REAL ACADEMIA DE MEDICINA DE VALENCIA

Valencia 17 de Mayo 2012

GENETICA Y PSIQUIATRÍA

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incliva
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Fundación Investigación Clínico de Valencia

MENU

1-Heredabilidad de las enfermedades psiquaitricas

2.Datos generales genetica molecular

-Estudios de todo el genoma amplio

-Cambios en expresión génica

3-Interacción genético-ambiental

4- El Futuro - Practica Clinica

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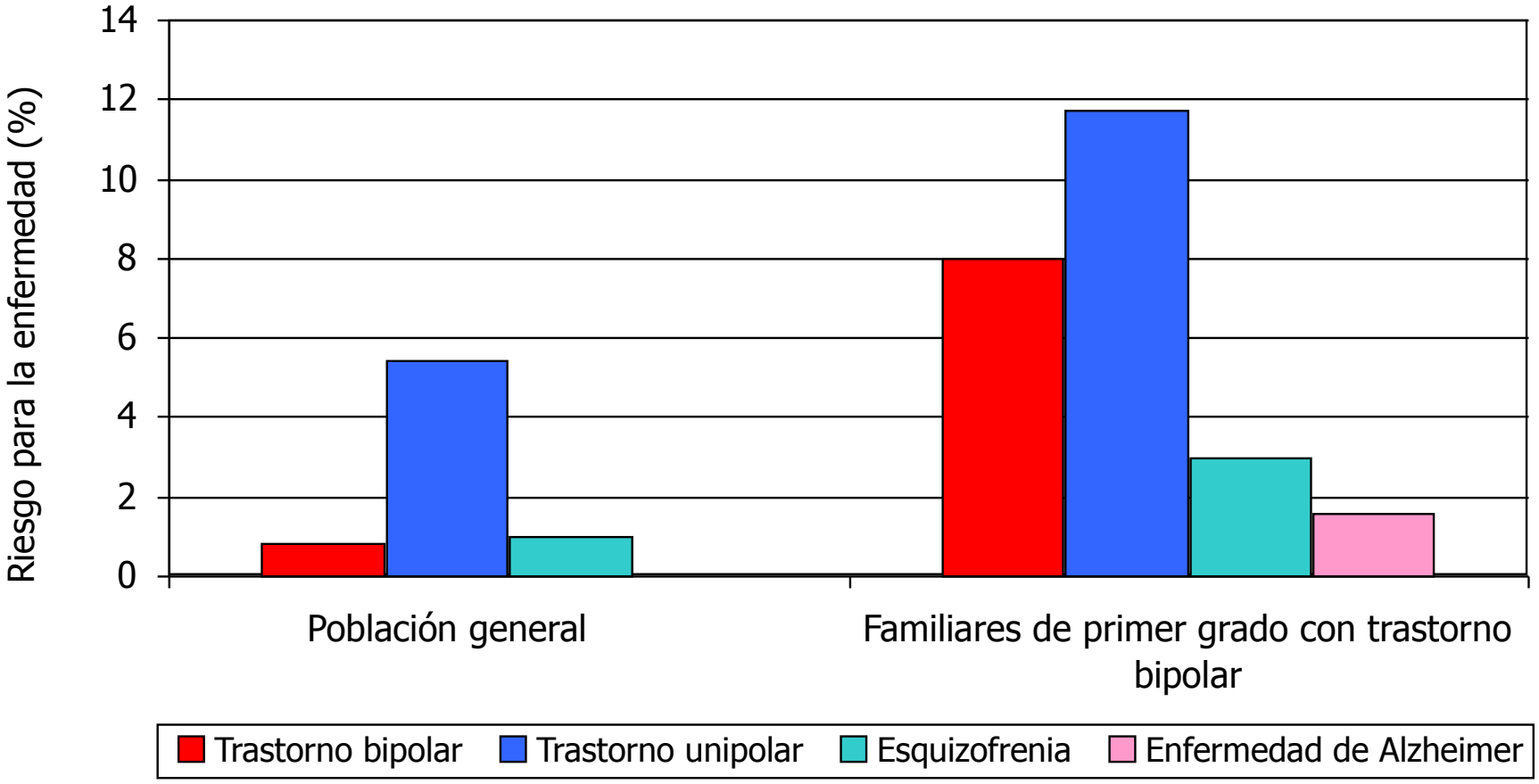
4-Futuro- Practica Clinica

Genética y Psiquiatría

Preguntas	Métodos
GENETICA CUANTITATIVA	
¿Se trata de una enfermedad familiar?	**Estudios familiares**
¿Cuál es la contribución relativa de los genes?	**Estudios de gemelos y adopción**
GENETICA MOLECULAR	
¿Dónde se localiza el gen/es?	**Estudios de ligamento**
¿Cual es el gen/es?	**Estudios de asociación**

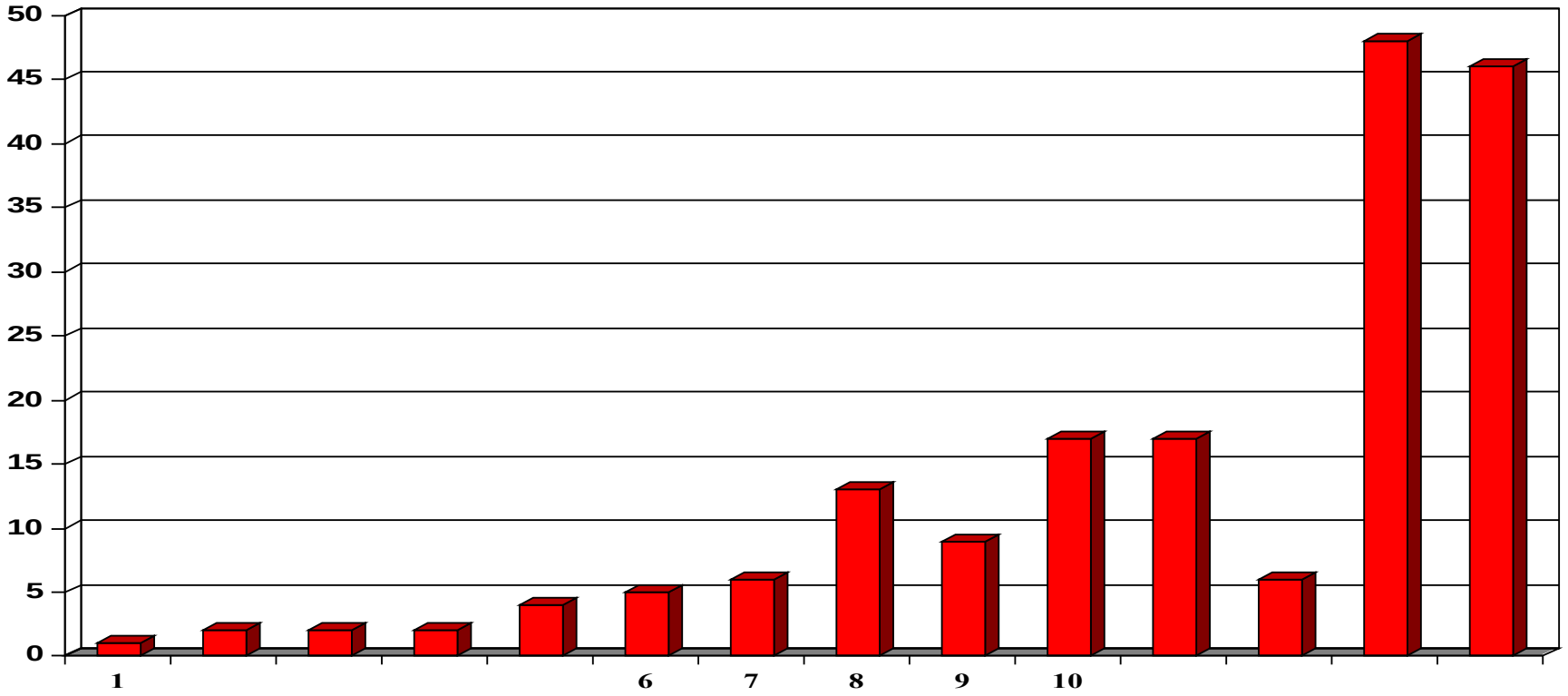
¿SE TRATA DE UNA ENFERMEDAD FAMILIAR?

