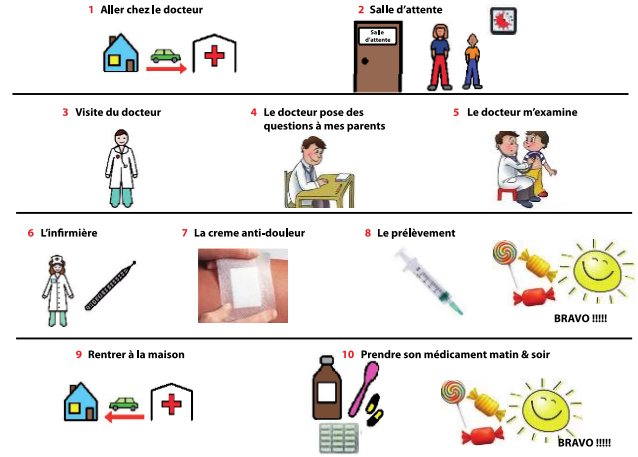


2016 EBioMedicine Published by THE LANCET

2020 Science Translational Medicine AAAS

NIH U.S. National Library of Medicine ClinicalTrials.gov

Good Clinical Practice NETWORK



LISPHEM : 16/22 patients included !

Richard Delorme

Anna Maruani

Anne Claude Tabet

Phelan McDermid Syndrome in Europe

Prof Conny van Ravenswaaij-Arts

ITHACA

European effort on PMS/SHANK3 and clinical trials

Merci !

GHFC

INSTITUT PASTEUR

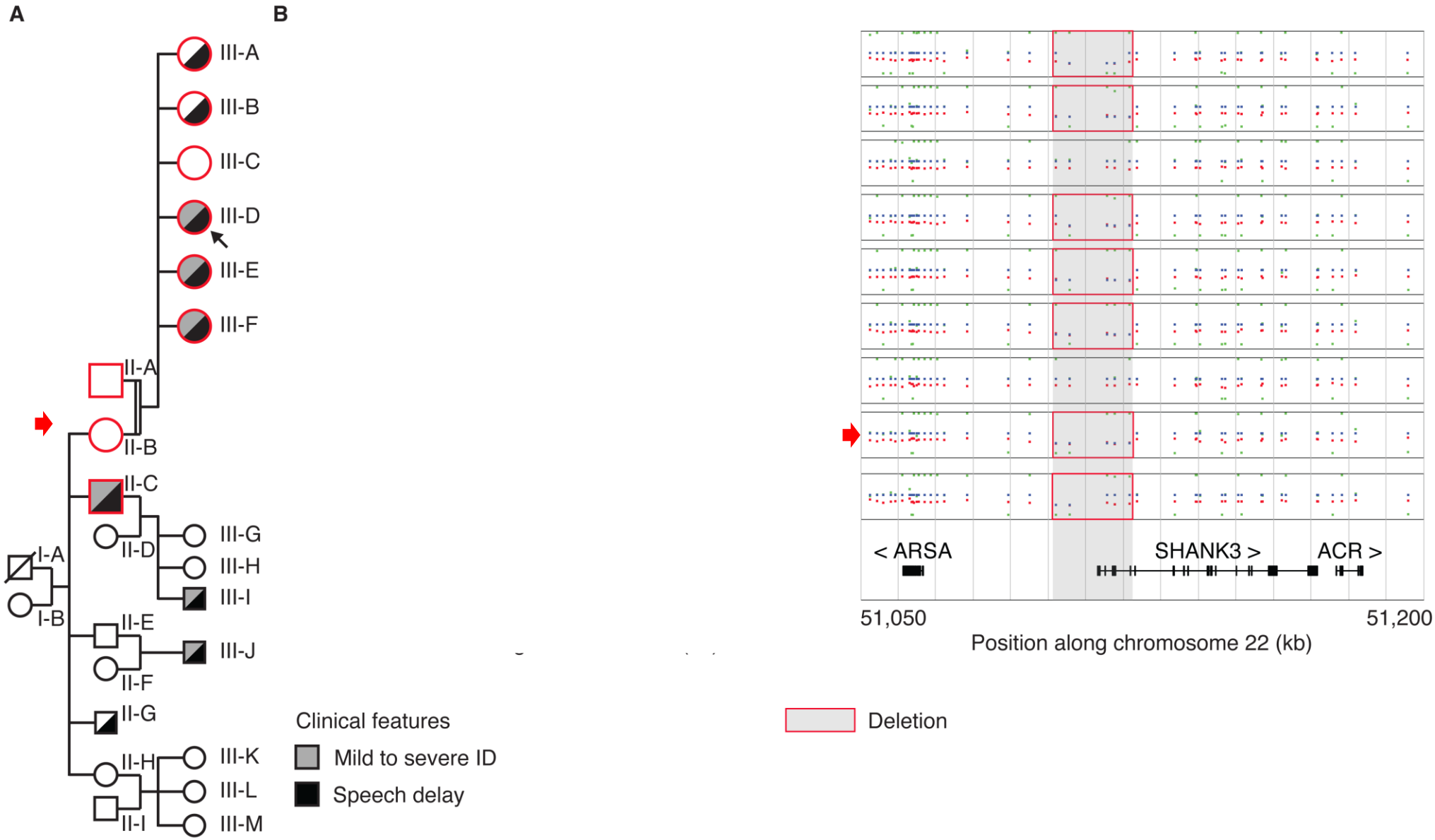
@thomas.bourgeron

Postdoctoral positions available !!

