Endophénotypes et génétique dans la schizophrénie : concept ou réalité ?

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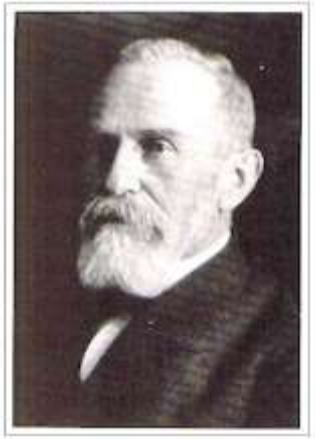
Créteil

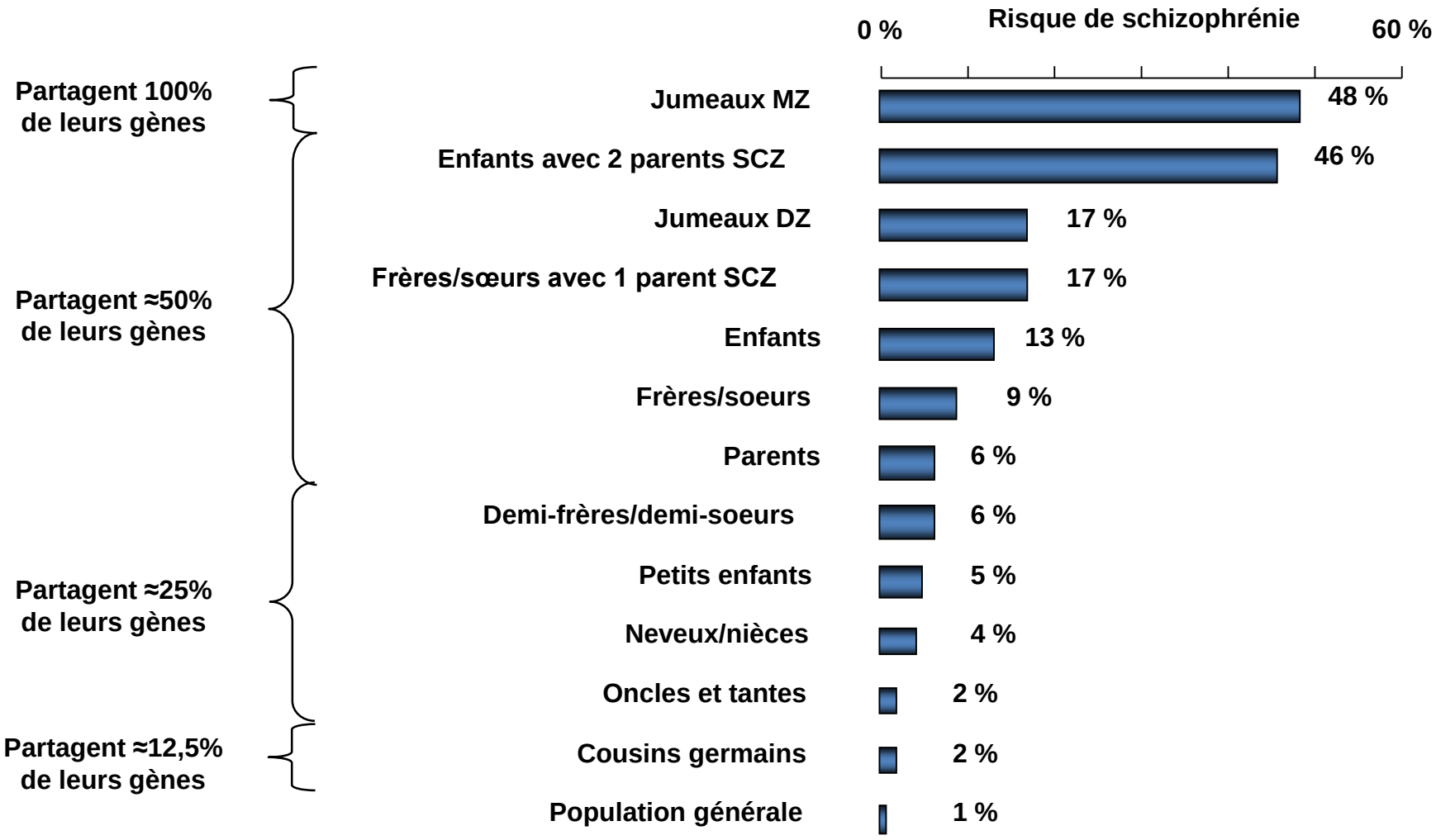
Hérédité des psychoses



« L'avenir de la psychiatrie, en tant que science, repose en majeure partie sur les recherches généalogiques concernant l'hérédité des maladies mentales. »

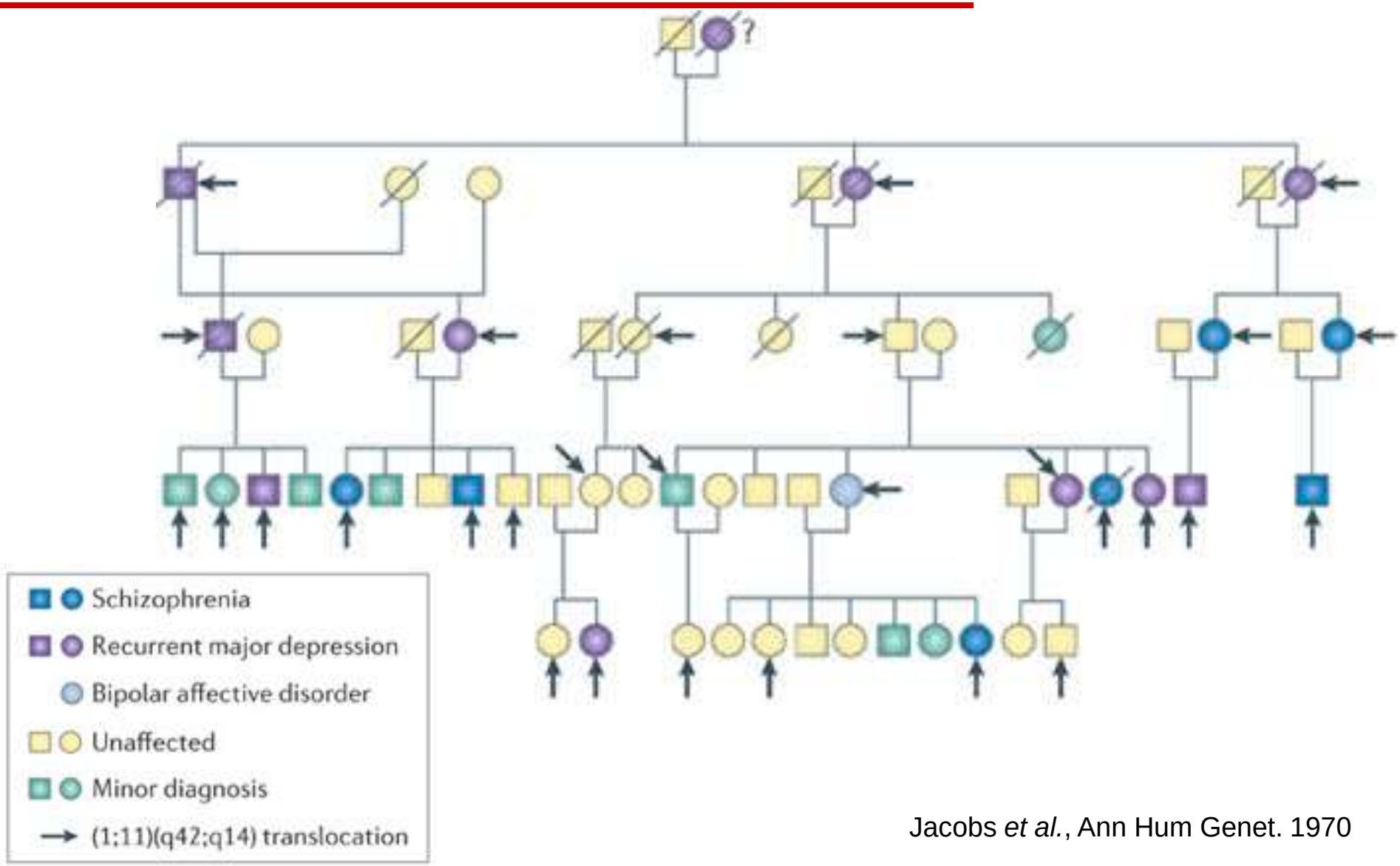
Bleuler E. Dementia praecox oder Gruppe der Schizophrenien, 1911

Hérédité des schizophrénies



Gottesman, 1991

La génétique de la schizophrénie : Les études familiales



Jacobs *et al.*, Ann Hum Genet. 1970

Facteurs génétiques et environnementaux dans les troubles bipolaires et les schizophrénies

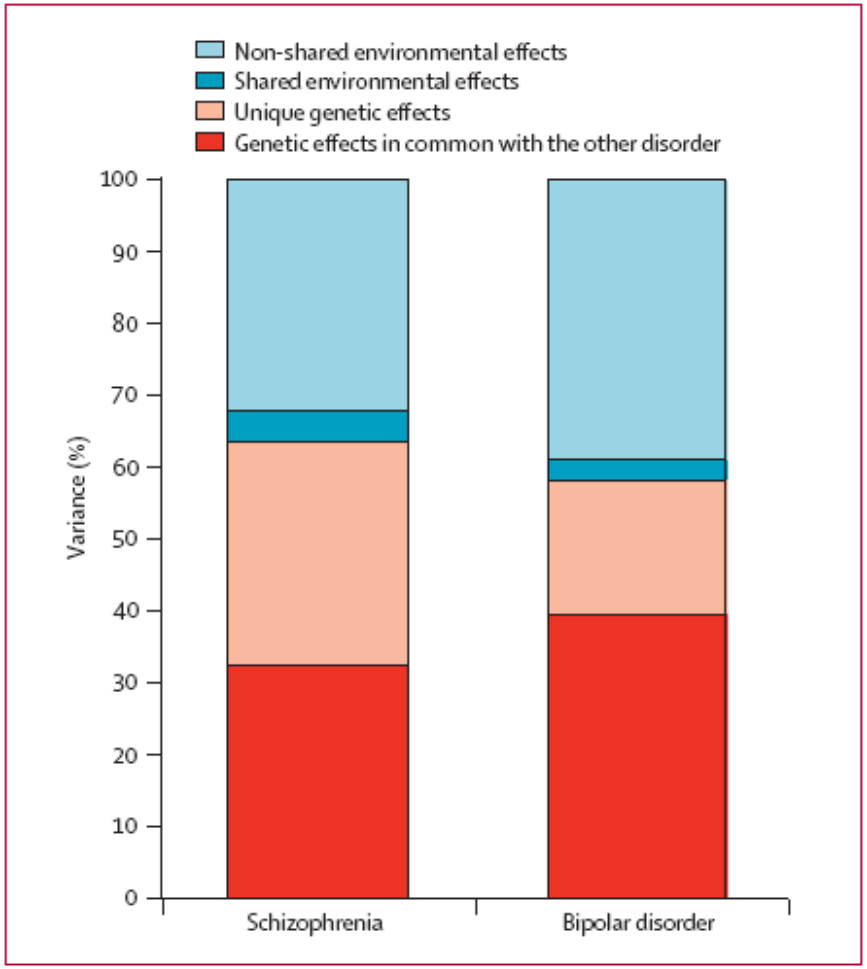


Figure: Variance accounted for by genetic, shared environmental, and non-shared environmental effects for schizophrenia and bipolar disorder

Très grande étude :

Registre des générations croisés aux registre des hôpitaux de 1973 à 2004

9 millions de suédois

40 487 patients avec un trouble bipolaire

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→ héritabilité de 60%

Mais également,

→ effets de l'environnement

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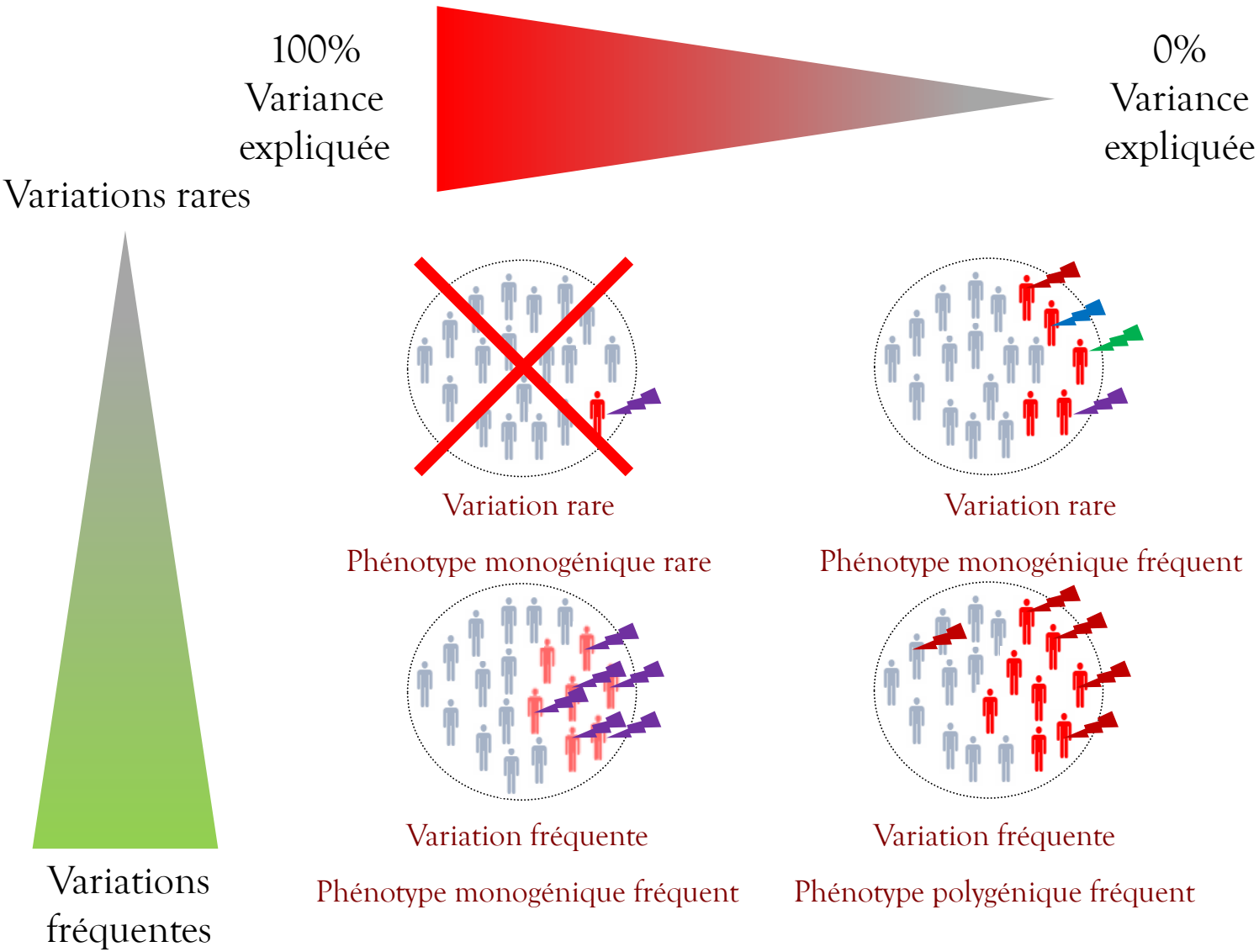
→ phénotypes chevauchants

Lichtenstein, Lancet 2009

Quel modèle génétique pour les schizophrénies ?



THE LANCET, APRIL 9, 1988

Preliminary Communication

PARTIAL TRISOMY CHROMOSOME 5 COSEGREGATING WITH SCHIZOPHRENIA

ANNE S. BASSETT BARBARA C. MCGILLIVRAY[1]
BARRY D. JONES J. TAPIO PANTZAR[1]

Department of Psychiatry, Health Sciences Centre Hospital, University of British Columbia, Vancouver, B.C., Canada V6T 2A1; and Department of Medical Genetics, Grace Hospital, University of British Columbia[1]

Summary Schizophrenia was associated with a distinct autosomal abnormality in two related mildly dysmorphic individuals. The finding of cosegregation of schizophrenia and a partial trisomy of chromosome 5 in the family suggests a potential location of a gene or genes linked to schizophrenia.