T. Bipolar
Riesgo en Familiares



Fañanás, 2002

Prevalencia en familias



1. Población general
2. Esposas de pacientes
3. Primos hermanos
4. Tios
5. Sobrinos
6. Nietos
7. Medios hermanos
8. Hijos
9. Hermanos
10. Hermanos con un padre esquizofrénico
11. Gemelos dizigóticos
12. Padres
13. Gemelos monozigóticos
14. Hijos de dos padres esquizofrénicos

Adaptación de Gottesman (1991)

2. ¿Cuál es la contribución relativa de los genes?

ESTUDIOS DE GEMELOS

MONOCIGOTOS (100%)

DICIGOTOS (50%)

Heredabilidad de distintos trastornos mentales

Trastorno	Heredabilidad (%)
Trastorno de ansiedad generalizada	30
Fobias	35
Depresión mayor	30-40
Trastorno de angustia	40
Suicidio	45
Alcoholismo	60
Esquizofrenia	**60-80**
Trastorno bipolar	**70-80**

CONCLUSIONES

-Hay un claro componente genético

-Pero el componente genético explica solo una parte del origen de la enfermedad

-Existe una influencia ambiental

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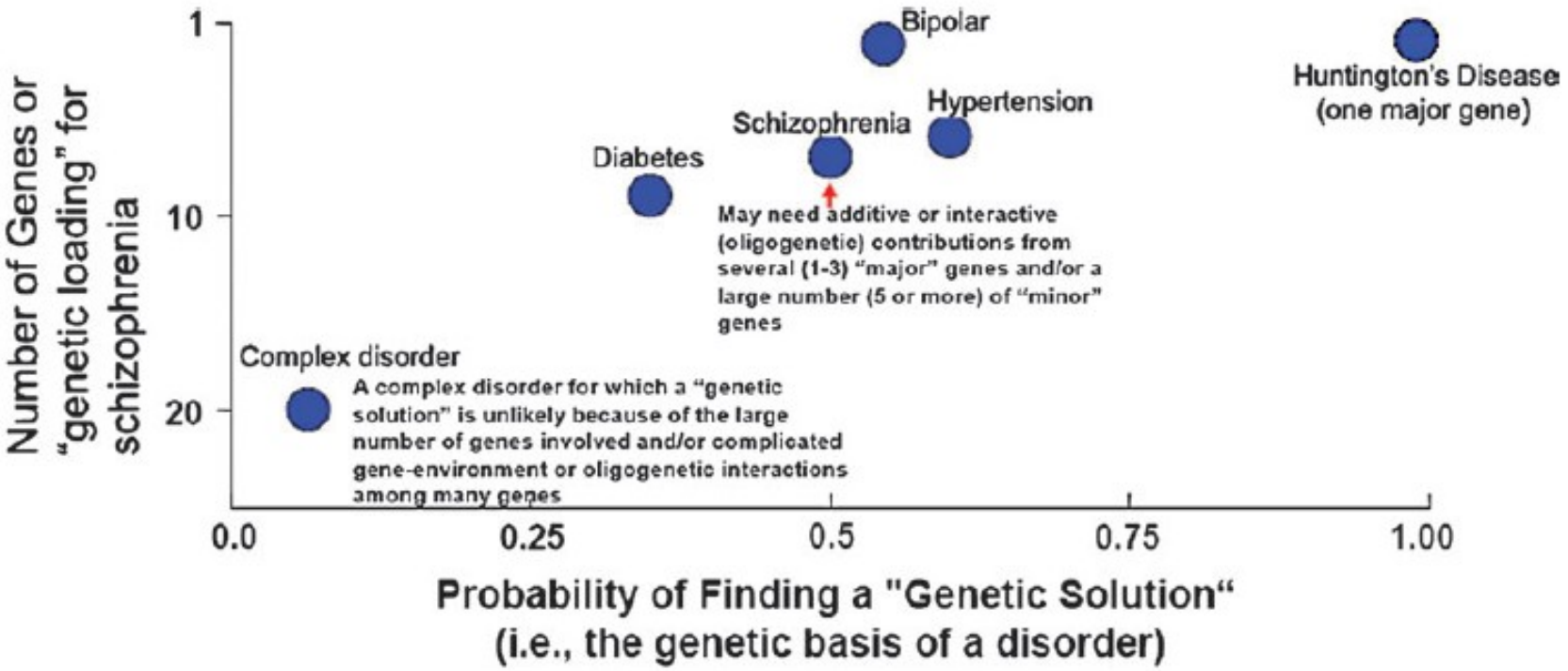
4- Futuro- Practica Clinica


Number of Genes or "genetic loading" for schizophrenia
1
10
20
Bipolar
Huntington's Disease (one major gene)
Hypertension
Schizophrenia
Diabetes
May need additive or interactive (oligogenetic) contributions from several (1-3) "major" genes and/or a large number (5 or more) of "minor" genes
Complex disorder
A complex disorder for which a "genetic solution" is unlikely because of the large number of genes involved and/or complicated gene-environment or oligogenetic interactions among many genes
0.0
0.25
0.5
0.75
1.00
Probability of Finding a "Genetic Solution"
(i.e., the genetic basis of a disorder)

Schizophrenia genes at last?

Table 1 Schizophrenia susceptibility genes and the strength of evidence in four domains

Gene[a]	*Locus*	*Strength of evidence (0 to + + + + +) for*			
		Association with schizophrenia[b]	*Linkage to gene locus*[c]	*Biological plausibility*[d]	*Altered expression in schizophrenia*[e]
COMT	22q11	+ + + +	+ + + +	+ + + +	Yes, +
DTNBP1	6p22	+ + + + +	+ + + +	+ +	Yes, + +
NRG1	8p12–21	+ + + + +	+ + + +	+ + +	Yes, +
RGS4	1q21–22	+ + +	+ + +	+ + +	Yes, + +
GRM3	7q21–22	+ + +	+	+ + + +	No, + +
DISC1	1q42	+ + +	+ +	+ +	Not known
G72	13q32–34	+ + +	+ +	+ +	Not known
DAAO	12q24	+ +	+	+ + + +	Not known
PPP3CC	8p21	+	+ + + +	+ + + +	Yes, +
CHRNA7	15q13–14	+	+ +	+ + +	Yes, + + +
PRODH2	22q11	+	+ + + +	+ +	No, +
Akt1	14q22–32	+	+	+ +	Yes, + +