GILLBERG NEUROPSYCHIATRY CENTRE
SAHLGRENSKA ACADEMY

ghfc1@pasteur.fr

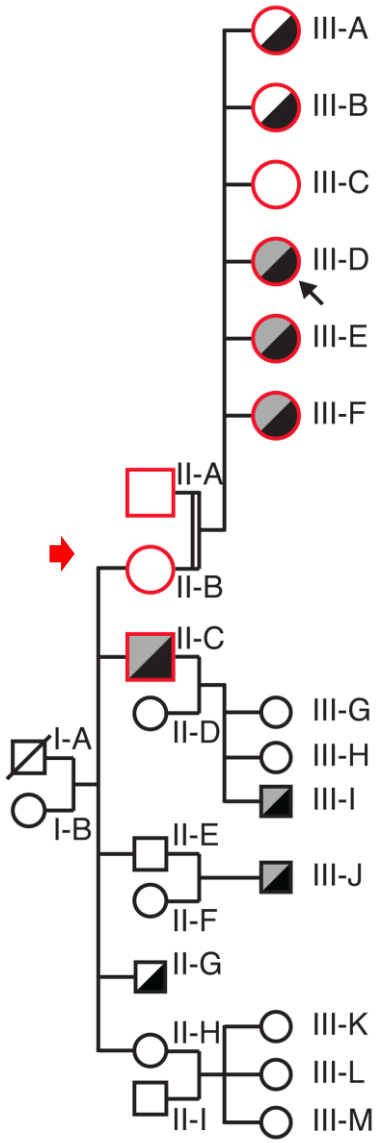
“Resilience” and *SHANK3*

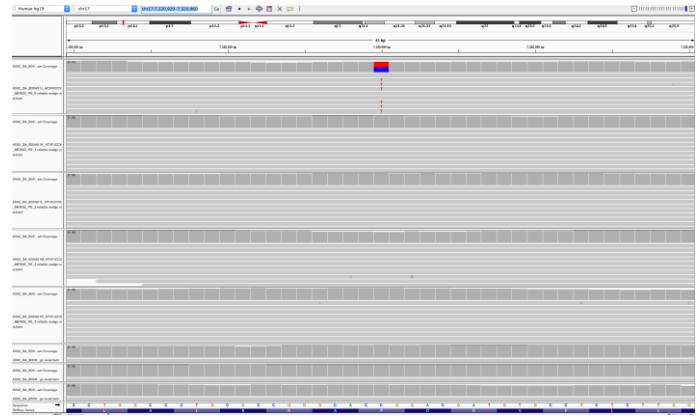


Tabet, Rolland *npj Genomic Medicine* 2017

a *de novo* NLGN2 p.P777L deleterious mutation

A





PolyPhen-2 report for Q8NFZ4 P777L

Query

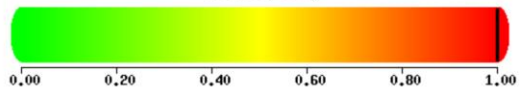
Protein Acc	Position	AA_1	AA_2	Description
Q8NFZ4	777	P	L	Canonical; RecName: Full=Neuroligin-2; Flags: Precursor; Length: 835