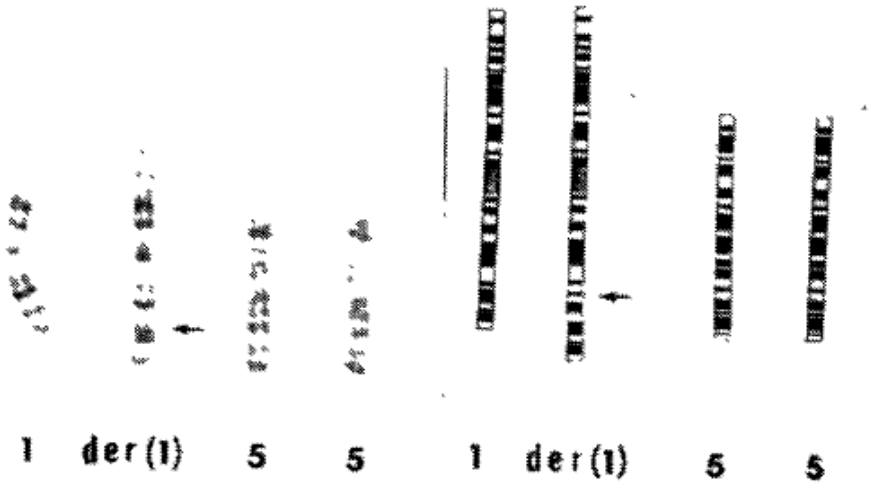


Fig 1—Partial G-banded karyotype and ISCN[20] idiogram of chromosomes 1 and 5 of the proband (identical to that of the affected maternal uncle).

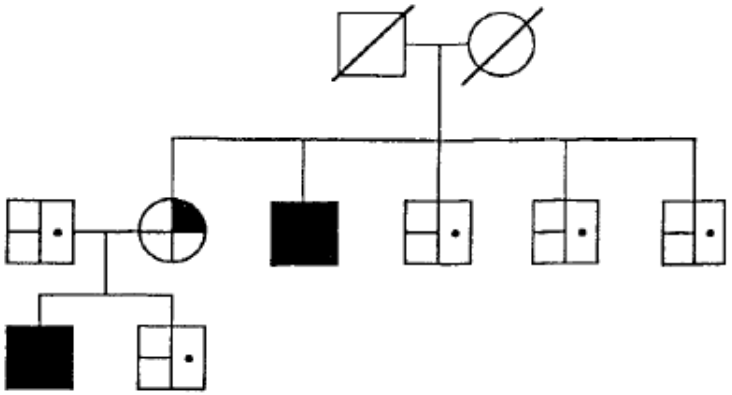


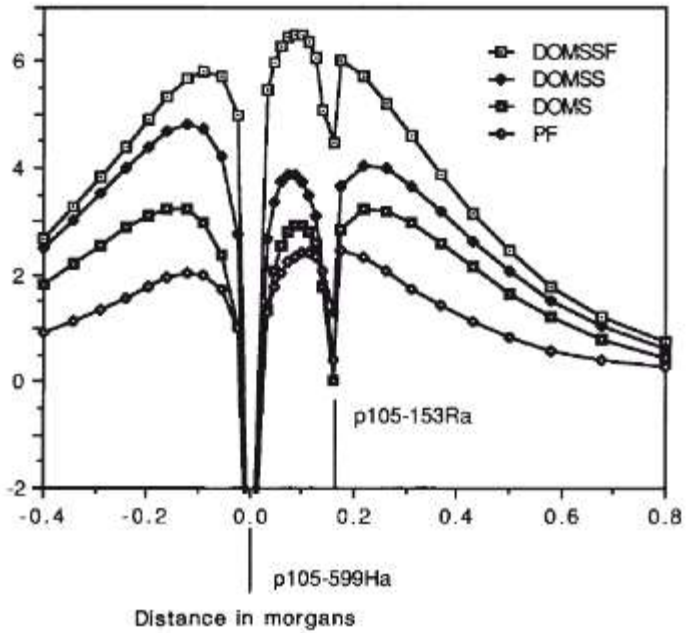
Fig 3—Family pedigree showing cosegregation of schizophrenia, physical abnormalities, and a partial trisomy of chromosome 5.

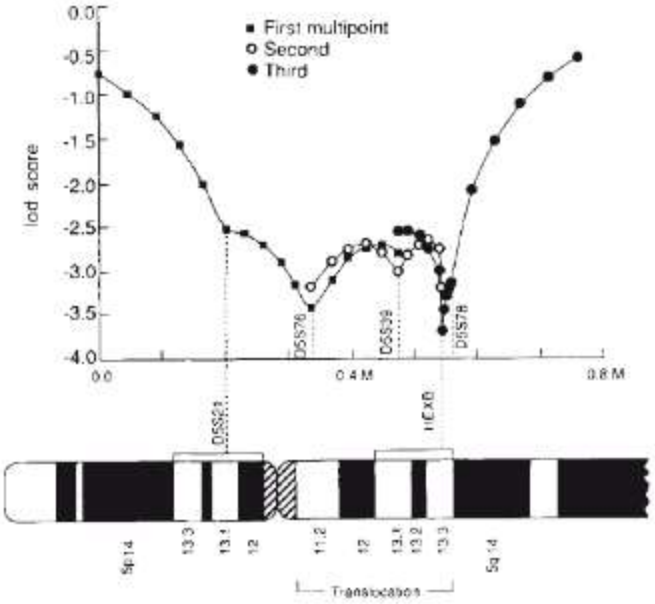
partial trisomy chromosome 5; balanced translocation carrier; normal chromosomes; schizophrenia; no mental illness; physical abnormalities; no physical abnormalities.

Localization of a susceptibility locus for schizophrenia on chromosome 5

Robin Sherrington*, Jon Brynjolfsson†, Hannes Petursson†, Mark Potter*, Keith Dudleston‡, Brian Barraclough‡, John Wasmuth§, Mark Dobbs§ & Hugh Gurling*‖

NATURE VOL. 336 10 NOVEMBER 1988





Evidence against linkage of schizophrenia to markers on chromosome 5 in a northern Swedish pedigree

James L. Kennedy*†, Luis A. Giuffra‡, Hans W. Moises§, L. L. Cavalli-Sforza§, Andrew J. Pakstis*, Judith R. Kidd*, Carmela M. Castiglione*, Barbro Sjogren‖, Lennart Wetterberg‖ & Kenneth K. Kidd*†¶

NATURE VOL. 336 10 NOVEMBER 1988

nature

Where next with psychiatric illness?

New research has shown some schizophrenia to be, in part, genetically determined, which promises new insight into psychiatric illness. But the need for enlightened social policies remains urgent.

[...] What the Icelandic families appear to show is that the link between the inheritance of a defective gene and its carriers' predisposition to schizophrenia may be part of a more complicated story. If it should eventually be shown that those inheriting the defective gene inherit a predisposition to several psychiatric conditions, among which schizophrenia is merely one, the result will be of great benefit in the understanding of psychiatric illness in general.

Splitting schizophrenia

Two papers in this issue, despite reporting apparently contradictory findings, pave the way for a genetic approach to the diagnosis of schizophrenia.

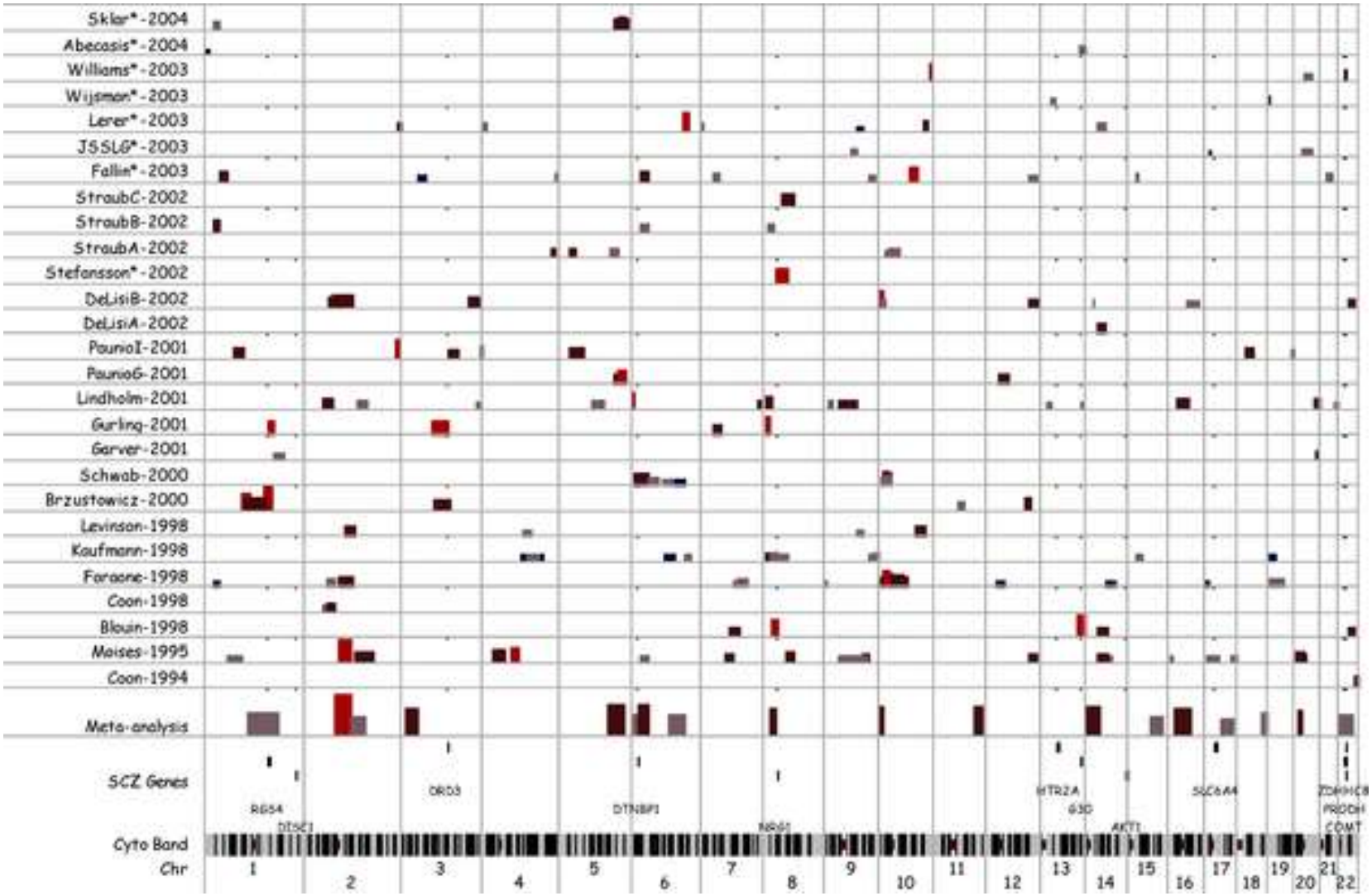
[...] that schizophrenia is a heterogeneous disorder with multiple causes. Together, these papers pave the way for a genetic approach to splitting schizophrenia into a collection of distinct diseases.

[...] Even if the locus on chromosome 5q does turn out to be a minor cause, it represents the first step in using genetics to subdivide patients into more homogeneous groups, which is likely to help the evaluation of potential therapies [...]

In short, psychiatrists have now joined the ranks of experimental geneticists. To be successful in dissecting their particularly complex system, they will need to exploit the full range of tricks of that trade.