Th
[a]G
[b]B
in
[c]B
[d]B
[e]A

at least three positive

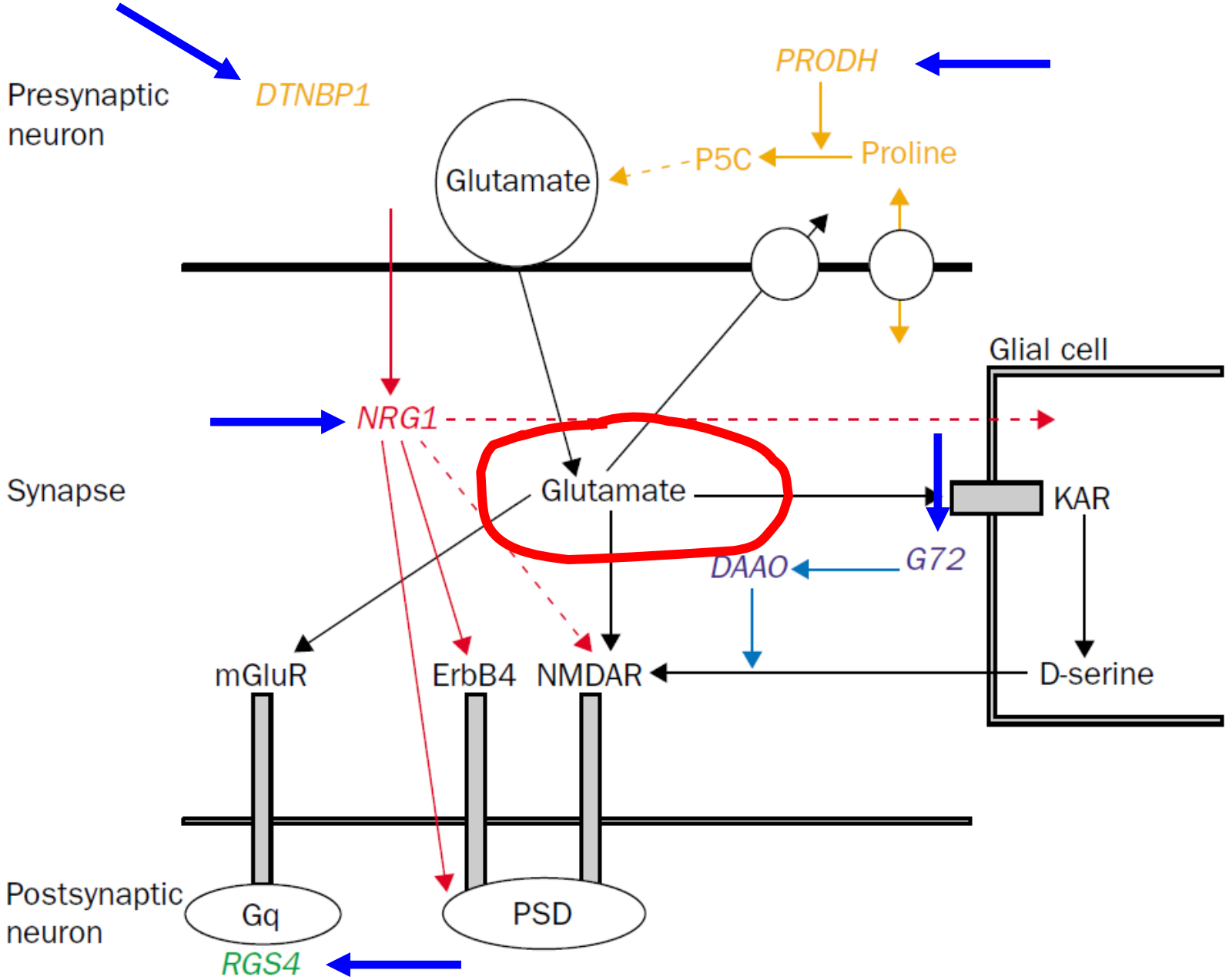
Review TRENDS in Genetics Vol.21 No.9 September 2005

ELSEVIER

Schizophrenia: genes at last?

M.J. Owen, N. Craddock and M.C. O'Donovan

Harrison y Weinberger, Mol Psychiatry 2005



Harrison & Owen Lancet 2003; 361: 417–19

RESULTS

Association of schizophrenia with *DTNBP1* but not with *DAO*, *DAOA*, *NRG1* and *RGS4* nor their genetic interaction

Elisabet Vilella [a,*], Javier Costas [b,h], Julio Sanjuan [c], Míriam Guitart [d], Yolanda De Diego [e], Angel Carracedo [b,h], Lourdes Martorell [a], Joaquín Valero [a], Antonio Labad [a], Rosa De Frutos [f], Carmen Nájera [f], M. Dolores Moltó [f], Ivette Toirac [f], Roser Guillamat [d], Anna Brunet [d], Vicenç Vallès [g], Lucía Pérez [e], Melquíades Leon [e], Fernando Rodríguez de Fonseca [e], Christopher Phillips [h], María Torres [h]

In Spanish sample of 800 patients 800 controls

Only significant Association with DTNB1

We were unable to detect any significant gene-gene interaction

between SNPs DAO, DAOA, DTNBP1, NRG1, RGS4.

Vilella et al J Psychiatry Research January 2008

Schizophrenia Candidate Genes: Are We Really Coming Up Blank?

1.900 patients y 2000 controls, 789 SNPs

RGS4, DISC1, DTNBP1, STX7, TAAR6, PPP3CC, NRG1, DRD2, HTR2A, DAOA, AKT1, CHRNA7, COMT, and *ARVCF*.

NO SIGNIFICANT ASSOCIATION

Hamilton SP Am J Psychiatry April 2008

THE OPTIMISTIC VIEW

SureGene, LLC
Utilizes modern genetic technology
to discover the underlying genetic basis for psychiatric diseases.

Our primary goal is to empower patients and physicians with knowledge to make the best possible healthcare decisions based on individual genetic profiles. SureGene, LLC will accomplish these goals through DNA-based diagnostic tests that predict drug response and aid in the diagnosis and classification of disease, such as the AssureGeneTM Test for Schizophrenia

SENTENCIA PROVISIONAL

HAS NGUN

2007 WGS en PSICOSIS

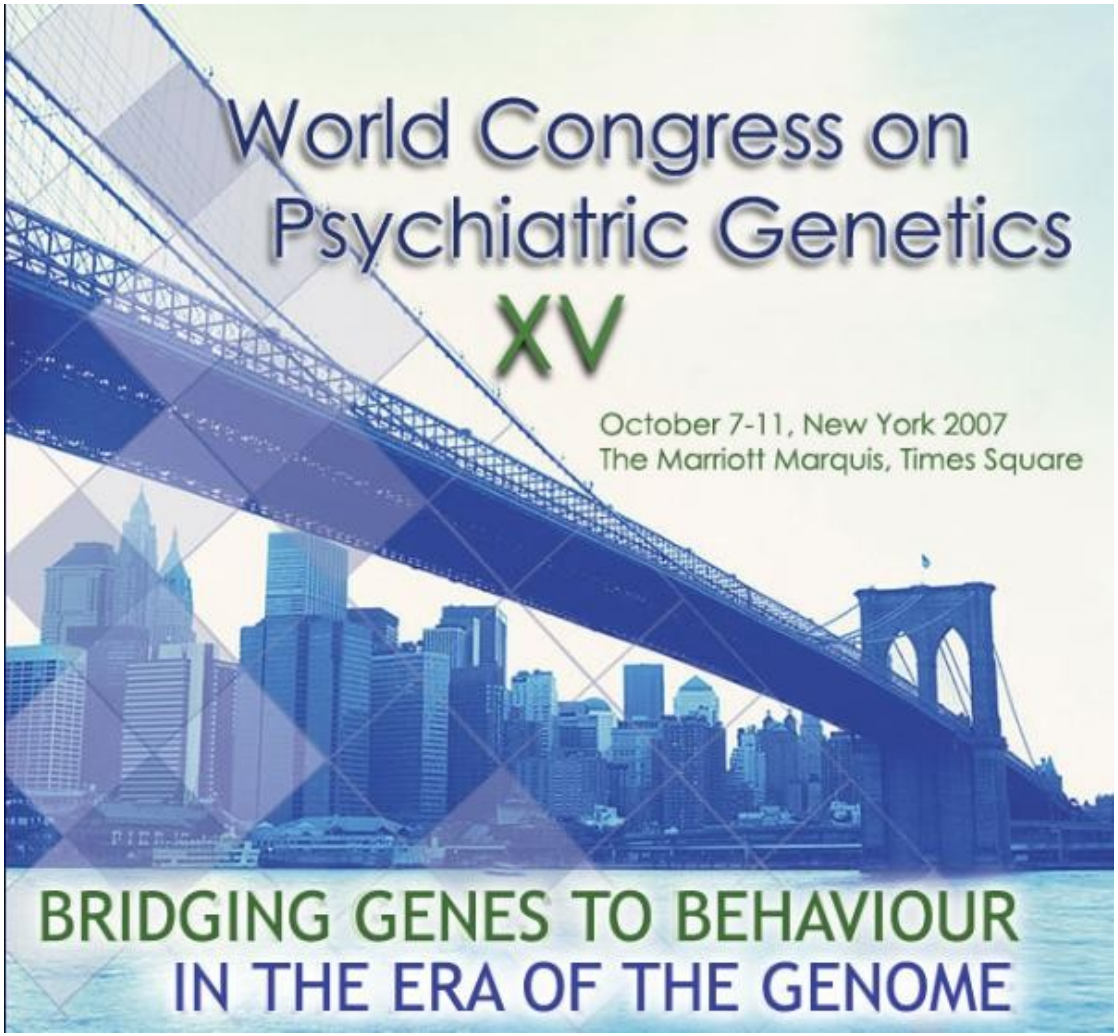
International Schizophrenia Consortium

3.800 casos

4.200 controles

1.000.000 SNPs

Resultados preliminares:



Se ha encontrado alguna asociación con P = 10^{-8}

pero NO en los genes candidatos reconocidos enestudios previos

Common variants conferring risk of schizophrenia

Hreinn Stefansson[1]*, Roel A. Ophoff[2,3]*, Stacy Steinberg[1]*, Ole A. Andreassen[4], Sven Cichon[5], Dan Rujescu[6], Thomas Werge[7], Olli P. H. Pietiläinen[8,9], Ole Mors[10], Preben B. Mortensen[11], Engilbert Sigurdsson[12,13], Omar Gustafsson[1], Mette Nyegaard[14], Annamari Tuulio-Henriksson[15], Andres Ingason[1], Thomas Hansen[7], Jaana Suvisaari[15], Jouko Lonnqvist[15], Tiina Paunio[16], Anders D. Børglum[10,14], Annette Hartmann[6], Anders Fink-Jensen[17], Merete Nordentoft[18], David Hougaard[19], Bent Norgaard-Pedersen[19], Yvonne Böttcher[1], Jes Olesen[20], René Breuer[21], Hans-Jürgen Möller[22], Ina Giegling[6], Henrik B. Rasmussen[7], Sally Timm[23], Manuel Mattheisen[5], István Bitter[24], János M. Réthelyi[24], Brynja B. Magnusdottir[12,13], Thordur Sigmundsson[12,13], Pall Olason[1], Gisli, Masson[1], Jeffrey R. Gulcher[1], Magnus Haraldsson[12,13], Ragnheidur Fossdal[1], Thorgeir E. Thorgeirsson[1], Unnur Thorsteinsdottir[1,13], Mirella Ruggeri[25], Sarah Tosato[25], Barbara Franke[26], Eric Strengman[2], Lambertus A. Kiemeney[27], GROUP†, Ingrid Melle[4], Srdjan Djurovic[28], Lilia Abramova[29], Vasily Kaleda[29], Julio Sanjuan[30], Rosa de Frutos[31], Elvira Bramon[32], Evangelos Vassos[32,33], Gillian Fraser[34], Ulrich Ettinger[32,33], Marco Picchioni[32], Nicholas Walker[35], Timi Toulopoulou[33], Anna C. Need[36], Dongliang Ge[36], Joeng Lim Yoon[37], Kevin V. Shianna[36], Nelson B. Freimer[3], Rita M. Cantor[3,37], Robin Murray[32,33], Augustine Kong[1], Vera Golimbet[29], Angel Carracedo[38], Celso Arango[39], Javier Costas[40], Erik G. Jönsson[41], Lars Terenius[41], Ingrid Agartz[41], Hannes Petursson[12,13], Markus M. Nöthen[42], Marcella Rietschel[21], Paul M. Matthews[43], Pierandrea Muglia[44], Leena Peltonen[8,9], David St Clair[34], David B. Goldstein[36], Kari Stefansson[1,13] & David A. Collier[32,45]

Stefansson et al Nature Vol 460|6 2009

Table 1 | Genome-wide significant association of seven markers with schizophrenia

Chromosome/ megabases	SNP[allele]	Frequency	SGENE-plus* (2,663 cases; 13,498 controls)		Follow-up (4,999 cases; 15,555 controls)		SGENE-plus + follow-up (7,662 cases; 29,053 controls)		SGENE-plus + follow-up + ISC + MGS (12,945 cases; 34,591 controls)		Region/ neighbouring gene
			OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	
6/27.2	rs6913660[C]†☆	0.85	1.22 (1.10, 1.36)	0.00023	1.11 (1.04, 1.19)	0.0021	1.14 (1.08, 1.21)	4.7×10^{-6}	1.15 (1.10, 1.21)	1.1×10^{-9}	MHC/ *HIST1H2BJ*
6/27.3	rs13219354[T]‡☆	0.90	1.25 (1.11, 1.42)	0.00043	1.19 (1.08, 1.30)	0.00022	1.21 (1.12, 1.30)	4.4×10^{-7}	1.20 (1.14, 1.27)	1.3×10^{-10}	MHC/ *PRSS16*
6/27.4	rs6932590[T]§☆	0.78	1.15 (1.05, 1.26)	0.0024	1.17 (1.10, 1.25)	4.9×10^{-7}	1.17 (1.11, 1.23)	4.4×10^{-9}	1.16 (1.11, 1.21)	1.4×10^{-12}	MHC/ *PRSS16*
6/28.4	rs13211507[T]‖☆	0.92	1.24 (1.08, 1.42)	0.0027	1.27 (1.15, 1.40)	3.1×10^{-6}	1.26 (1.16, 1.36)	3.1×10^{-8}	1.24 (1.16, 1.32)	8.3×10^{-11}	MHC/ *PGBD1*
6/32.3	rs3131296[G]¶☆	0.87	1.21 (1.08, 1.36)	0.0011	1.20 (1.11, 1.30)	5.3×10^{-6}	1.21 (1.13, 1.29)	2.1×10^{-8}	1.19 (1.13, 1.25)	2.3×10^{-10}	MHC/ *NOTCH4*
11/124.1	rs12807809[T]	0.83	1.19 (1.08, 1.32)	0.00045	1.13 (1.06, 1.21)	0.00022	1.15 (1.09, 1.22)	5.0×10^{-7}	1.15 (1.10, 1.20)	2.4×10^{-9}	*NRGN*
18/51.3	rs9960767[C]#☆	0.056	1.30 (1.11, 1.51)	0.0011	1.20 (1.08, 1.33)	0.00044	1.23 (1.13, 1.34)	2.2×10^{-6}	1.23 (1.15, 1.32)	4.1×10^{-9}	*TCF4*

Allelic OR and *P* values (two-sided) based on the multiplicative model are shown. Frequency in the superset allelic control frequency in SGENE-plus. Members in from the National Centre for

Histocompatibility complex (MHC) 6p21.322.1

Neurogranin gene (NRGN) on 11q24.2

New candidate genes are not related with previous candidates

Stefensson et al Nature August 2009

Table 2 | Significant association of deletions at 1q21.1, 15q11.2 and 15q13.3 with schizophrenia and related psychoses in the combined samples