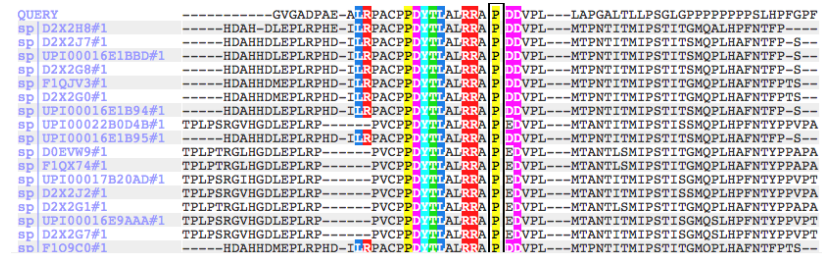
Results

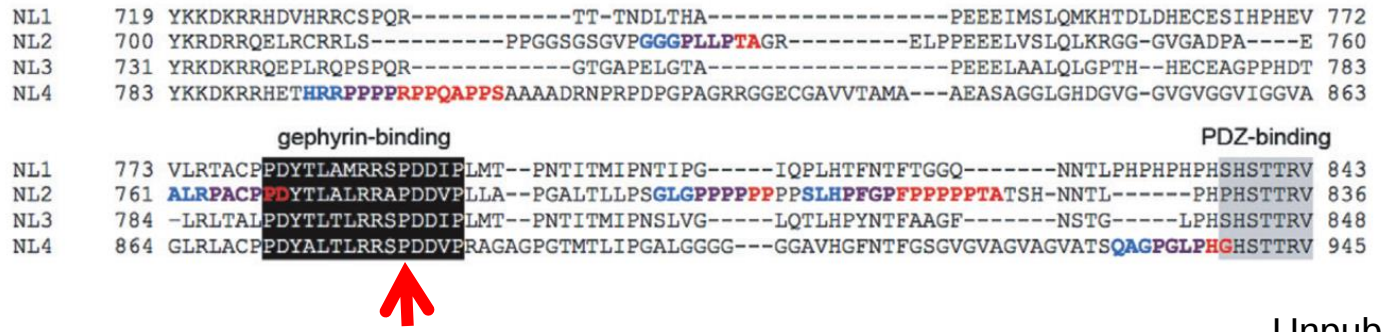
Prediction/Confidence — *PolyPhen-2 v2.2.2r398*

HumDiv

This mutation is predicted to be **PROBABLY DAMAGING** with a score of **1.000** (sensitivity: **0.00**; specificity: **1.00**)