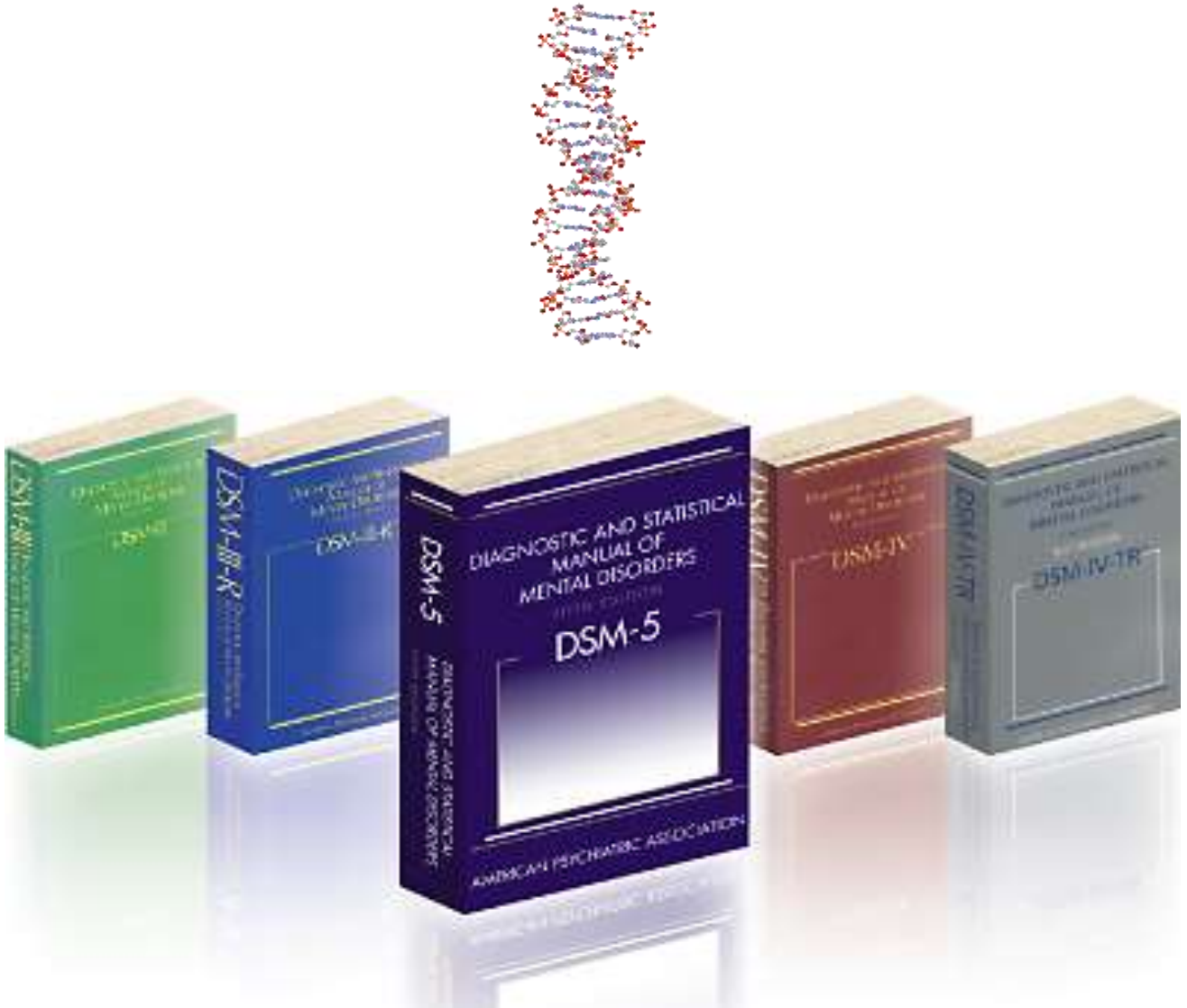
Eric S. Lander

Les études de liaison dans les schizophrénies

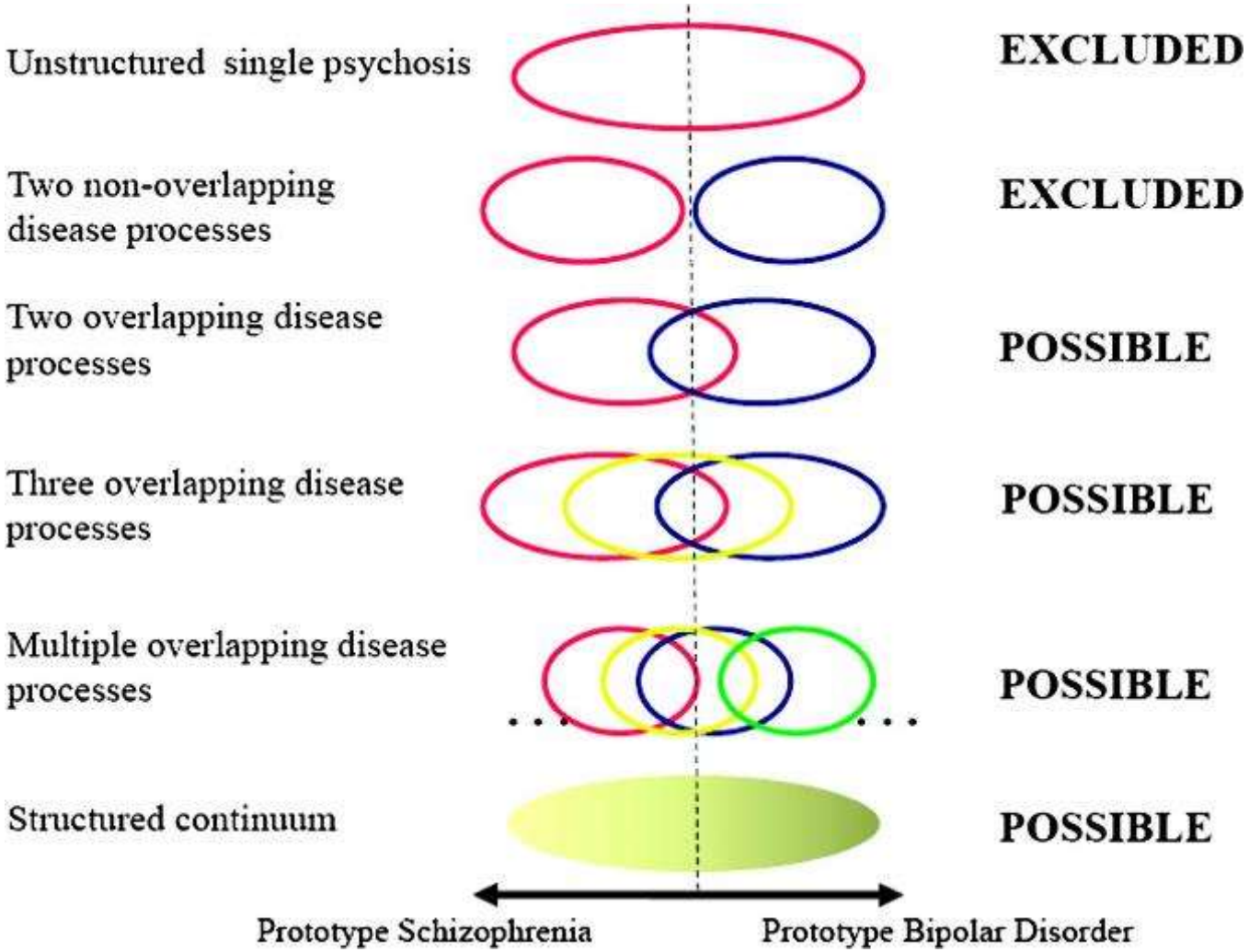


Sullivan, *PLoS Med* 2005

Quels phénotypes pour les études génétiques ?



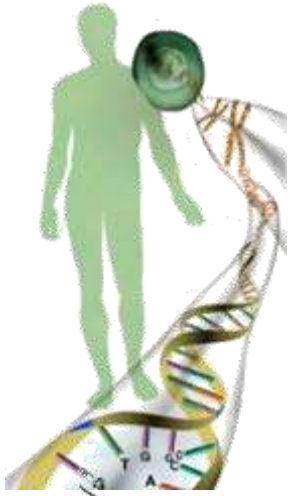
Models of the Possible Biological-Genetic Relationships Between Clinical Phenotypes on a 1-Dimensional Schizophrenia-Bipolar Disorder Clinical Spectrum.

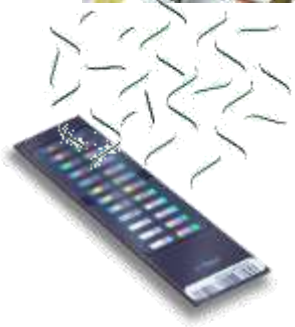


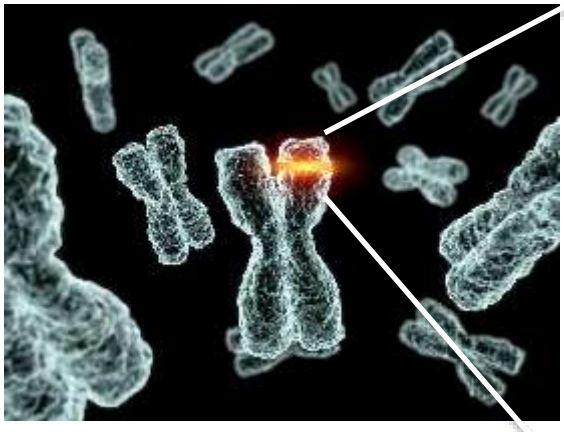
Craddock N et al. Schizophr Bull 2009;35:482-490

Schizophrenia Bulletin

Etude des variations fréquentes du génome dans les schizophrénies







Patients

Témoins

Genome-wide association studies (GWAS) et schizophrénies

Identification of loci associated with schizophrenia by genome-wide association and follow-up

Michael C O'Donovan[1] , *et al.*

We carried out a genome-wide association study of schizophrenia (479 cases, 2,937 controls) and tested loci with $P < 10^{-5}$ in up to 16,726 additional subjects. Of 12 loci followed up, 3 had strong independent support ($P < 5 \times 10^{-4}$), and the overall pattern of replication was unlikely to occur by chance ($P = 9 \times 10^{-8}$). Meta-analysis provided strongest evidence for association around *ZNF804A* ($P = 1.61 \times 10^{-7}$) and this strengthened when the affected phenotype included bipolar disorder ($P = 9.96 \times 10^{-9}$).

NATURE GENETICS VOLUME 40 | NUMBER 9 | SEPTEMBER 2008

Table 2 Combined schizophrenia and bipolar analysis

						UK SZ		UK BP		Meta SZ + BP	
			Allele freq.			Cases $n = 642$, Controls $n = 2,937$		Cases $n = 1,865$, Controls $n = 2,937$		Cases $n = 9,173$, Controls $n = 12,834$	
Chr./Mb	SNP	Risk allele	SZ	BP	CON	ATT(P)	OR	ATT(P)	OR	CMH(P)	OR
2/185.5	rs1344706	T	0.66	0.62	0.59	7.08×10^{-7}	1.38	4.07×10^{-4}	1.16	9.96×10^{-9}	1.12
11/29.1	rs1602565	C	0.15	0.12	0.11	7.81×10^{-6}	1.49	0.055	1.14	4.26×10^{-6}	1.15
12/116.2	rs6490121	G	0.40	0.35	0.34	4.33×10^{-6}	1.33	0.168	1.06	0.124	1.03
16/52.2	rs9922369	A	0.05	0.03	0.03	8.05×10^{-7}	2.06	0.261	1.15	0.002	1.20
16/13.0	rs7192086	T	0.30	0.25	0.24	3.32×10^{-5}	1.33	0.206	1.06	2.56×10^{-5}	1.10
11/132.1	rs3016384	C	0.56	0.51	0.49	5.82×10^{-5}	1.29	0.057	1.08	4.43×10^{-4}	1.07

SZ, schizophrenia; BP, bipolar; CON, control; ATT(P), trend test P value; meta SZ+BP, meta-analysis for all schizophrenia and bipolar samples reported in this study; CMH(P), Cochran-Mantel-Haenszel P value.

Genome-wide association studies (GWAS) et schizophrénies

Table 1

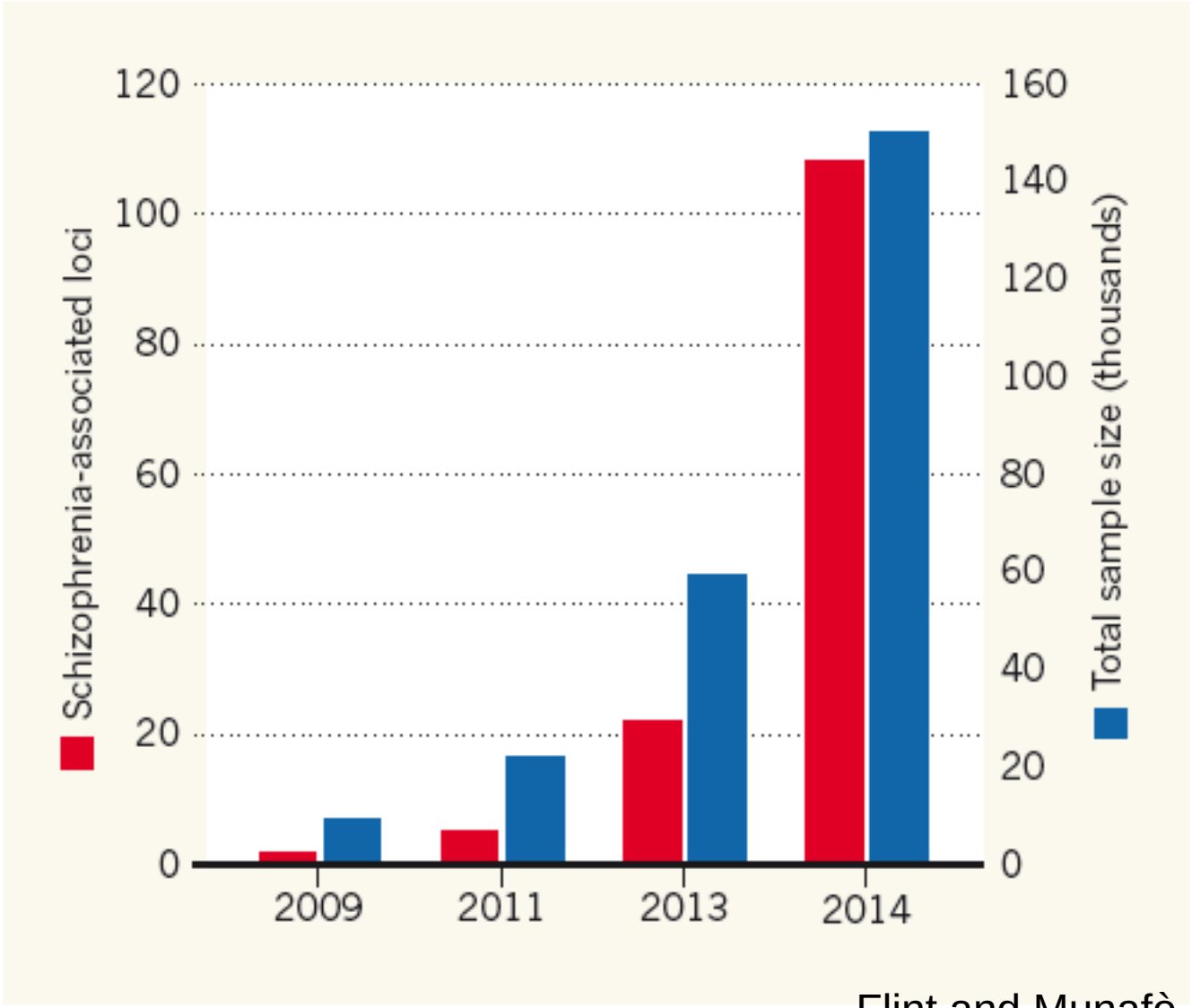
Summary of GWA studies in schizophrenia

Study	Type	#Cases	#Controls	Loci	*p*-Value	OR	Comments
Mah *et al.* [5]	Pooled DNA	320	325	*PLXNA2*[a]	0.006	1.49	
Shifman *et al.* [9]	Pooled DNA	660	1,100	*RELN*[b]	2.9×10^{-4}	1.58	Only in female
Kirov *et al.* [14]	Pooled DNA	574	605	*CCDC60*	1.2×10^{-6}	–	
				RBP1	0.00016	–	
Lencz *et al.* [15]	Individual genotype	178	144	*CSF2RA*	3.7×10^{-7}	3.23	
Sullivan *et al.* [16]	Individual genotype	738	733	-	–	–	No significant association reported
O'Donovan [17]	Individual genotype	479	2,937	*ZNF804A*[c]	1.61×10^{-7}	1.12	
Stefansson *et al.* [21•]	Individual genotype	2,663	13,498	*MHC*	1.1×10^{-9} to 1.4×10^{-12}	1.14–1.24	Strong evidence point out *NOTCH4*, located inside the MHC
				NRGN	2.4×10^{-9}	1.15	
				TCF4	4.1×10^{-9}	1.23	
Purcell *et al.* [22•]	Individual genotype	3,322	3,587	*MHC*	3.66×10^{-7}	0.733	
				MYO18B	3.44×10^{-7}	0.8	
				ZNF804A	0.029	1.08	
Chen *et al.* [26]	Meta-analysis	17,198	11,380	*CMYA5*	3.0×10^{-4}	1.03–1.11	
Wang *et al.* [29]	Meta-analysis	1,172	1,379	*ASTN2*	2.38×10^{-6}	1.28–1.29	
				GABR1[d]	2.67×10^{-4}	1.27–1.31	
				CNTNAP2[d]	8.92×10^{-4}	1.70–2.03	

[a] *p*-Value was calculated using recessive model.
[b] The *p*-value and OR were calculated using only the female dataset, as the sex-effect was significant ($p = 1.8 \times 10^{-4}$).
[c] Original results did not meet GWAS significance, but have been reached through meta analyses.
[d] These signals were significant when considering both SCZ and BP dataset.