Locus	Chromosome 1: 144.94–146.29 (Mb)		Chromosome 15: 20.31–20.78 (Mb)		Chromosome 15: 28.72–30.30 (Mb)	
	Cases	Controls	Cases	Controls	Cases	Controls
Germany	2 of 911	0 of 1,297	3 of 911	4 of 1,297	0 of 911	0 of 1,297
Scotland	2 of 451	0 of 441	5 of 451	1 of 441	0 of 451	0 of 441
The Netherlands	0 of 806	0 of 4,039	4 of 806	12 of 4,039	3 of 806	1 of 4,039
Norway	0 of 237	0 of 272	0 of 237	0 of 272	1 of 237	0 of 272
Denmark*	3 of 442	0 of 1,437	4 of 442	3 of 1,432	0 of 375	0 of 501
China*	0 of 438	0 of 463	0 of 438	0 of 463	NA	NA
Phase II						
OR		∞ (2.85, ∞)		2.18 (1.01, 4.60)		16.47 (1.52, 833.38)
P-value		5.6×10^{-4}		0.032		7.9×10^{-3}
Phase I and II						
OR		14.83 (3.55, 60.40)		2.73 (1.50, 4.89)		11.54 (2.53, 49.58)
P-value		2.9×10^{-5}		6.0×10^{-4}		5.3×10^{-4}

MICRODELETIÓN	**OR**	FREQUENCY
1Q21.1 (N = 7)	14. 80	0.15
15Q11.2 (N = 16)	2.73	0.35
15Q.13.3 (N = 4)	11.54	0.08

Nature vol 455, september 2008

CONCLUSIONES (PROVISIONALES) ESTUDIOS DE GENOMA AMPLIO

-Descubrimiento de formas genéticas de esquizofrenia pero muy poco frecuentes. Apaprecen tambien en otros Trastornos Psiquiatricos

-Descubrimiento de nuevos Polimorfismos con un alta asociación pero con una OR muy baja. Tambien aparecen en otros Tyrastornos Psiquiatricos.

-Necesidad de modelos matematicos que permitan analizar combinaciones de mas de 1.000.000 de SNPs

1. **EXPRESIÓN GENICA EN ESTUDIO POSTMORTEM EN LA ESQUIZOFRENIA**

    A. EXPRESIÓN DE GENES ESPECIFICOS

    B. MICRORRAYS: TRANSCRIPTOMICA

ABNORMAL GENE EXPRESSION

THE REELIN PATHWAY TO SCHIZOPHRENIA

Reelin promoter hypermethylation in schizophrenia

Dennis R. Grayson*, Xiaomei Jia, Ying Chen, Rajiv P. Sharma, Colin P. Mitchell, Alessandro Guidotti, and Erminio Costa

Cellular Basis of Reduced Cortical Reelin Expression in Schizophrenia

Sharon L. Eastwood, D.Phil.
Paul J. Harrison, D.M. (Oxon), F.R.C.Psych.

Results: Reelin mRNA was expressed by layer I neurons, i
neurons, and interstitial white matter neurons. In subjects
schizophrenia, less reelin mRNA was expressed by inters

Associate editor: B.L. Roth

The human reelin gene: Transcription factors (+), repressors (−) and the methylation switch (+/−) in schizophrenia

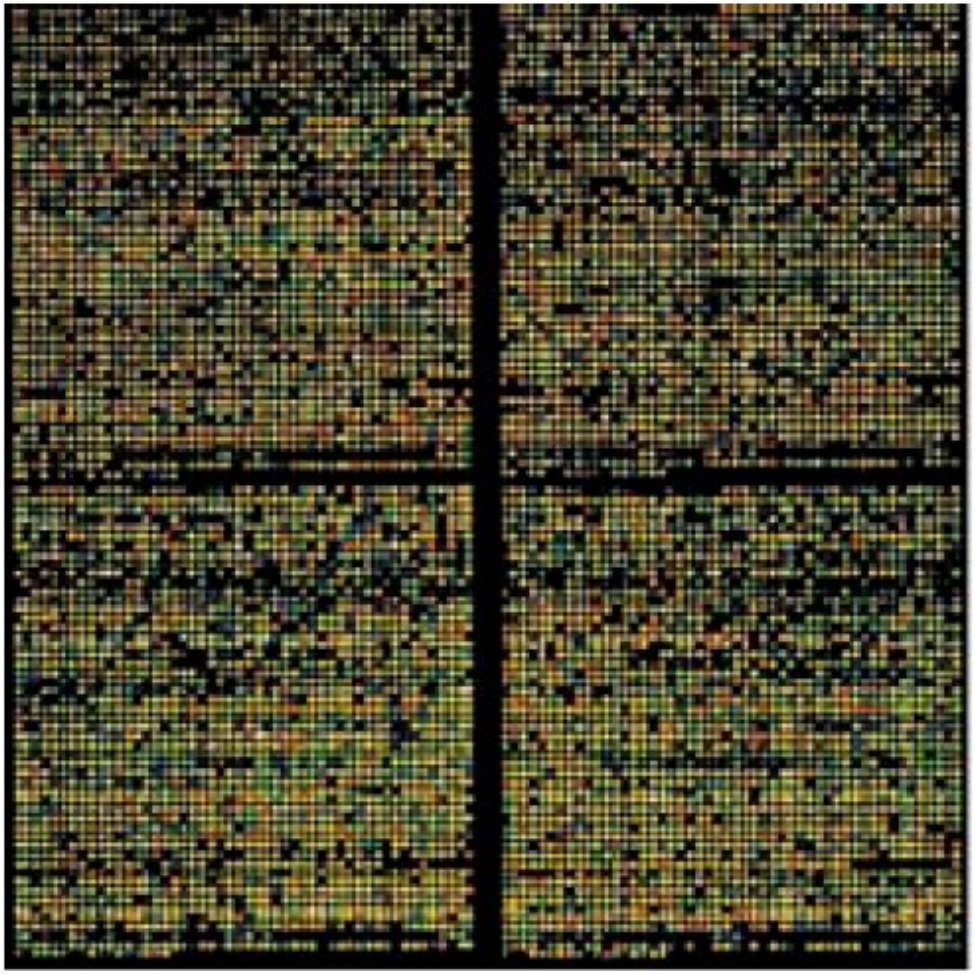
Dennis R. Grayson *, Ying Chen, Erminio Costa, Erbo Dong, Alessandro Guidotti, Marija Kundakovic, Rajiv P. Sharma

chiatric Institute, Department of Psychiatry, College of Medicine, University of Illinois at Chicago, 1601 W. Taylor St., Chicago, IL 60612, United State

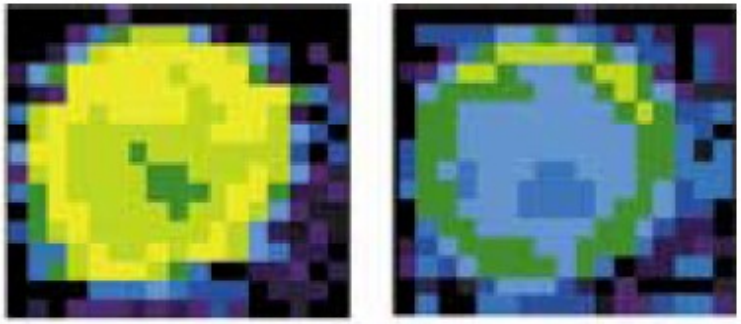
B. MICRORRAYS: TRANSCRIPTOMICA

The Human Genome

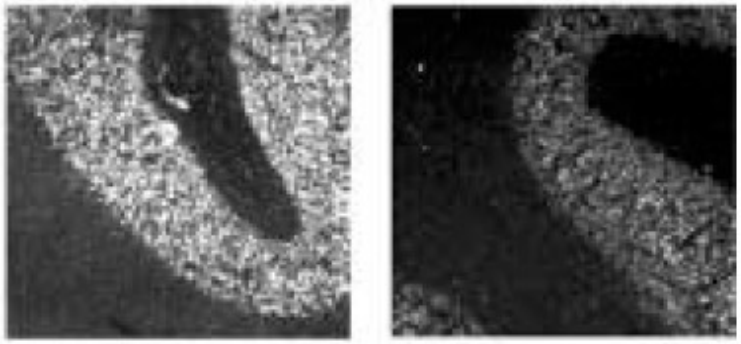
UniGEM-V Microarray



NSF Microarray



NSF in Situ Hybridization



Mirmics Am J Psychiatry 2001

B. MICRORRAYS: TRANSCRIPTOMICA

RESULTADOS PRINCIPALES (18 estudios revisados 2001-2011)