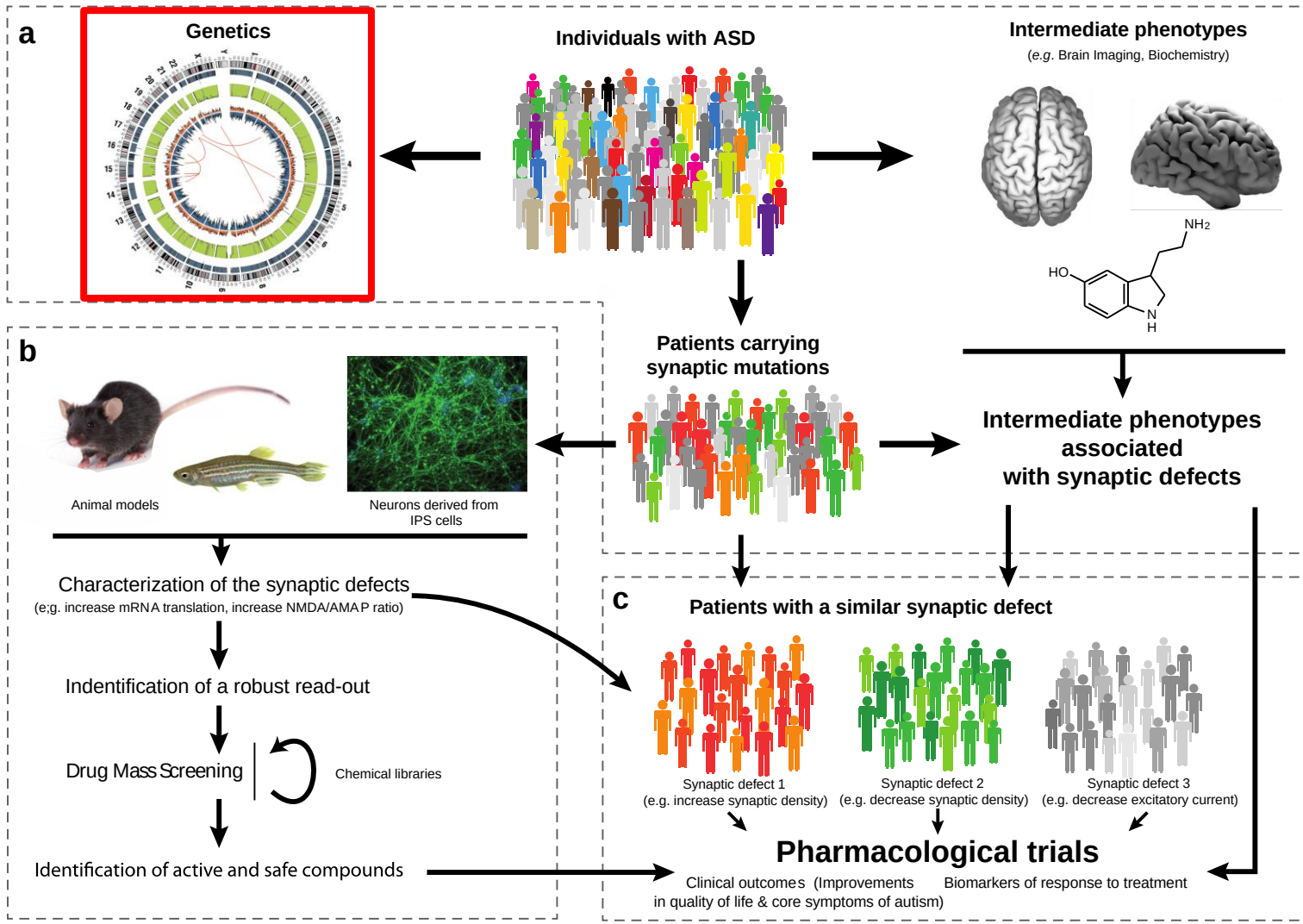




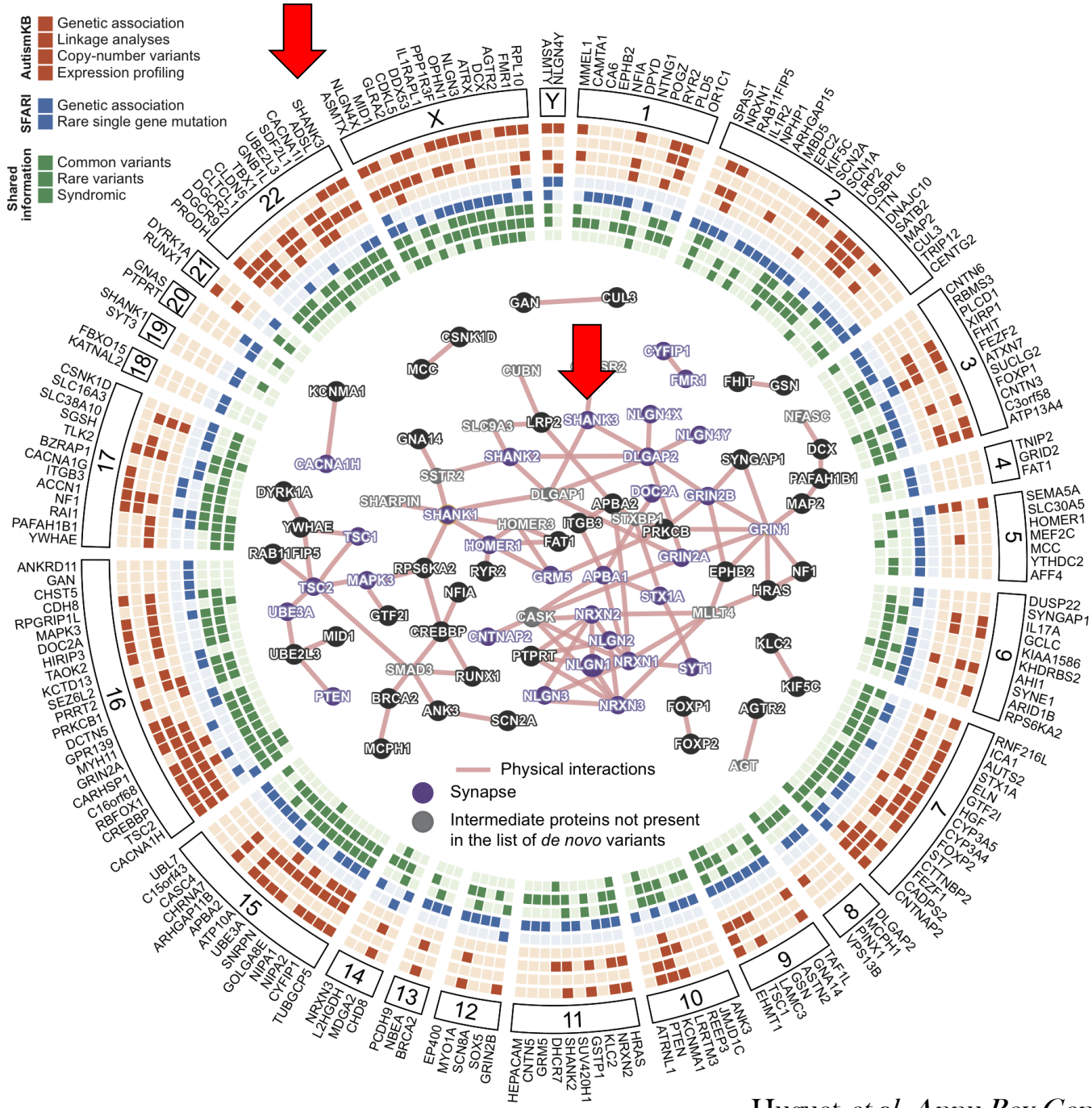
Unpublished


Merci !
GHFC
INSTITUT PASTEUR
FaceTime HD Camera
Flouter mon arrière-plan
Cliquez pour inviter les participants