Girard *et al.*, *Curr Opin Genet Dev* 2011

Genome-wide association studies (GWAS) et schizophrénies

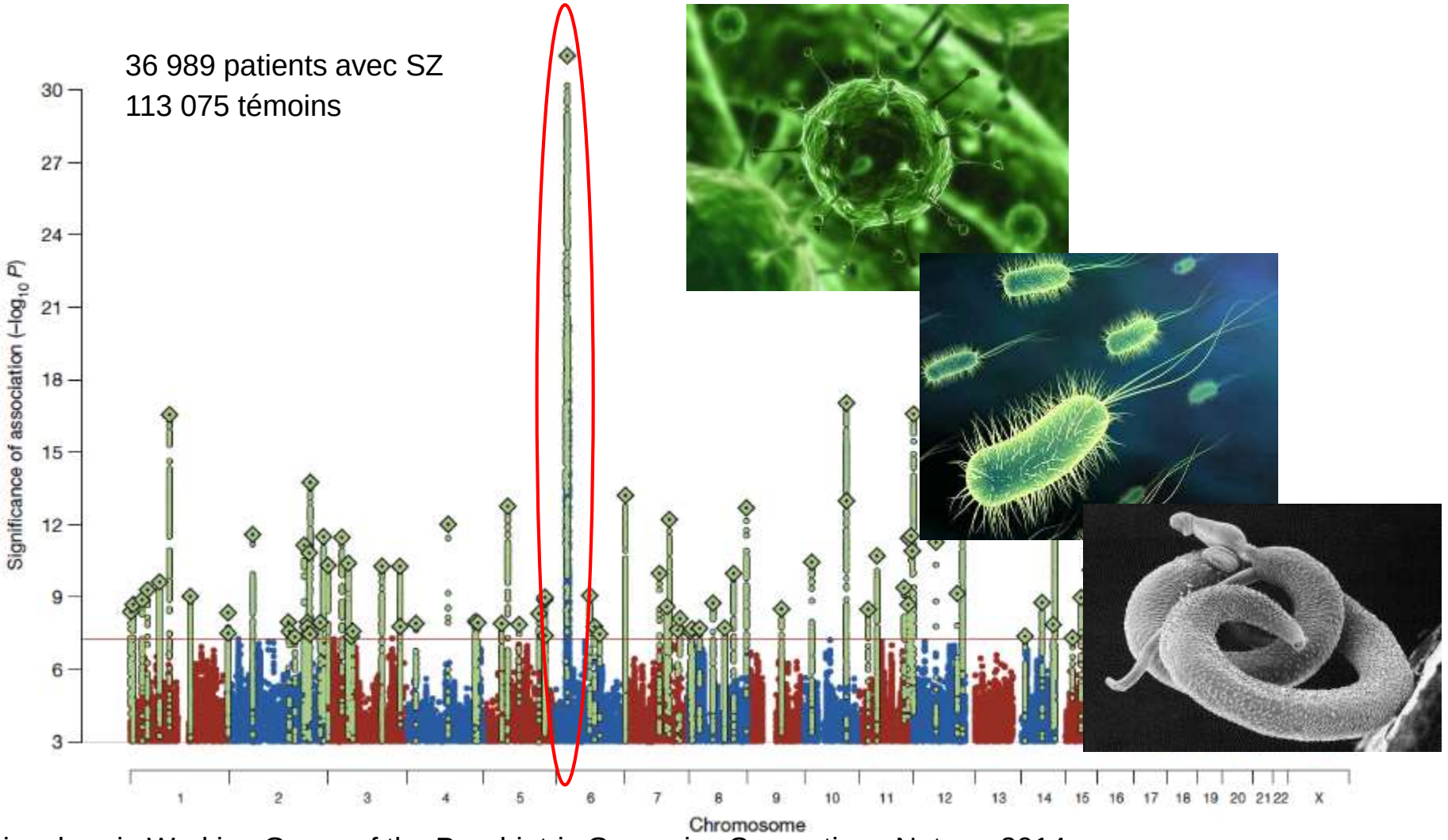


Flint and Munafò, *Nature* 2014

Biological insights from 108 schizophrenia-associated genetic loci

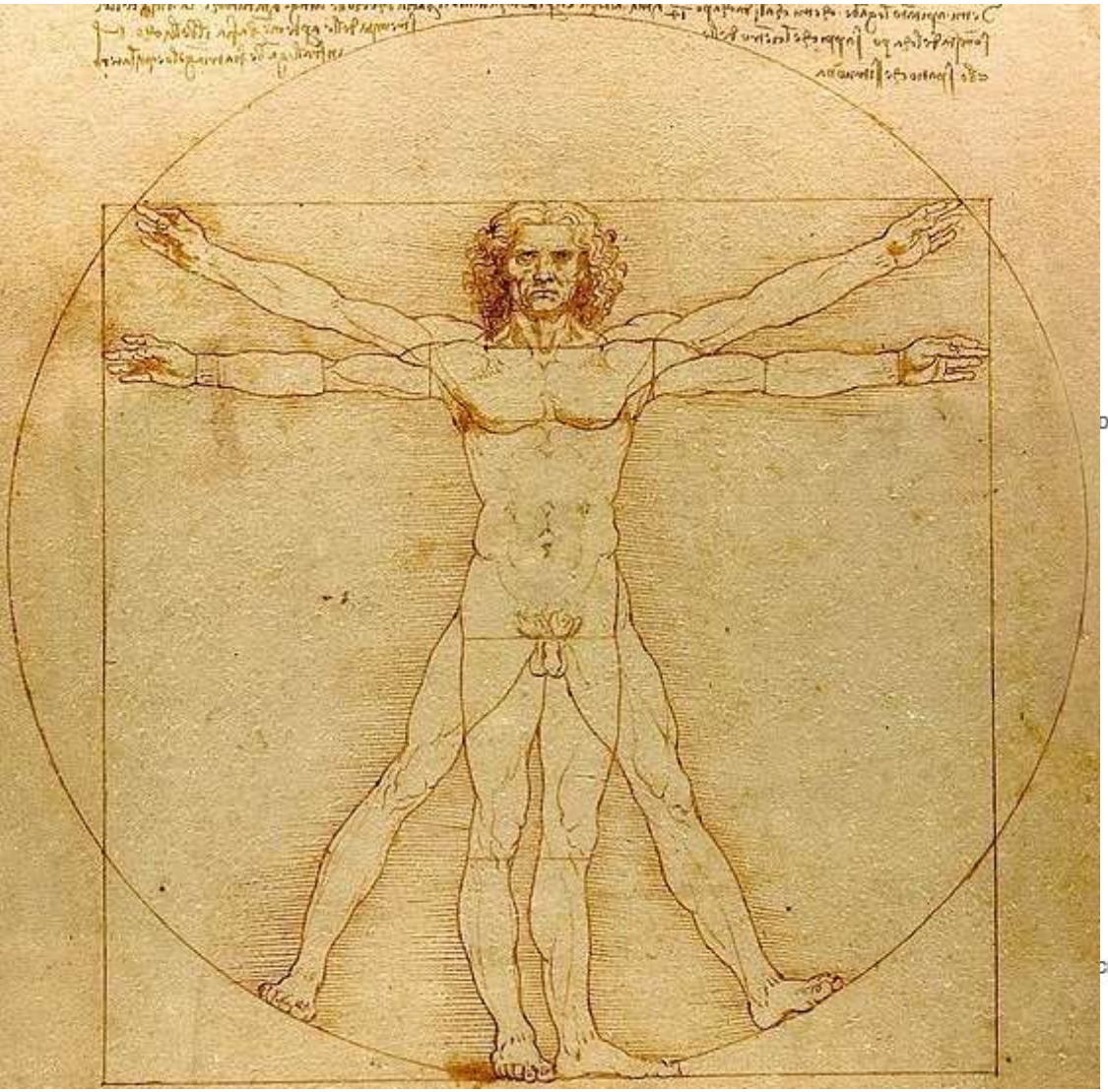
Schizophrenia Working Group of the Psychiatric Genomics Consortium*

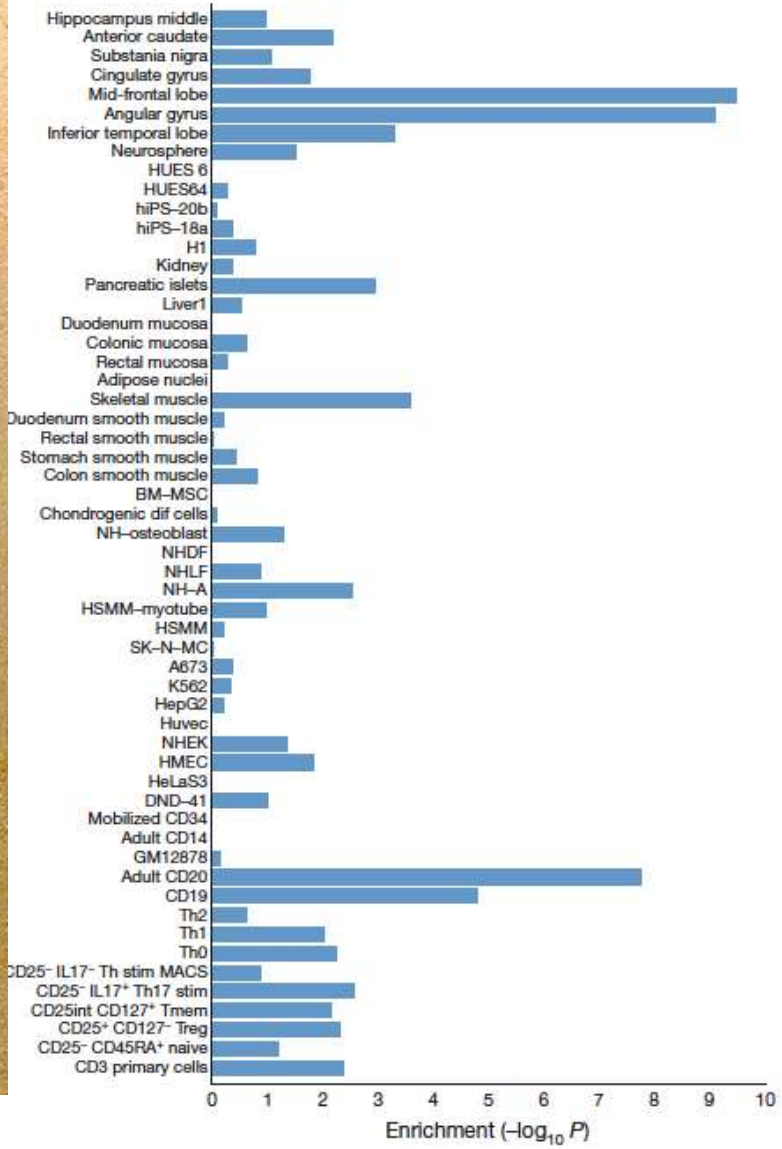
36 989 patients avec SZ
113 075 témoins



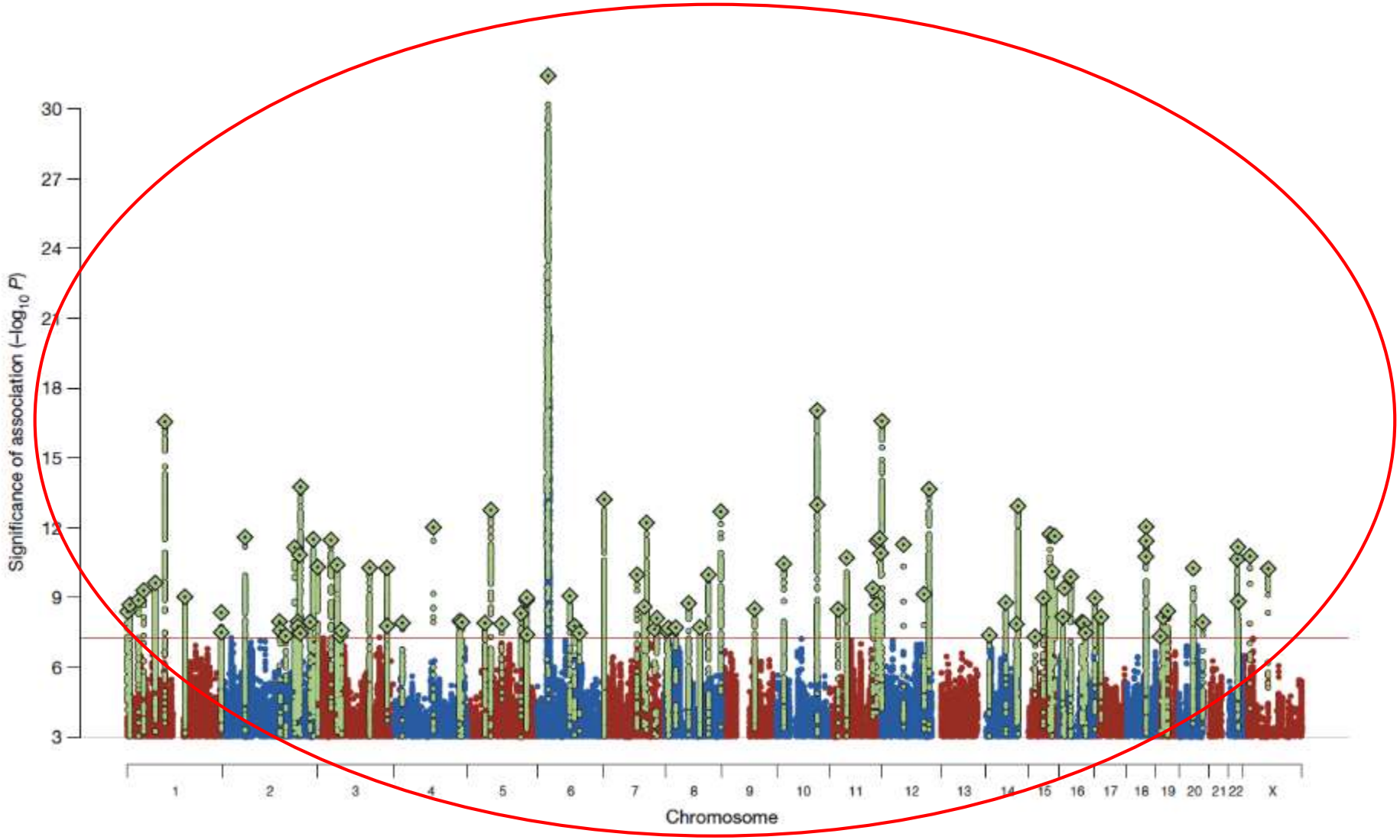
Schizophrenia Working Group of the Psychiatric Genomics Consortium, Nature, 2014.

Profil d'expression des gènes associés aux schizophrénies





Les schizophrénies sont des maladies polygéniques



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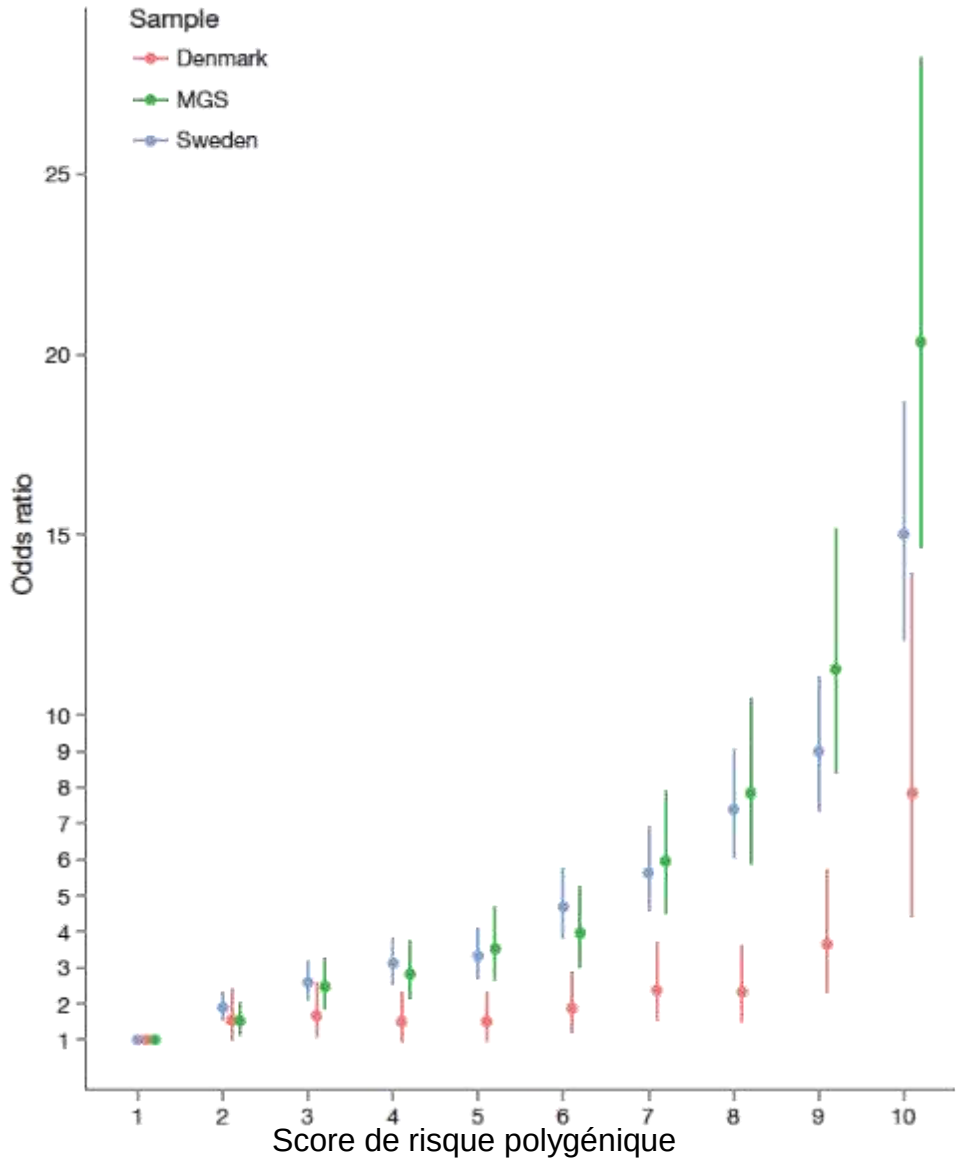
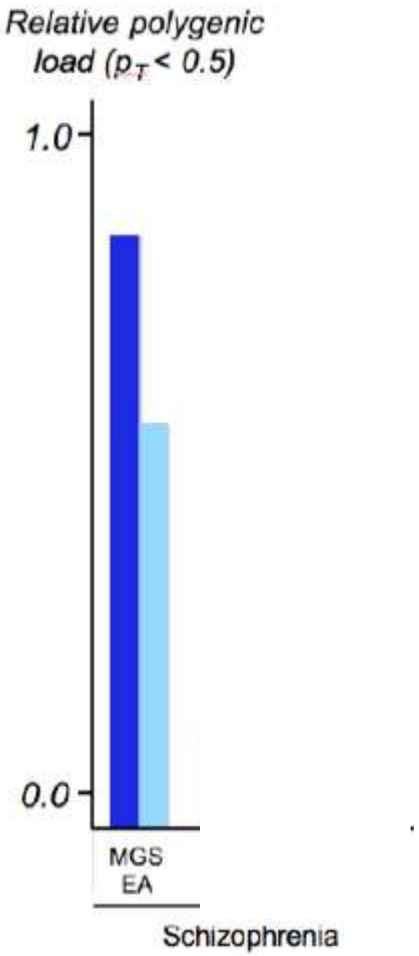