ALTERACIÓN EN LA EXPRESIÓN DE GENES IMPLICADOS EN:

- **MECANISMOS SINAPTICOS**
- **PROCESOS DE MIELINIZACIÓN**
- **METABOLISMO MITOCONDRIAL**
- **OLIGODENDROCITOS**
- **SISTEMA GABAERGCIO**
- **SISTEMA GLUTAMATERGICO**

EXPRESIÓN GENICA CEREBRAL
FACTORES DE CONFUSIÓN

-EDAD

-SEXO

-PH

-INTERVALO POSTMORTEM

-CALIDAD TEJIDO

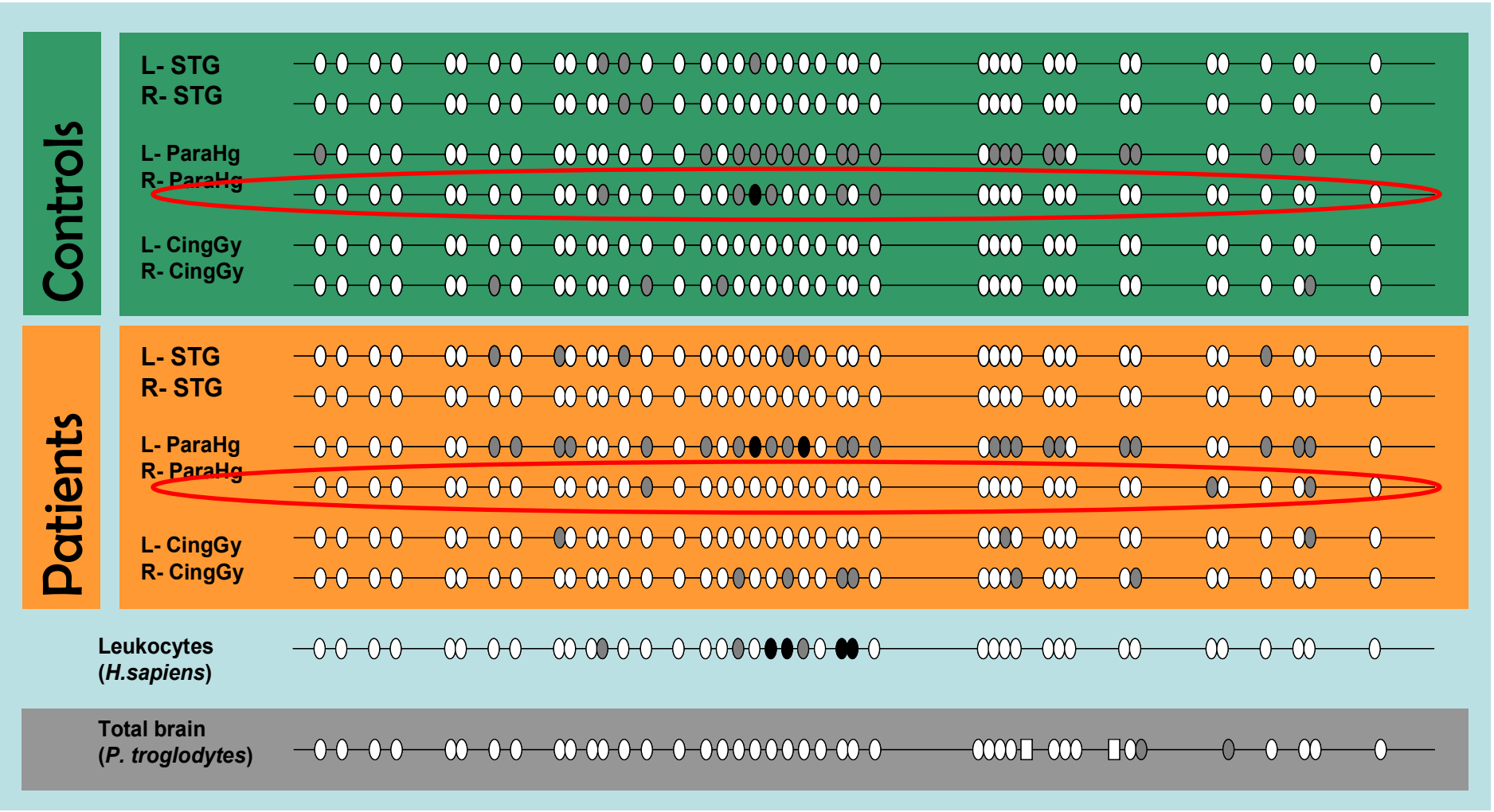
-MEDICACIÓN PREVIA

-ENFERMEDADES MEDICAS-CEREBRALES ASOCIADAS

-FORMA DE MUERTE

-PSICOPATOLOGÍA PREVIA

EPIGENETIC CHANGES OF FOXP2 IN SCHIZOPHRENIA

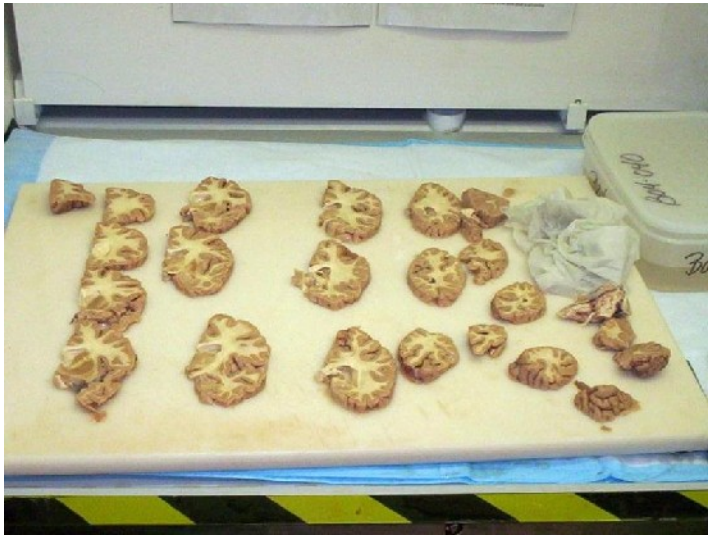


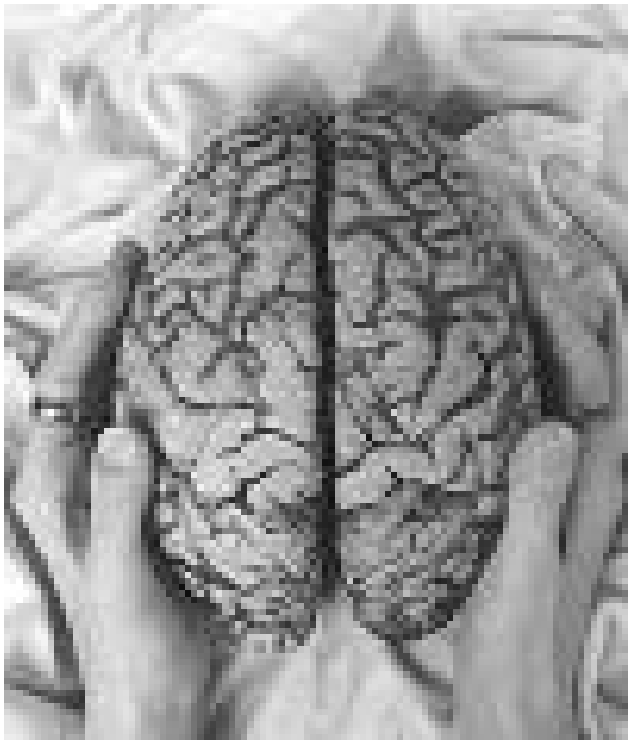
Tolosa et al Schizophrenia Research 2010

1. BRAIN BANK FROM SAN JOAN DE DEU

NOW 32 BRAINS OF PATIENTS WITH SCHIZOPHRENIA

SANT JOAN DE DÉU
SERVEIS DE SALUT MENTAL





CONCLUSIONES (PROVISIONALES) ESTUDIOS DE EXPRESIÓN GENICA

-Hallazgos prometedores en anormal expresión de algunos genes (Reelina)

-Hallazgos sugestivos pero no concluyentes con las tecnicas de micro-rrays

-Necesidad de nuevos bancos de cerebros con control de las variables de confusión.