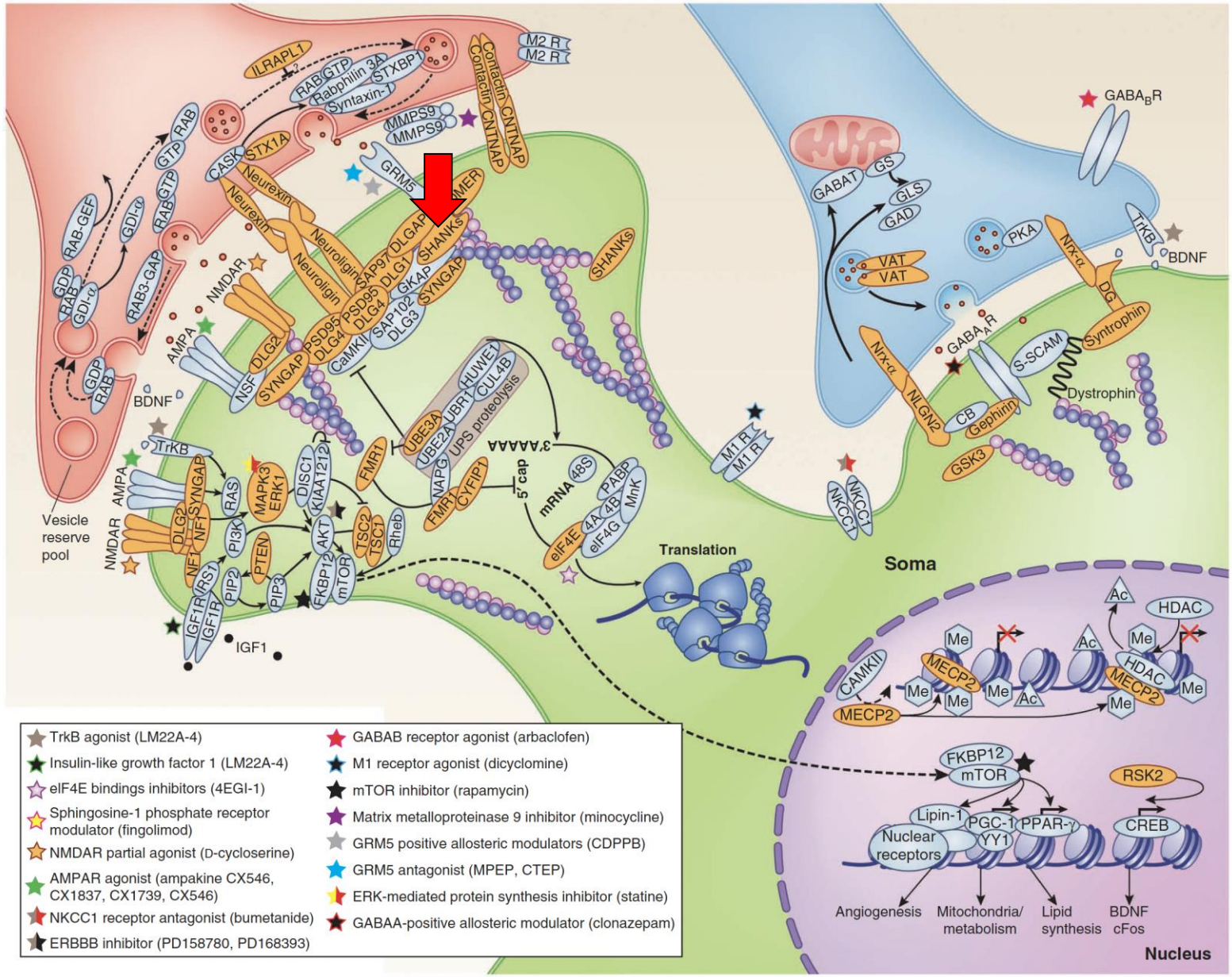
Strategy



Delorme *et al.* *Nature Medicine* 2013

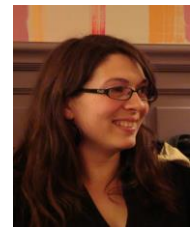


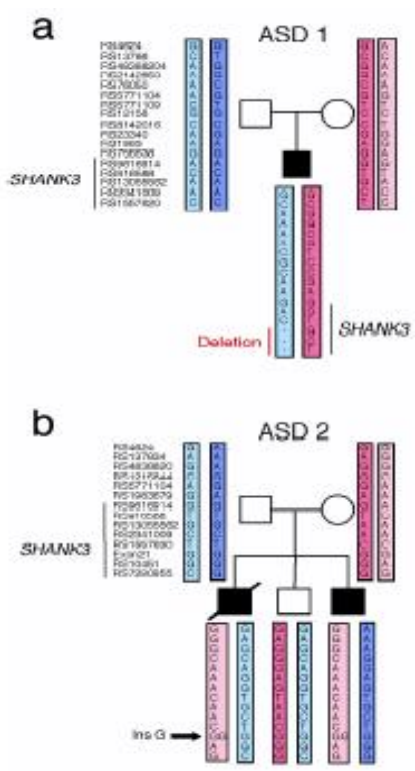
Huguet *et al. Annu Rev Genomics Hum Genet. 2013*