Une contribution génétique polygénique commune entre les troubles bipolaires et les schizophrénies



- 74 062 SNP
- r^2 < 0,25
- MAF > 2%

International Schizophrenia Consortium, Nature 2009

Facteurs génétiques et environnementaux dans les troubles bipolaires et les schizophrénies

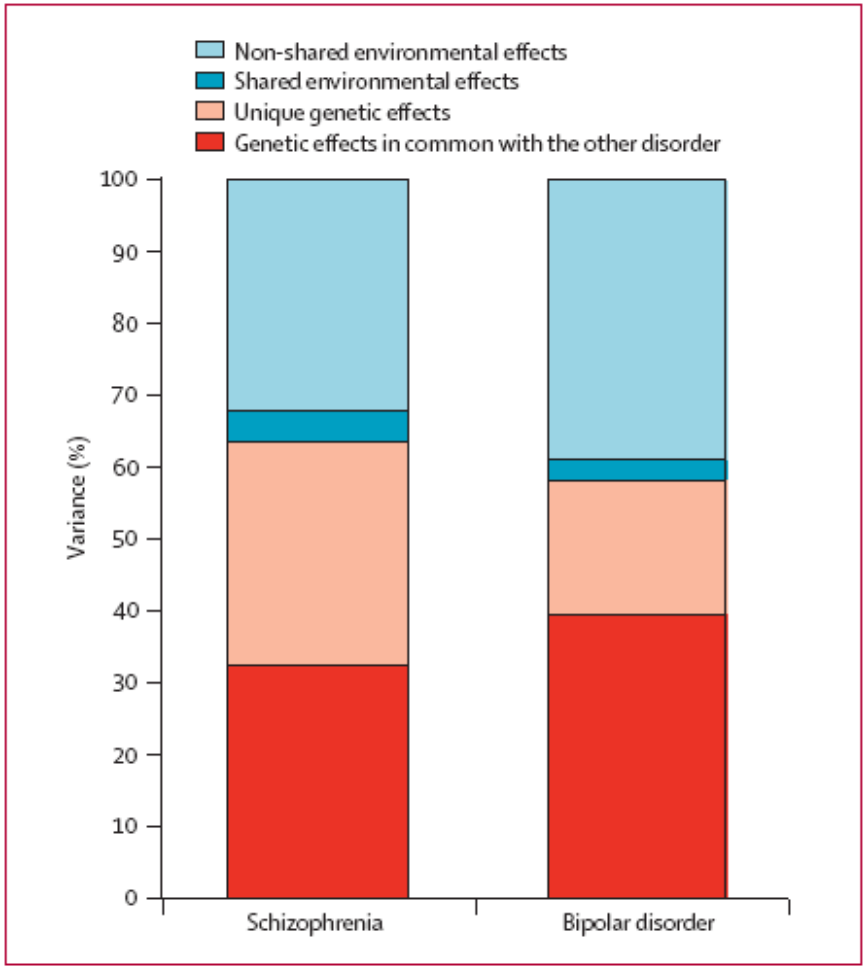


Figure: Variance accounted for by genetic, shared environmental, and non-shared environmental effects for schizophrenia and bipolar disorder

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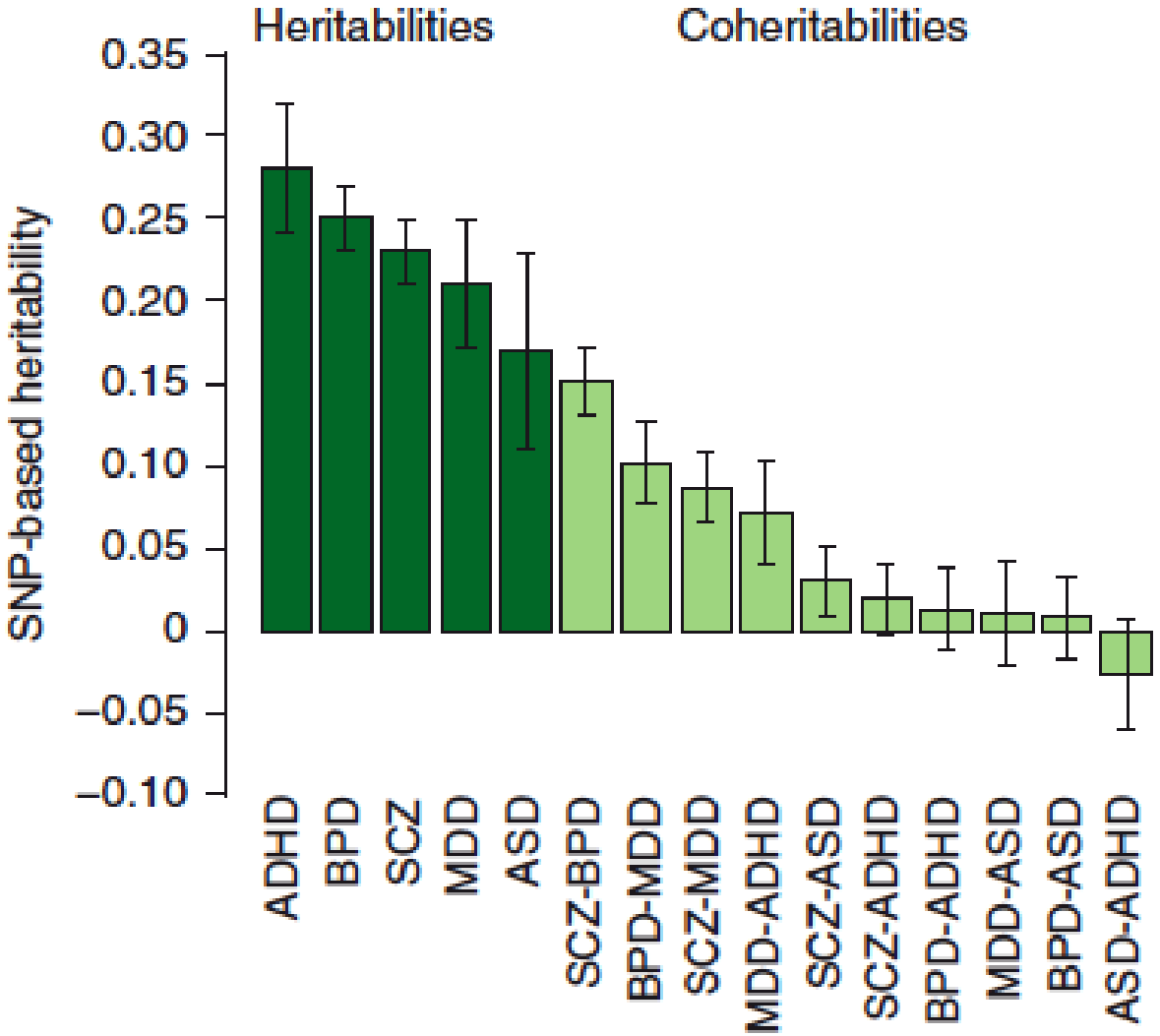
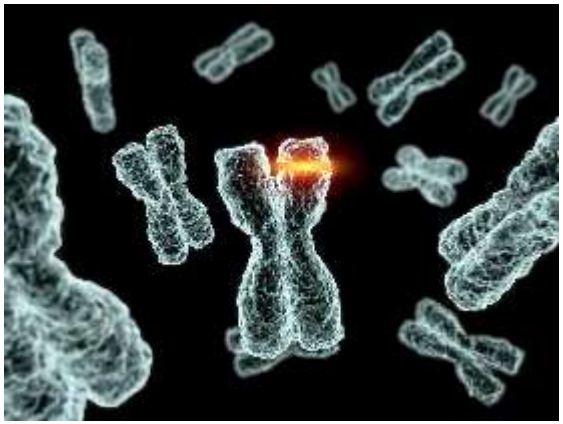
Lichtenstein, Lancet 2009

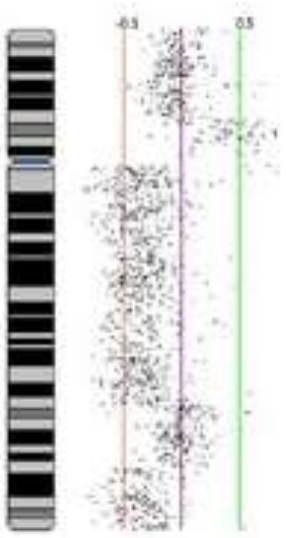
Co-héritabilité dans les troubles psychiatriques

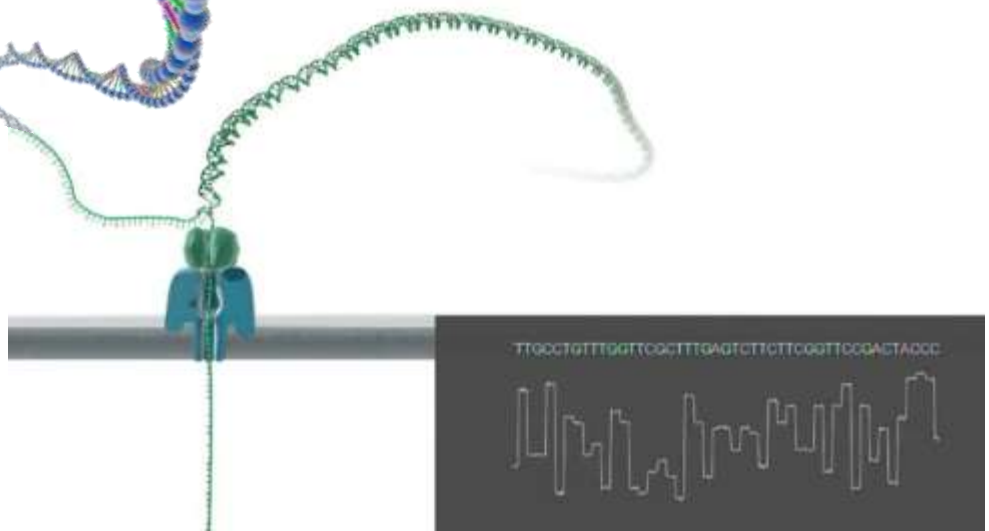


Cross-disorder group of the PGC, Nat Genet 2013

Etude des variations rares du génome dans les schizophrénies





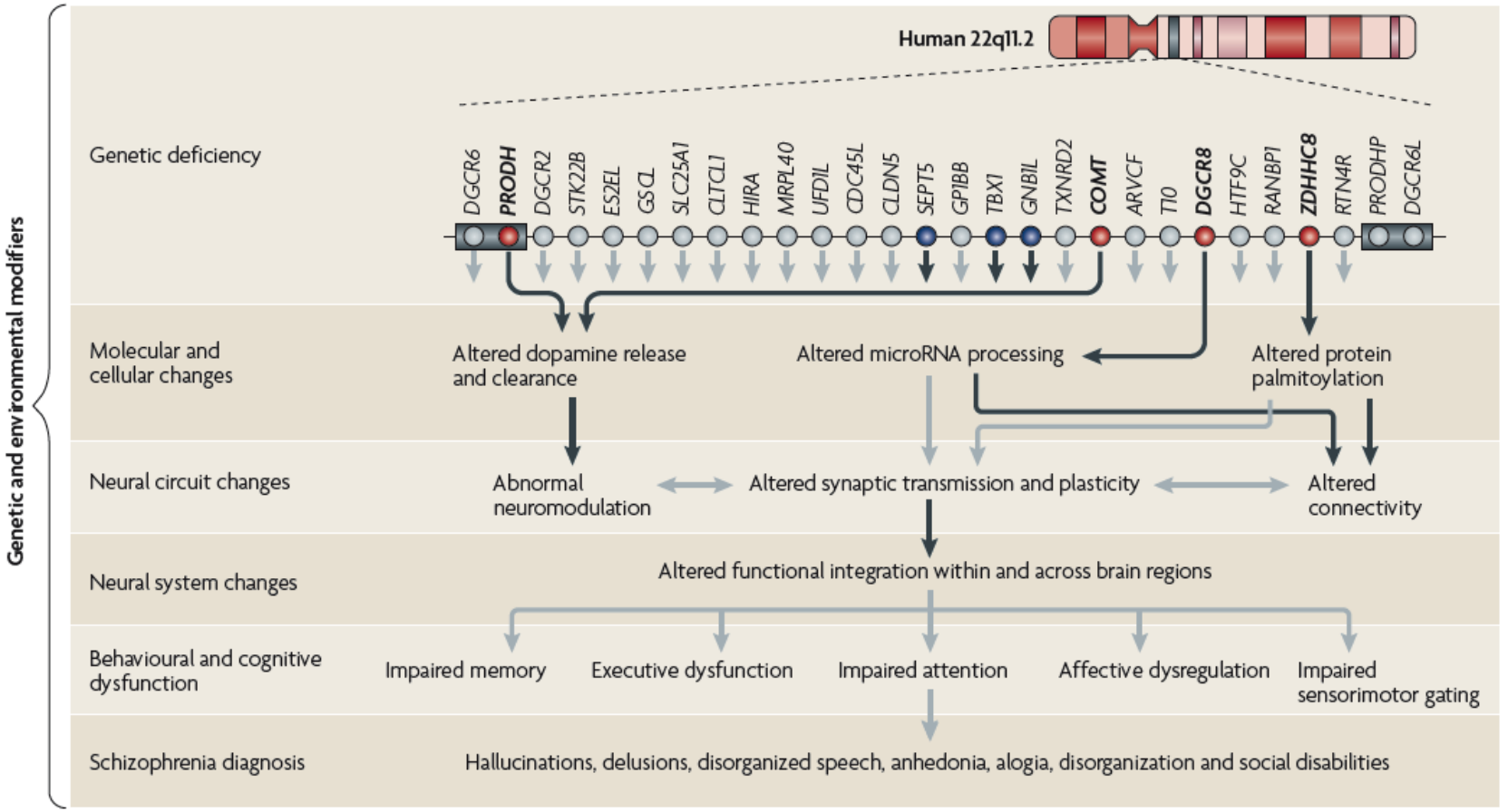


Variations du nombre de copies et schizophrénies

22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia

Maria Karayiorgou[*‡], *Tony J. Simon*[§] *and Joseph A. Gogos*[‖¶]

Abstract | Recent studies are beginning to paint a clear and consistent picture of the impairments in psychological and cognitive competencies that are associated with microdeletions in chromosome 22q11.2. These studies have highlighted a strong link between this genetic lesion and schizophrenia. Parallel studies in humans and animal models are starting to uncover the complex genetic and neural substrates altered by the microdeletion. In addition to offering a deeper understanding of the effects of this genetic lesion, these findings may guide analysis of other copy-number variants associated with cognitive dysfunction and psychiatric disorders.