MENU

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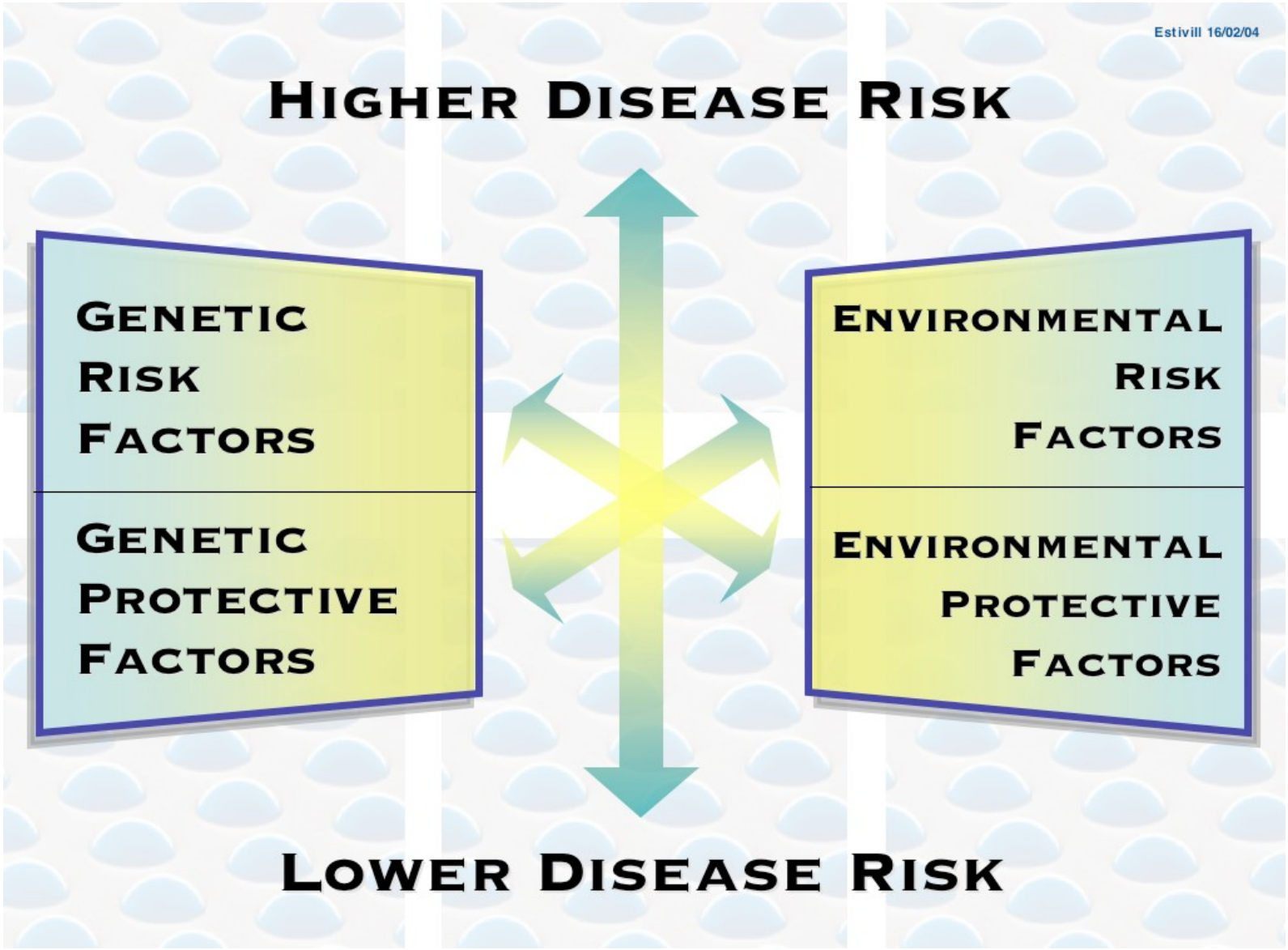
4-Implicaciones Practica Clinica