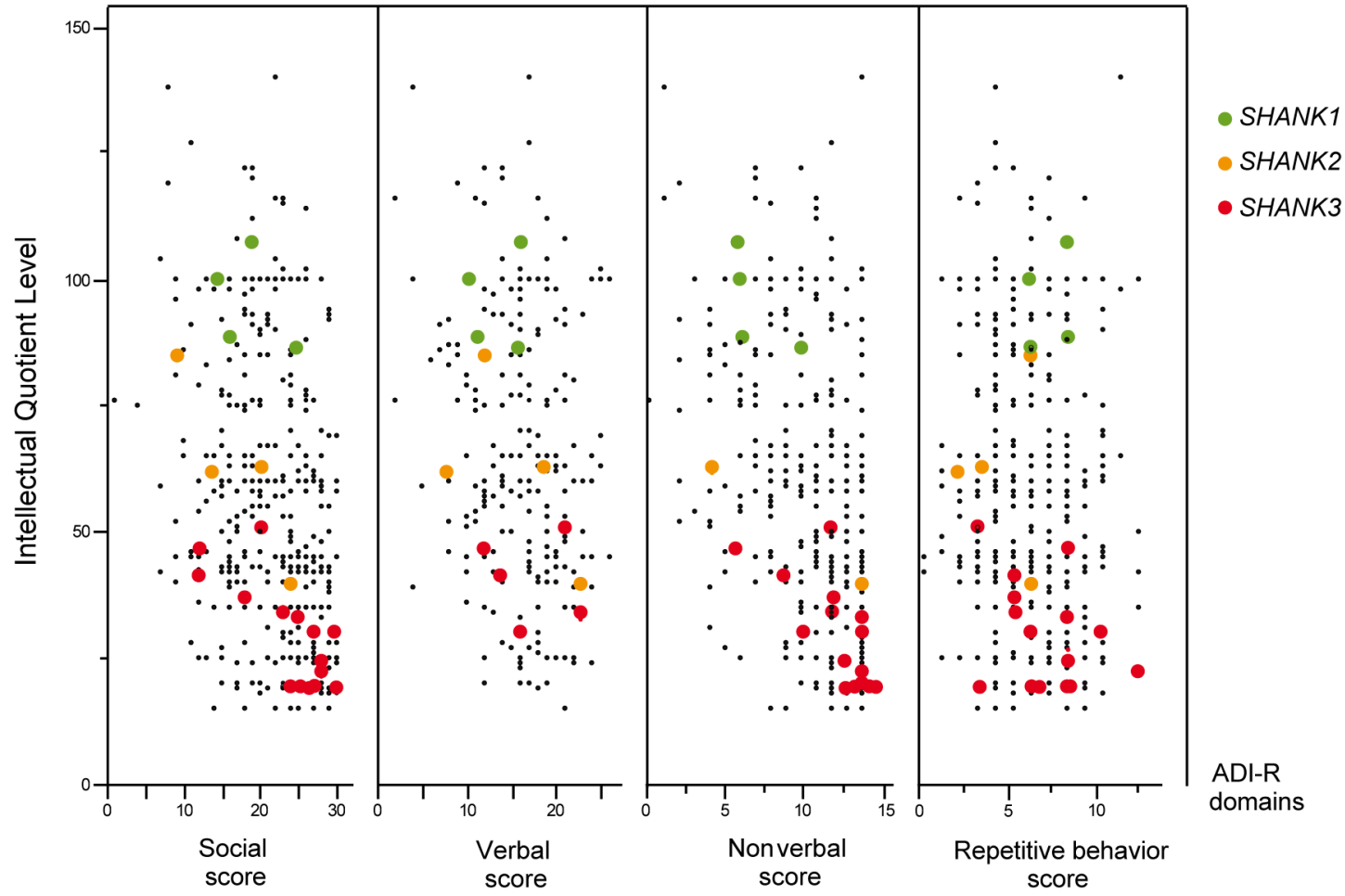


Delorme *et al.* *Nature Medicine* 2013

SHANKOPATHIES

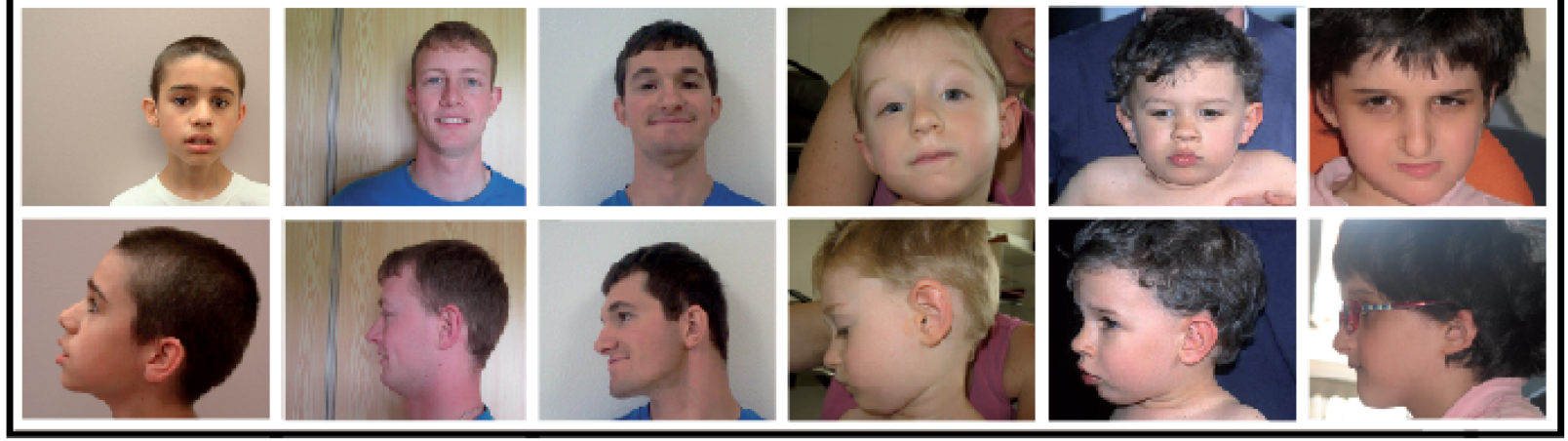





Durand *et al. Nat. Genet.* 2007

Sato *et al. Am. J. Hum. Genet.* 2010; Leblond *et al. PLOS Genet* 2012; Leblond *et al. PLOS Genet* 2014; Tabet, Rolland *et al. Npj Genomic Medicine.* 2017

Patients with *SHANK2* mutations

	Del_exon 6-7 Pinto et al. 2010	Del_exon 14-15 Pinto et al. 2010	Del_exon 4-15 Leblond et al. 2012	Del_11q13.3q13.4 This study	t(1;7;11)(p35;q33;q12)dn This study	Del_11q13.2q13.4 Wischmejier et al. 2010
SHANK2						
A	▪ Autism ▪ Early DD (mild motor & language delay) ▪ Mild ID / verbal	▪ Autism ▪ Early DD (mild motor & language delay) ▪ Mild ID / verbal ▪ Neonatal hypotonia	▪ Autism ▪ Early DD (mild motor & language delay) ▪ Mild ID /verbal	▪ Autism ▪ Global DD ▪ Severe ID / non verbal	▪ Autism ▪ Global DD ▪ Severe ID / non verbal ▪ Neonatal hypotonia	▪ Autism ▪ Global DD ▪ Severe ID / non verbal ▪ Neonatal hypotonia