Variations du nombre de copies et schizophrénies

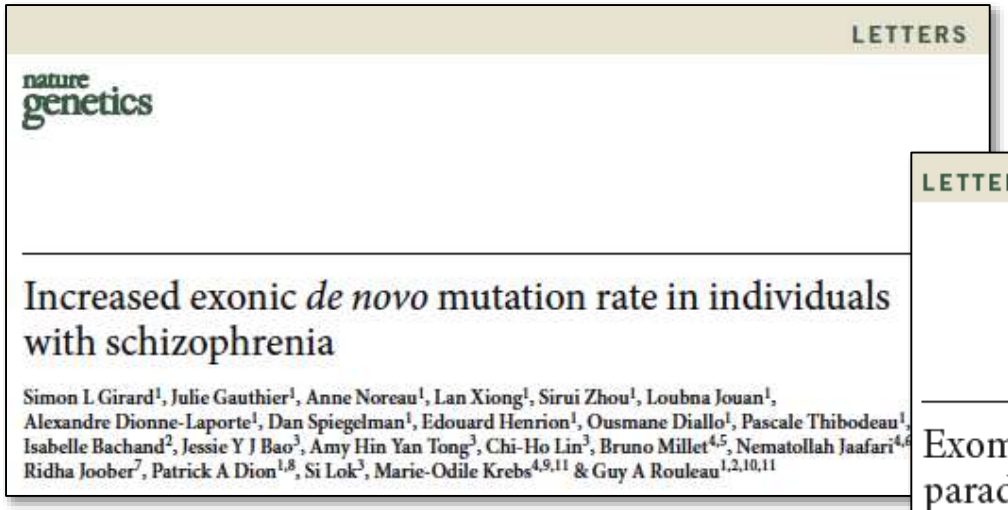
Table 2

Summary of genome-wide CNV studies for schizophrenia

Study	Type	#Cases	#Controls	Loci	OR	Comments
Walsh *et al*. [32•]	CGH	150	268			General prevalance of rare structural variant higher in SCZ
Xu *et al*. [33••]	SNPchip	359 (trios)	159	–	–	Higher impact of *de novo* CNV is higher in SCZ
Stone *et al*. [34]	SNPchip	479	2.937	22q11.2	21.6	The CNV burden is higher in SCZ (number of CNVs in an ID + number of genes in a CNV)
				15q13.3	17.9	
				1q21.1	6.6	
Stefansson *et al*. [38]	SNPchip	1.433	33.25	1q21.1	14.83	
				15q11.2	2.73	
				15q13.3	11.54	
McCarthy *et al*. [39]	SNPchip	4.551	6.391	16p11.2	14.5	Not a genome-wide study
Ingason *et al*. [43]	SNPchip	4.345	35.079	16p13.1	1.65–3.27	Not a genome-wide study
Mulle *et al*. [44]	SNPchip	245	490	3q29	17	

Girard *et al*., *Curr Opin Genet Dev* 2011

Le séquençage d'exomes dans les schizophrénies

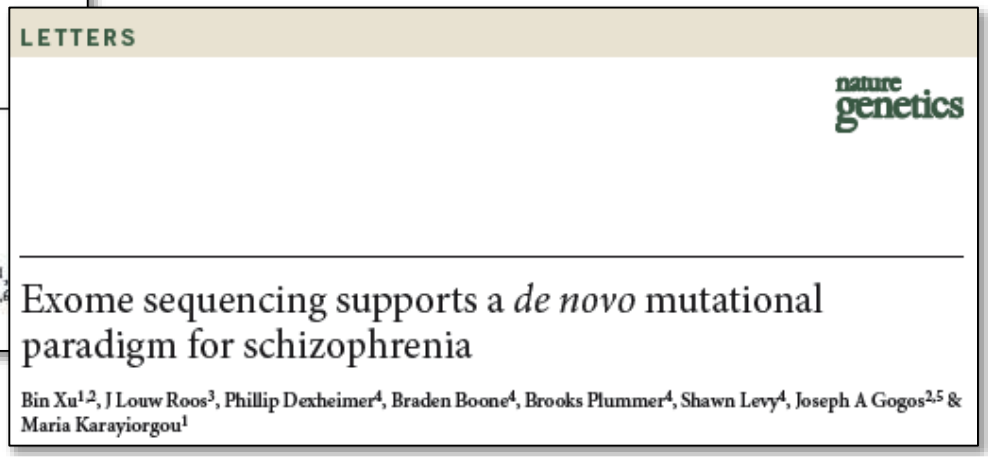


LETTERS

nature genetics

Increased exonic *de novo* mutation rate in individuals with schizophrenia

Simon L Girard[1], Julie Gauthier[1], Anne Noreau[1], Lan Xiong[1], Sirui Zhou[1], Loubna Jouan[1], Alexandre Dionne-Laporte[1], Dan Spiegelman[1], Edouard Henrion[1], Ousmane Diallo[1], Pascale Thibodeau[1], Isabelle Bachand[2], Jessie Y J Bao[3], Amy Hin Yan Tong[3], Chi-Ho Lin[3], Bruno Millet[4,5], Nematollah Jaafari[4,6], Ridha Joober[7], Patrick A Dion[1,8], Si Lok[3], Marie-Odile Krebs[4,9,11] & Guy A Rouleau[1,2,10,11]



LETTERS

nature genetics

Exome sequencing supports a *de novo* mutational paradigm for schizophrenia

Bin Xu[1,2], J Louw Roos[3], Phillip Dexheimer[4], Braden Boone[4], Brooks Plummer[4], Shawn Levy[4], Joseph A Gogos[2,5] & Maria Karayiorgou[1]

Table 3 NS:S ratio comparison between *de novo* and rare inherited mutations in schizophrenia trios

	Cases					Controls				
Class	Total number	NS	S	NS:S	*P*[a]	Total number	NS	S	NS:S	*P*[a]
De novo mutations	34	32	2	16.0		7	4	3	1.33	
Novel inherited variants	14,378	8,867	5,511	1.61	0.0002	6,213	3,825	2,388	1.60	0.81
Private inherited variants	6,727	4,223	2,504	1.69	0.0003	3,079	1,956	1,123	1.74	0.73

S, synonymous variants; NS, non-synonymous variants.
[a]*P* value for *de novo* compared to inherited mutations.

ARTICLE

doi:10.1038/nature12975

A polygenic burden of rare disruptive mutations in schizophrenia

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Schizophrenia is a common disease with a complex aetiology, probably involving multiple and heterogeneous genetic factors. Here, by analysing the exome sequences of 2,536 schizophrenia cases and 2,543 controls, we demonstrate a polygenic burden primarily arising from rare (less than 1 in 10,000), disruptive mutations distributed across many genes. Particularly enriched gene sets include the voltage-gated calcium ion channel and the signalling complex formed by the activity-regulated cytoskeleton-associated scaffold protein (ARC) of the postsynaptic density, sets previously implicated by genome-wide association and copy-number variation studies. Similar to reports in autism, targets of the fragile X mental retardation protein (FMRP, product of *FMR1*) are enriched for case mutations. No individual gene-based test achieves significance after correction for multiple testing and we do not detect any alleles of moderately low frequency (approximately 0.5 to 1 per cent) and moderately large effect. Taken together, these data suggest that population-based exome sequencing can discover risk alleles and complements established gene-mapping paradigms in neuropsychiatric disease.

ARTICLE

doi:10.1038/nature12929

De novo mutations in schizophrenia implicate synaptic networks

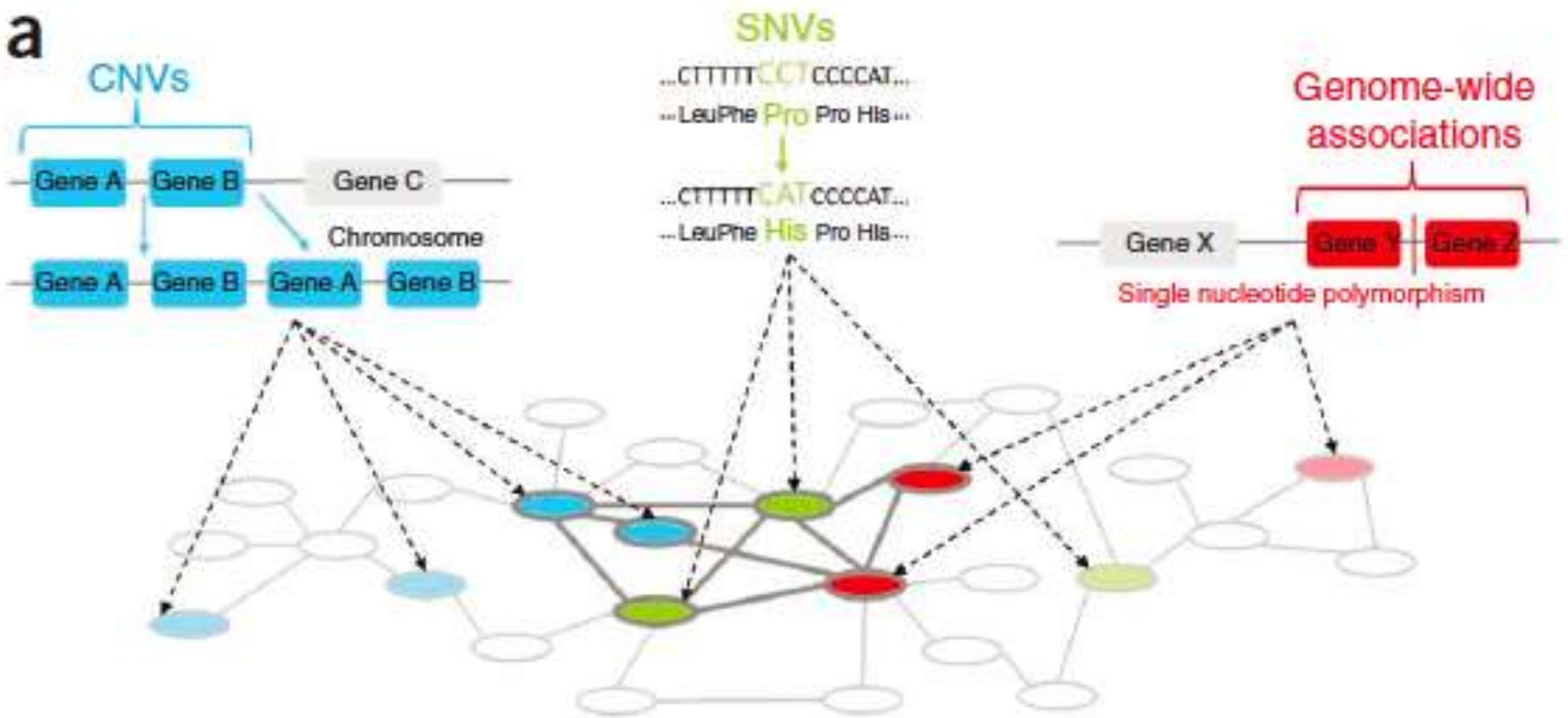
Menachem Fromer[1,2], Andrew J. Pocklington[3], David H. Kavanagh[3], Hywel J. Williams[3], Sarah Dwyer[3], Padhraig Gormley[4,5], Lyudmila Georgieva[3], Elliott Rees[3], Priit Palta[4,6,7], Douglas M. Ruderfer[1,3], Noa Carrera[3], Isla Humphreys[3], Jessica S. Johnson[1], Panos Roussos[1], Douglas D. Barker[2], Eric Banks[5], Vihra Milanova[8], Seth G. Grant[9], Eilis Hannon[3], Samuel A. Rose[2], Kimberly Chambert[2], Milind Mahajan[1], Edward M. Scolnick[2], Jennifer L. Moran[2], George Kirov[3], Aarno Palotie[4,5,7], Steven A. McCarroll[2,5,10], Peter Holmans[3], Pamela Sklar[1,11], Michael J. Owen[3], Shaun M. Purcell[1,2,12] & Michael C. O'Donovan[3]

Table 3 | Enrichment of *de novo* mutations in postsynaptic protein complexes

		Current study						Schizophrenia (ref. 14)		Schizophrenia (ref. 13)		Schizophrenia all (refs 12–14)		Autism spectrum disorder[6–9]		Intellectual disability[10,11]	
		Nonsynonymous (482)			Loss-of-function (64)			Non-synonymous (68)	Loss-of-function (12)	Non-synonymous (137)	Loss-of-function (20)	Non-synonymous (702)	Loss-of-function (100)	Non-synonymous (789)	Loss-of-function (134)	Non-synonymous (141)	Loss-of-function (34)
Gene set	Genes (*N*)	*P*	No. mut.	O/E	*P*	No. mut.	O/E	*P*	*P*	*P*	*P*	*P*	*P*	*P*	*P*	*P*	*P*
Postsynaptic density	681	**0.019**	34	1.46	0.091	6	1.92	0.84	0.45	0.65	0.64	0.091	0.12	0.47	0.064	**0.0015**	**0.00004**
ARC complex	28	**0.00048**	6	6.06	**0.005**	2	17.42	1	1	1	1	**0.0035**	**0.015**	0.22	0.22	**0.00002**	**0.0015**
NMDAR complex	60	**0.025**	6	2.74	**0.035**	2	6.99	1	1	0.13	0.086	**0.016**	**0.011**	**0.031**	0.46	**0.00002**	**0.00002**