B	▪ Large ears ▪ Long eyelashes ▪ Wide nasal bridge ▪ Clinodactyly(5th fingers)	▪ Large ears ▪ Pointed chin ▪ Wide nasal bridge ▪ Retrognathia	▪ Deepset eyes ▪ Large ears ▪ Pointed chin ▪ Wide nasal bridge ▪ Retrognathia ▪ Thin upper lip ▪ Clinodactyly(5th fingers)	▪ Deepset eyes ▪ Strabism & ptosis # ▪ Large ears ▪ Wide nasal bridge ▪ Retrognathia ▪ Thin upper lip ▪ Clinodactyly(5th fingers)	▪ Deepset eyes, epicanthus ▪ Large ears ▪ Long eyelashes ▪ Wide nasal bridge ▪ Retrognathia ▪ Clinodactyly(5th fingers)	▪ Deepset eyes, epicanthus ▪ Long eyelashes, ptosis ▪ Wide nasal bridge ▪ Retrognathia ▪ Thin upper lip ▪ Clinodactyly (5th fingers) & syndactylia (2nd - 3rd)
C		▪ Slight hypotonia ▪ Oral dyspraxia ▪ Signs of cerebellar dysfunction (dysmetria, dysdiadochokinesia)	▪ Slight hypotonia ▪ Oral dyspraxia ▪ Signs of cerebellar dysfunction (dysmetria dysdiadochokinesia)	▪ Hypotonia ▪ Oral dyspraxia ▪ Signs of cerebellar dysfunction (dysmetria dysdiadochokinesia)		▪ Hypotonia ▪ Oral dyspraxia