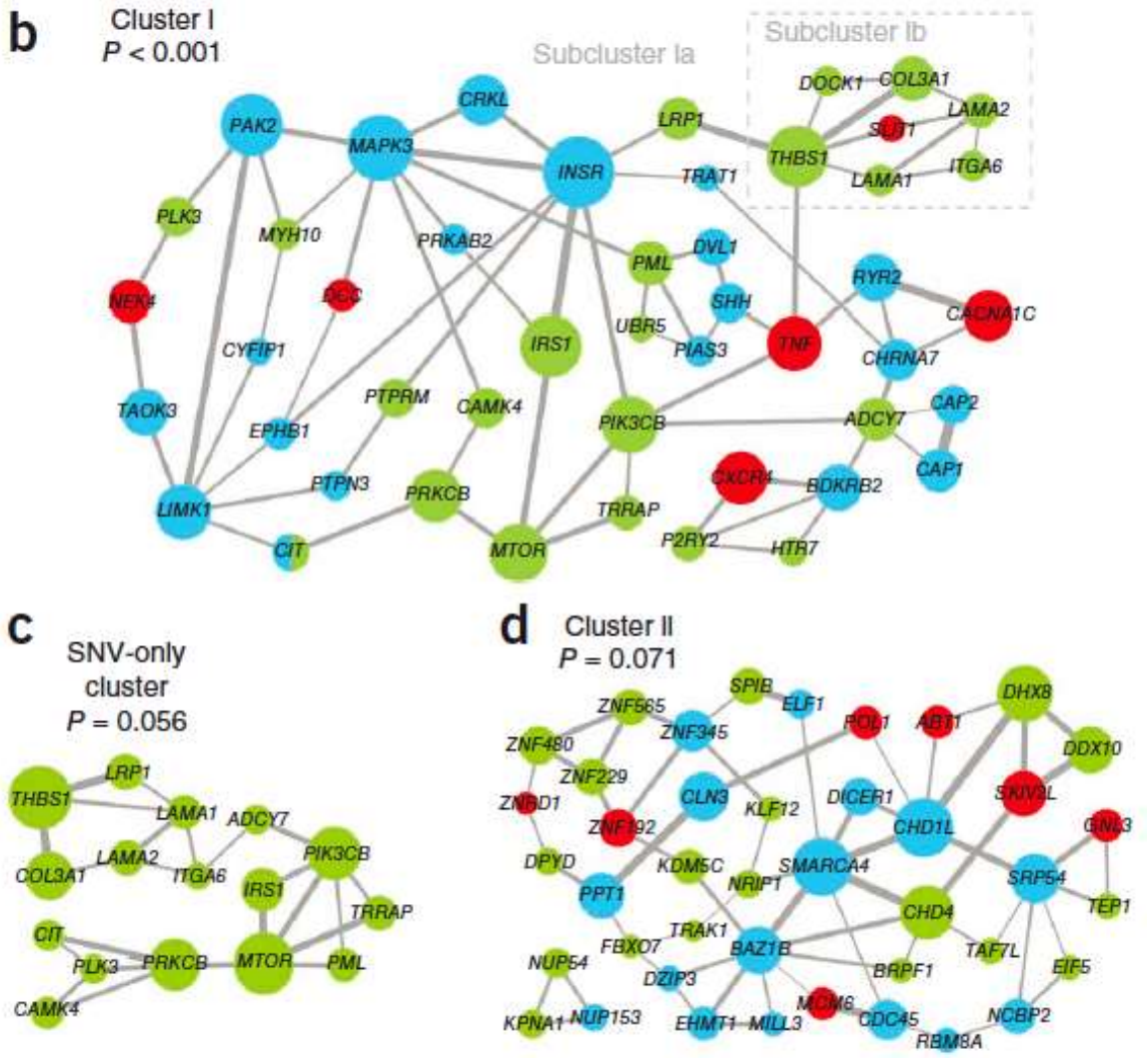
Fromer *et al.*, Nature 2014

Réseaux de gènes et schizophrénies

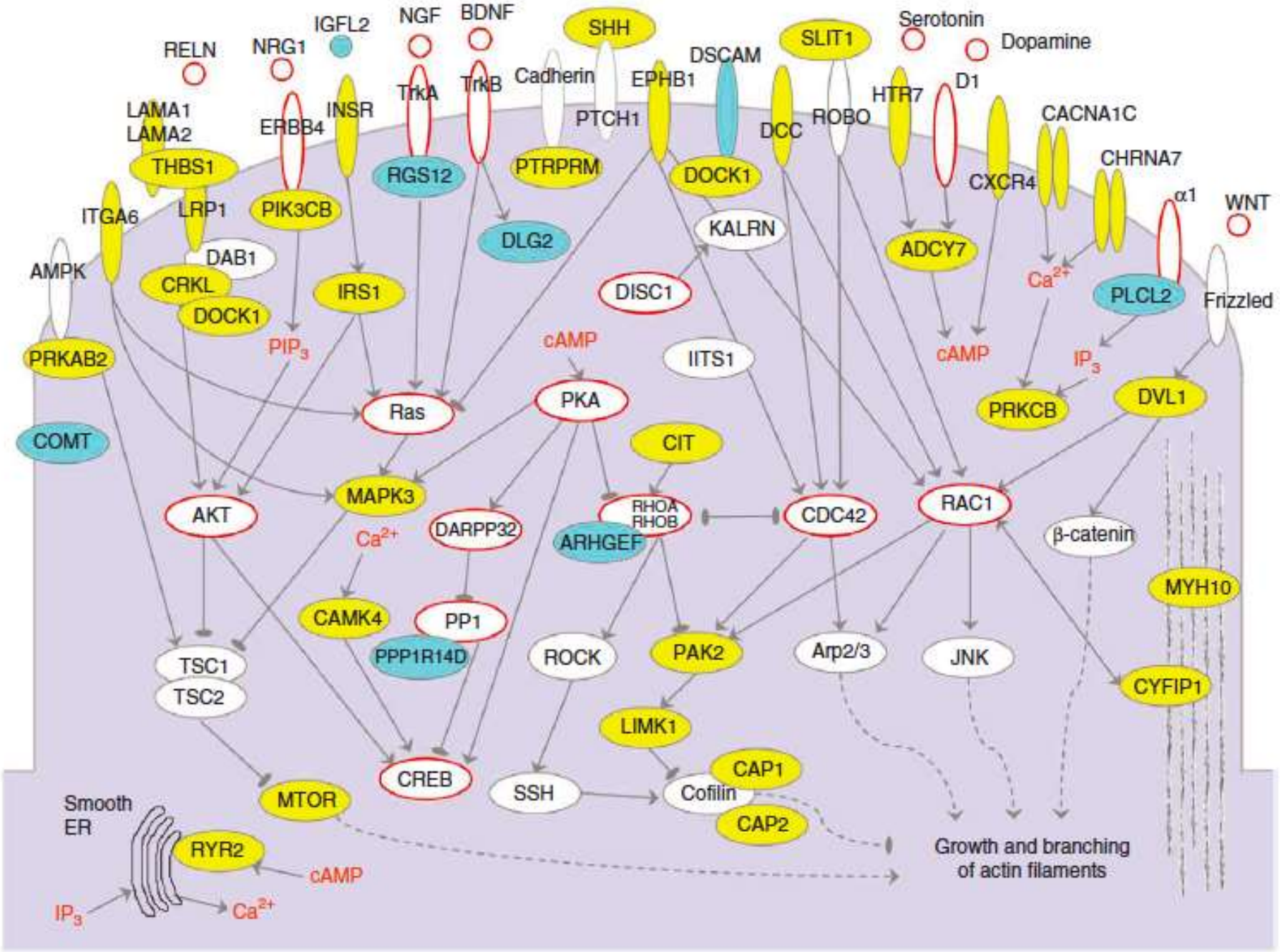


Gilman *et al*., Nature Neurosci 2012

Réseaux de gènes et schizophrénies

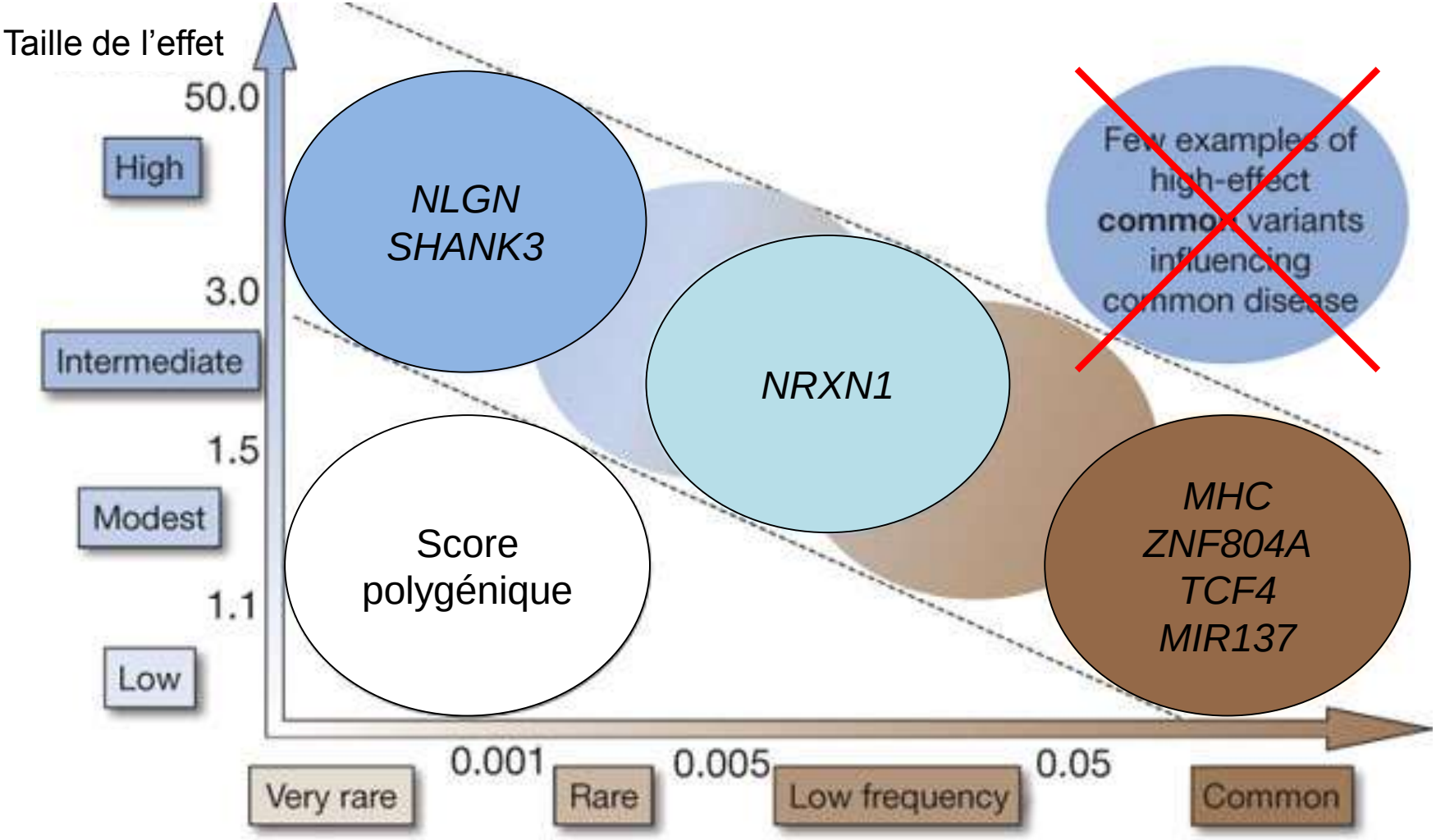


Gilman *et al*., Nature Neurosci 2012



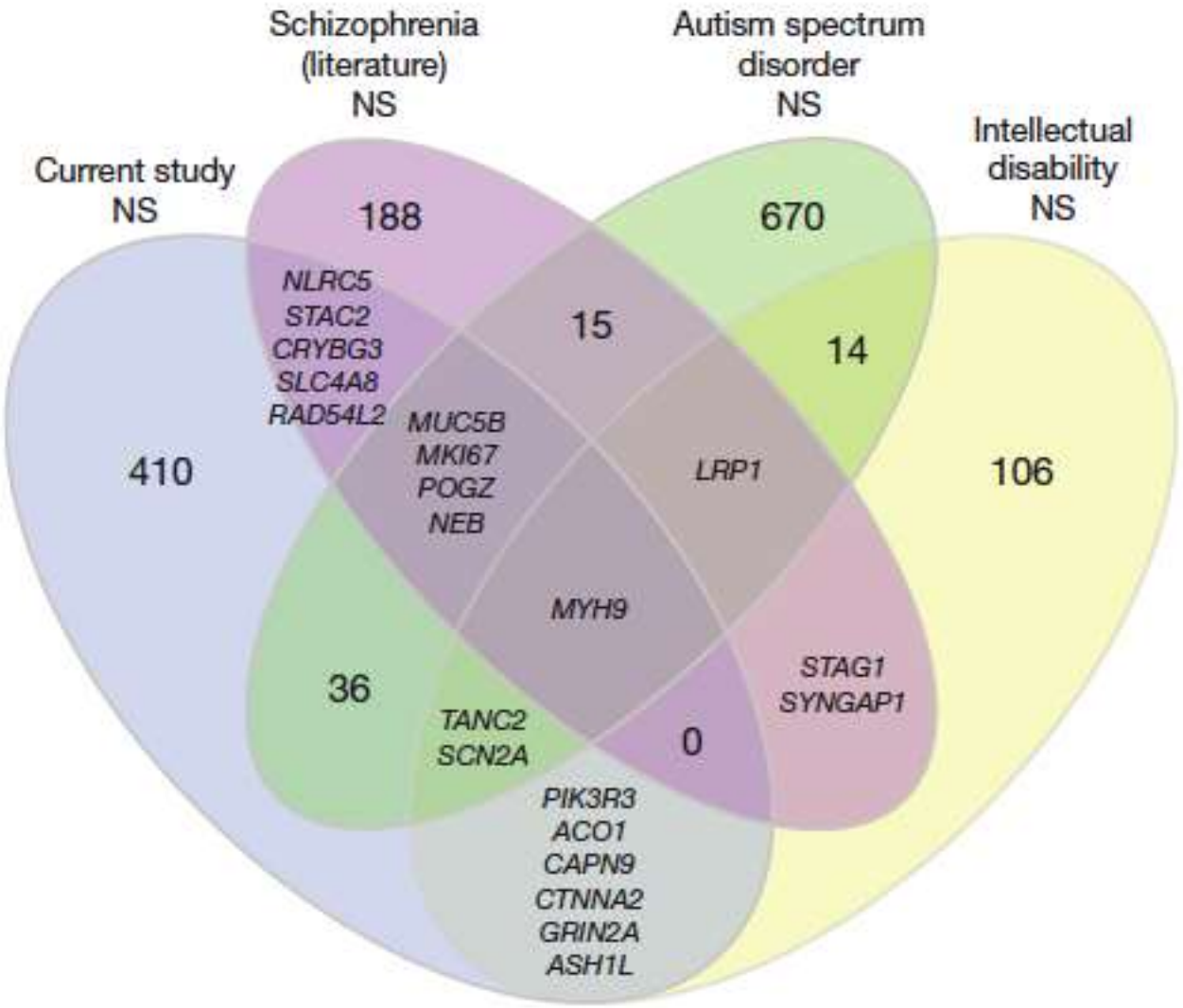
Gilman *et al*., Nature Neurosci 2012

Génétique des schizophrénies



Manolio *et al*. Nature 2009

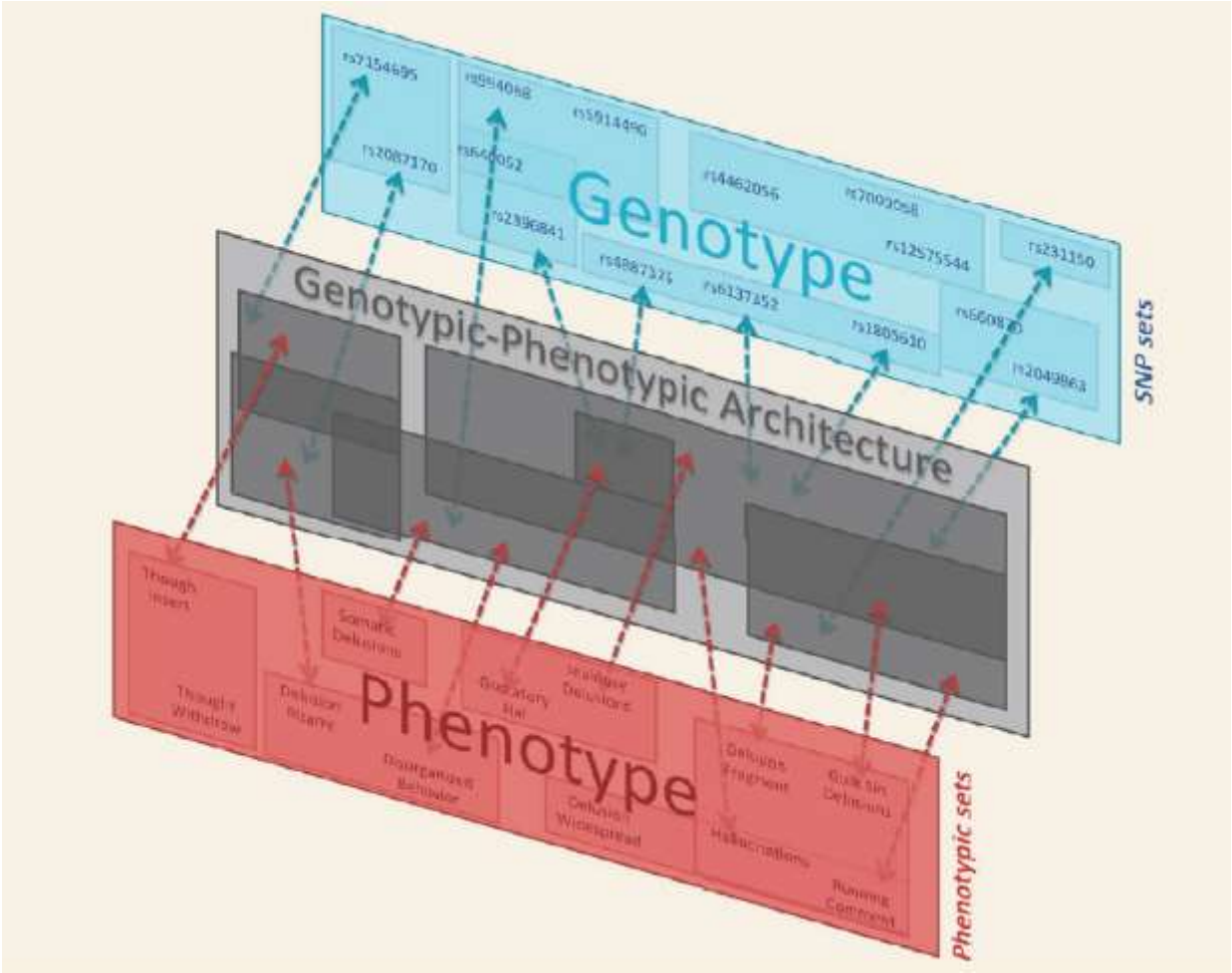
Mutation *de novo* et schizophrénies



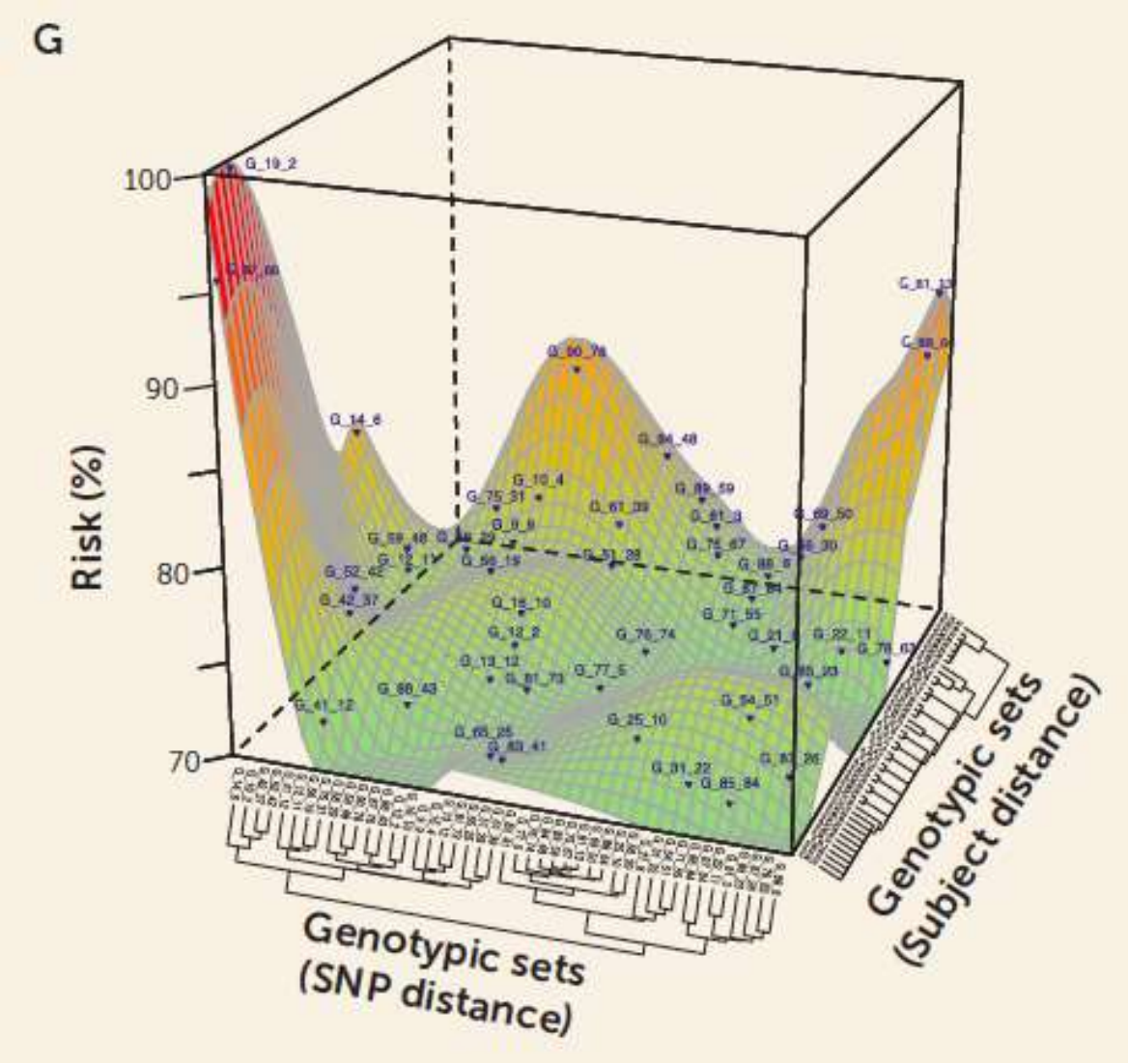
Fromer *et al*., Nature 2014

Uncovering the Hidden Risk Architecture of the Schizophrenias: Confirmation in Three Independent Genome-Wide Association Studies