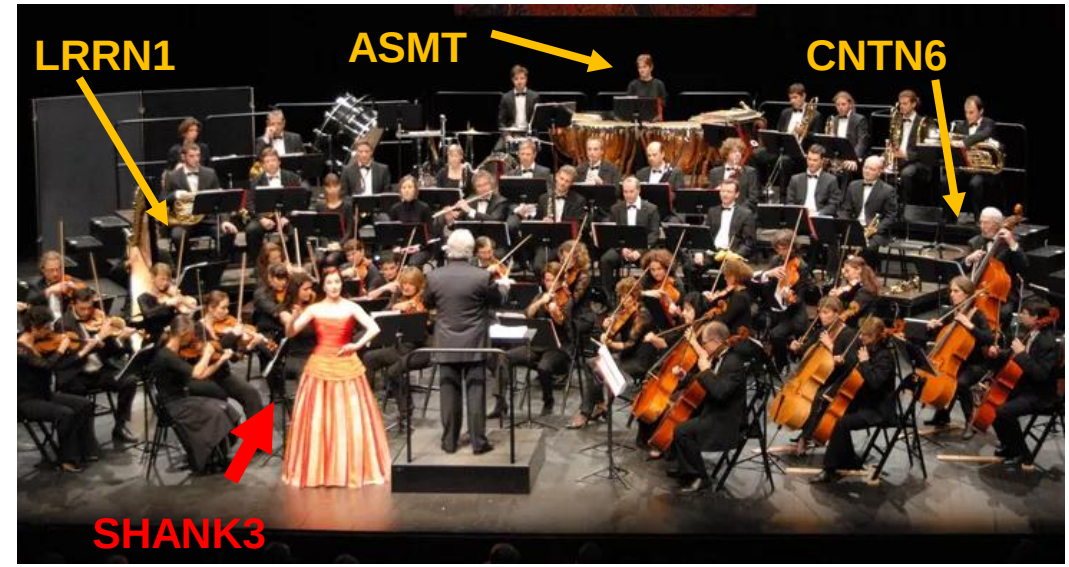
Leblond *et al. PLOS Genetics 2014*

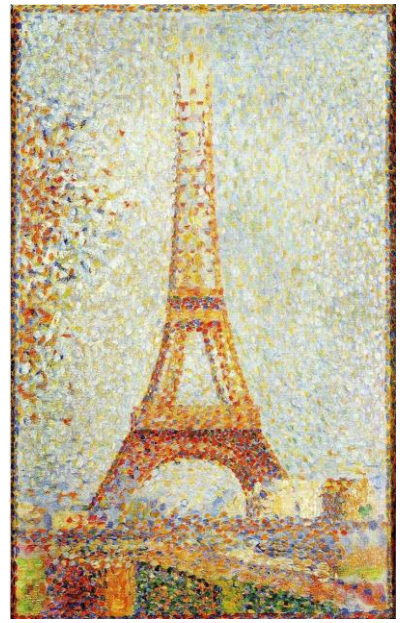
Patients with *SHANK3* mutations

	P1005Rfs*73	G1339Efs*5	E809X	S1202Cfs*81	Q1243X	L1142Vfs*153
	This study	This study	This study	This study	This study	This study
SHANK3						
	▪ Autism	▪ Autism	▪ Autism	▪ Autism	▪ Autism	▪ Autism
A	▪ Global DD ▪ Severe ID/non verbal ▪ Early regression	▪ Global DD ▪ Severe ID/non verbal ▪ Late regression	▪ Global DD ▪ Moderate ID/ verbal ▪ Early regression	▪ Global DD ▪ Moderate ID/verbal ▪ Early regression	▪ Global DD ▪ Severe ID/non verbal	▪ Global DD ▪ Severe ID/non verbal ▪ Early regression
B	▪ Large ears ▪ Long eyelashes ▪ Wide nasal bridge ▪ Smoothing philtrum	▪ Long face ▪ Long eyelashes ▪ Deep-set eyes ▪ Smoothing philtrum ▪ Prognathia ▪ Dysplastic toe nails	▪ Large detached ears ▪ Bulbous nose ▪ Pointed chin ▪ Retrognathia		▪ Large ears ▪ Long eyelashes ▪ Deep-set eyes ▪ Wide nasal bridge ▪ Strabism ▪ Dental malocclusion	▪ Large ears ▪ Puffy eyelids ▪ Deep-set eyes ▪ Wide nasal bridge ▪ Bulbous nose ▪ Pointed chin
C	▪ Hypotonia	▪ Hypotonia ▪ Ataxia, dysmetria	▪ Hypotonia		▪ Hypotonia	▪ Severe stereotypies
D	▪ Cycling vomiting	▪ GO reflux ▪ Seizures ▪ Chewing non-food items	▪ Cholesteatoma	▪ Migraines ▪ Seizures	▪ GO reflux	▪ Scoliosis ▪ Seizures

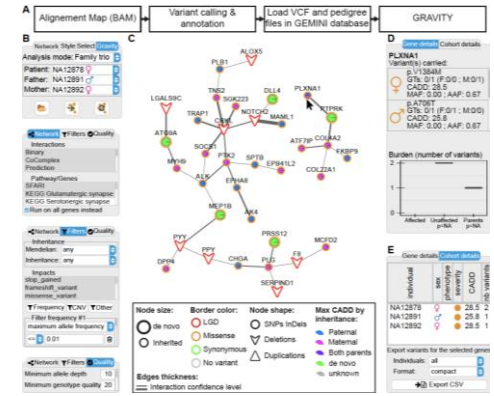
Leblond *et al. PLOS Genetics 2014*

Synaptic cocktail / orchestra





GRAVITY



http://gravity.pasteur.fr/