Javier Arnedo, M.S., Dragan M. Svrakic, M.D., Ph.D., Coral del Val, Ph.D., Rocío Romero-Zaliz, Ph.D., Helena Hernández-Cuervo, M.D., Molecular Genetics of Schizophrenia Consortium, Ayman H. Fanous, M.D., Michele T. Pato, M.D., Carlos N. Pato, M.D., Ph.D., Gabriel A. de Erausquin, M.D., Ph.D., C. Robert Cloninger, M.D., Ph.D., Igor Zwir, Ph.D.

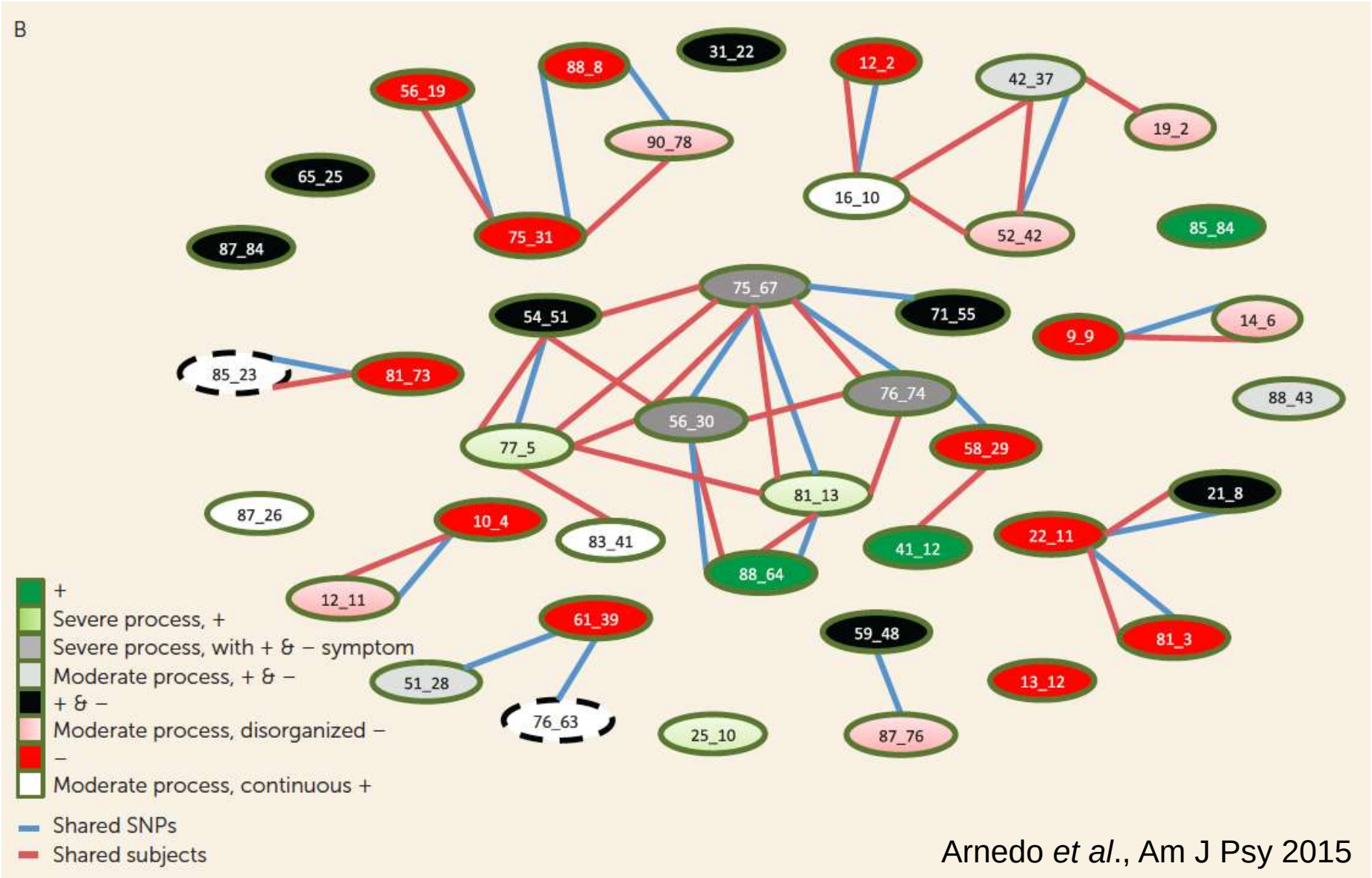


Risque de schizophrénies en fonction des panels de SNP



Arnedo *et al*., Am J Psy 2015

Génétique et phénotypique architecture des schizophrénies



Arnedo *et al.*, Am J Psy 2015

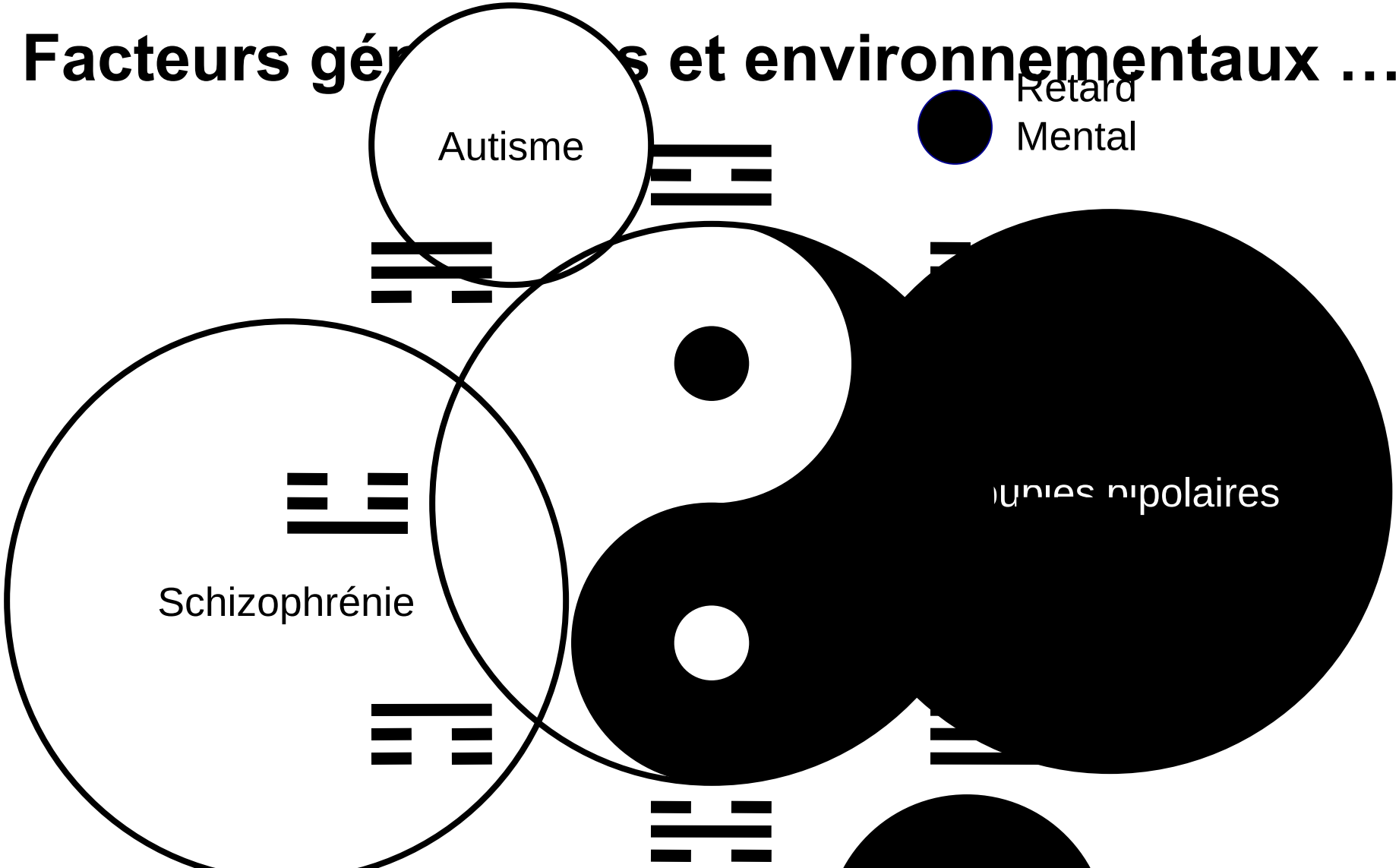
Génétique et phénotypique architecture des schizophrénies

TABLE 3. Subset of Genotypic-Phenotypic AND/OR Relationships (Hypergeometric Statistics)[a]

Schizophrenia Class, Symptoms[b], and DSM Ratings	Phenotypic Sets	SNP Sets	p
Severe process, with positive and negative symptom schizophrenia			
Positive symptoms; moderate severity of impairment; unable to function since onset	15_13	56_30	2.55E−05
Auditory hallucinations (2 or more voices; running commentaries)	12_11		1.79E−04
Auditory hallucinations (2 or more voices; running commentaries); thought echoing; withdrawal; insertion and broadcasting; delusions of mind reading	21_1		3.66E−04
Hallucinations (any); auditory hallucinations (ever; 2 or more voices); grossly disorganized behavior	50_46		5.70E−04
Hallucinations (mood incongruent); auditory hallucinations; somatic hallucinations (olfactory; gustatory; tactile); religious delusions; delusions of mind reading; delusions of control; thought echoing; withdrawal; insertion and broadcasting	9_6		4.45E−03
Hallucinations (mood incongruent); persecutory delusions; delusions of reference; jealousy delusions; bizarre delusions; disorganized odd behavior; disorganized odd speech; delusions, fragmented (unrelated themes); delusions, widespread (intrude into most aspects of life); thought insertion; flat affect; avolition and apathy	46_23		4.15E−03
Continuously positive symptoms; severe impairment; continuous course; no affective symptoms	15_13	75_67	2.31E−13
Grossly disorganized behavior; severe impairment; continuous course	54_11		4.90E−06
Delusions of persecution and reference; disorganized speech; severe impairment; unable to function since onset	30_17		2.56E−04
Auditory hallucinations (ever; 2 or more voices; running commentaries); jealousy delusions	18_13		3.50E−04
Thought insertion and withdrawal	27_6		3.62E−03

Arnedo *et al.*, Am J Psy 2015

Facteurs gé s et environnementaux …



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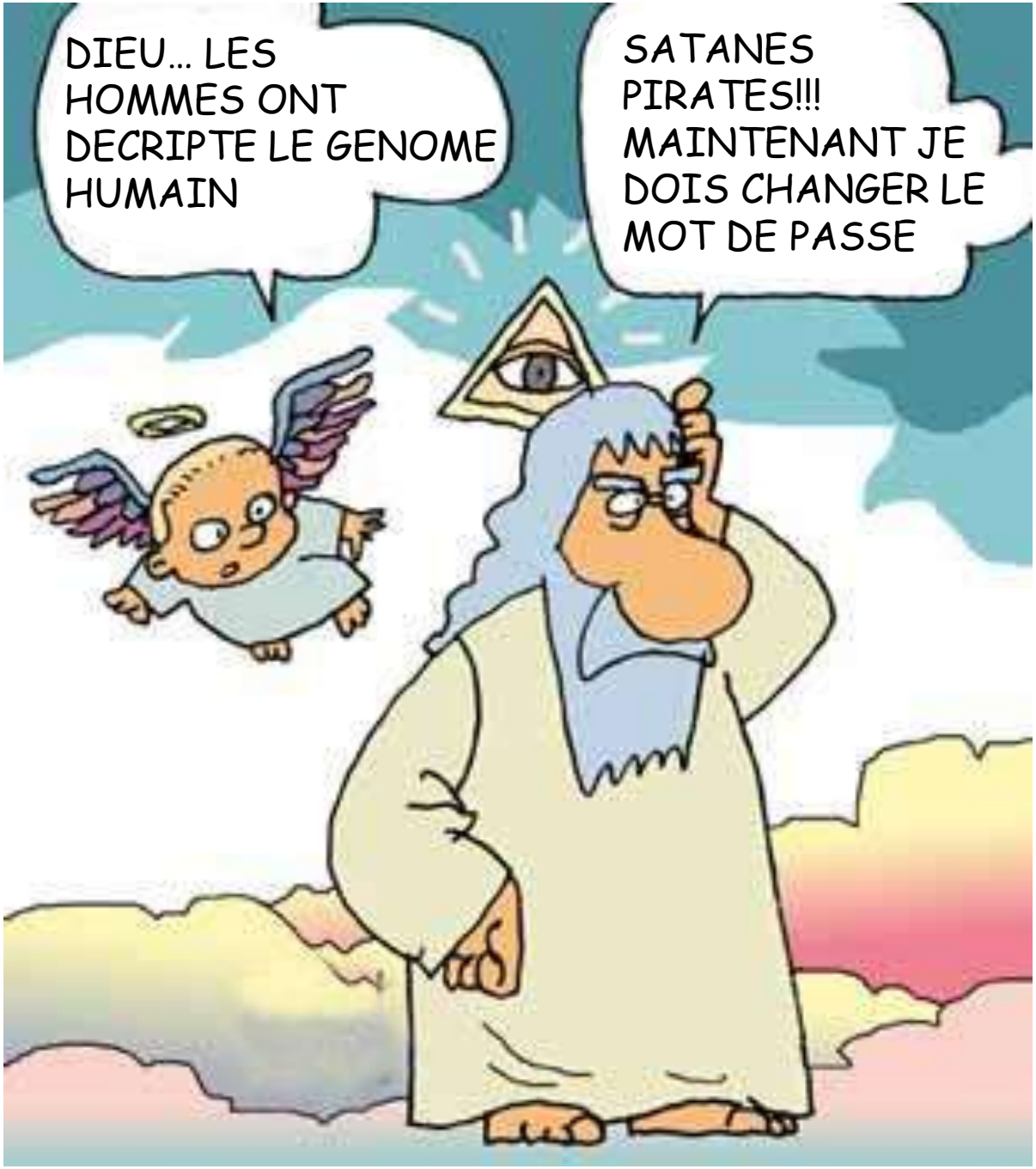
des ma TDAH es psyc es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