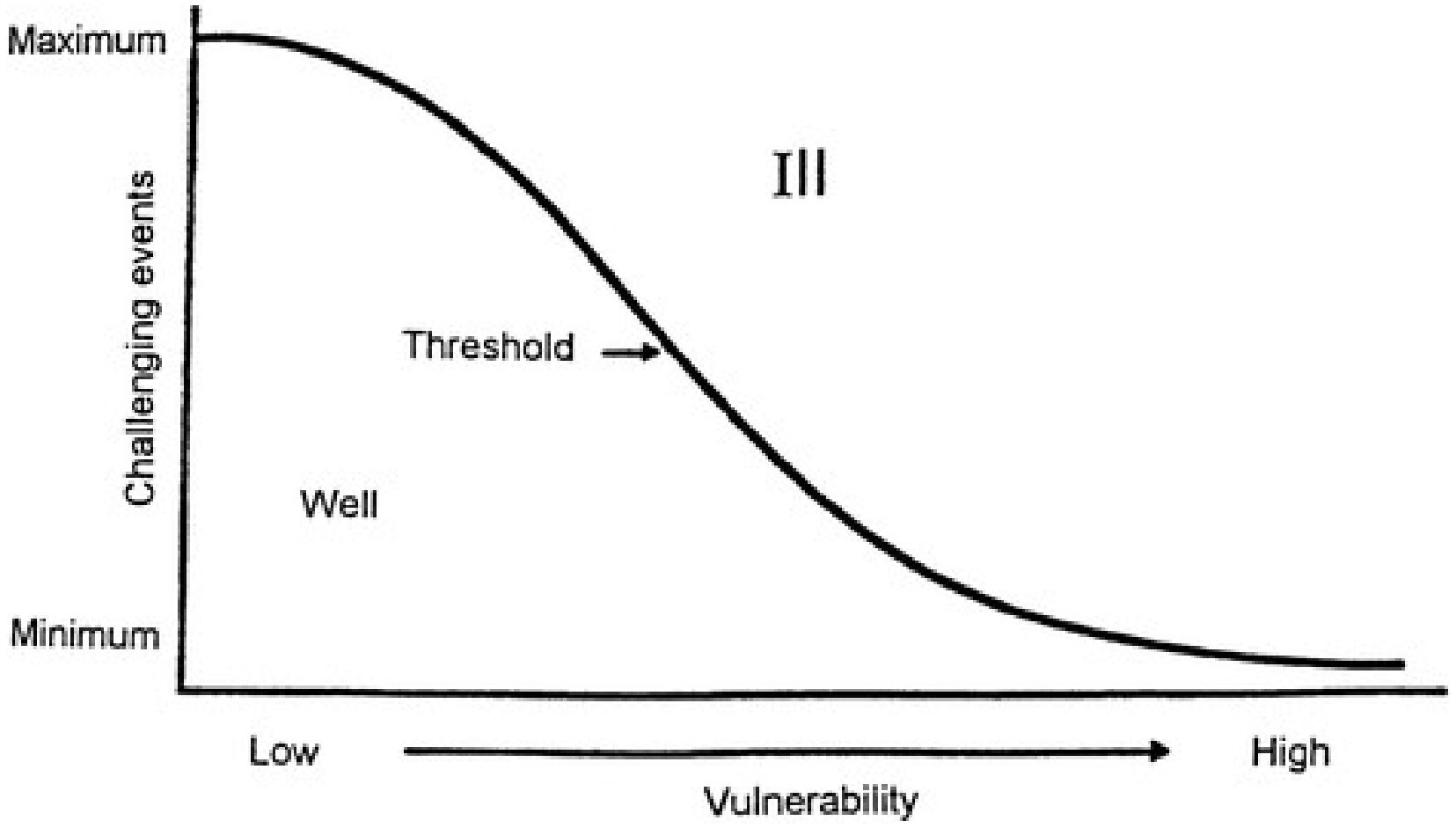
MEDICAL MODEL OF COMPLEX DISEASE



EXAMPLES OF GENE-ENVIROMENTAL INTERACTION IN COMPLEX MEDICAL DISSEASE

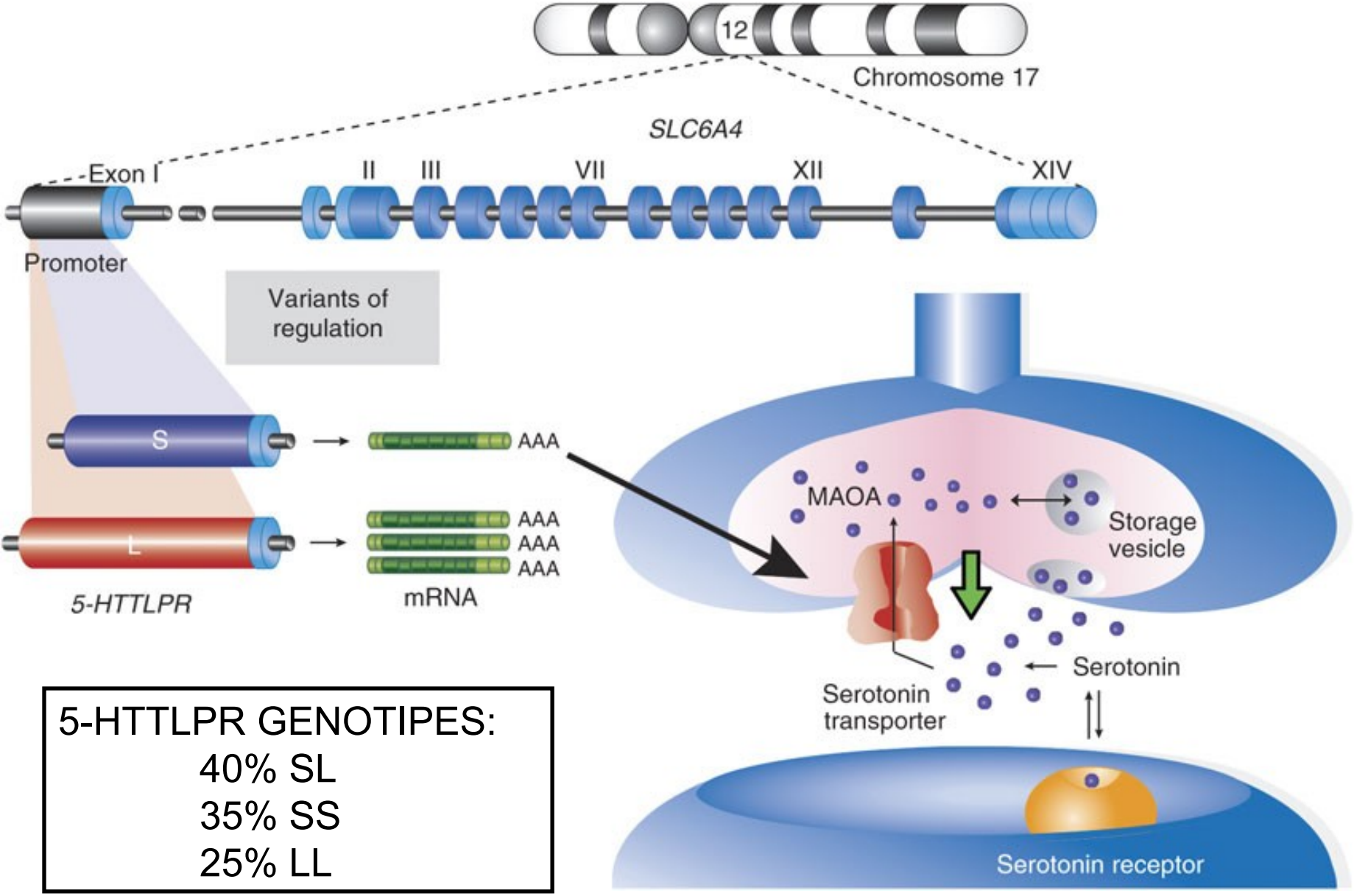
Gene symbol	Variant(s)	Environmental exposure	Outcome and nature of interaction	
Genes for skin pigmentation (for example, *MC1R*)	Variants for fair skin colour	Sunlight or ultraviolet light B	Risk of skin cancer is higher in people with fair skin colour that are exposed to higher amounts of sunlight	SKIN CANCER
CCR5	Δ-32 deletion	HIV	Carriers of the receptor deletion have lower rates of HIV infection and disease progression	HIV
MTHFR	Ala222Val polymorphism	Folic acid intake	Homozygotes for the low activity Ala222Val variant are at different risk of colorectal cancer and adenomas if nutritional folate status is low	COLORECTAL CANCER
NAT2	Rapid versus slow acetylator SNPs	Heterocyclic amines in cooked meat	Red meat intake is more strongly associated with colorectal cancer among rapid acetylators	COLORECTAL CANCER
F5	Leiden prothrombotic variant	Hormone replacement	Venous thromboembolism risk is increased in factor V Leiden carriers who take exogenous steroid hormones	VASCULAR
UGT1A6	Slow-metabolism SNPs	Aspirin	Increased benefit of prophylactic aspirin use in carriers of the slow metabolism variants	ASPIRINE BENFIT
APOE	*E4* allele	Cholesterol intake	Exaggerated changes in serum cholesterol in response to dietary cholesterol changes in *APOE4* carriers	COLESTEROL
ADH1C	γ-2 alleles	Alcohol intake	Inverse association between ethanol intake and myocardial infarction; risk is stronger in carriers of slow-oxidizing γ-2 alleles	MYOCARDIAL
PPARG2	Pro12Ala	Dietary fat intake	Stronger relation between dietary fat intake and obesity in carriers of the Pro12Ala allele	OBESITY
HLA-DPB1	Glu69	Occupational beryllium	Exposed workers who are carriers of the Glu69 allele are more likely to develop chronic beryllium lung disease	LUNG DISEASE
TPMT	Ala154Thr and Tyr240Cys	Thiopurine drugs	Homozygotes for the low-activity alleles of *TPMT* are likely to experience severe toxicity when exposed to thiopurine drugs	THIOPURINE
ADRB2	Arg16Gly	Asthma drugs	Arg16Gly homozygotes have a greater response in the airway to albuterol	ASTMA DRUG

VULNERABILITY STRESS MODEL



1997

5-HTTLPR AND EMOTIONAL RESPONSE



5-HTTLPR GENOTIPES:

40% SL

35% SS

25% LL

5-HTTLPR: Association Studies Before 2003

The Same Gene –variant relate with many Psychiatric Disorder

Anxiety and hostility	*Brummett BH 2003*
Anxiety disorders	*Ohara K et al. 1998*
Anxiety symptoms	*Evans J et al. 1997*
Anxiety traits	*Murakami F et al. 1999*
Anxiety-related temperament	*Jorm AF et al. 2000*
Anxiety-related traits	*Katsuragi S et al. 1999*
Anxiety-related traits	*Lesch KP et al. 1996*
Autism	*Klauck SM et al. 1997*
Alcoholism	*Ishiguro H et al. 1999*
Anorexia nervosa	*Fumeron F et al. 2001*
Personality traits	*Kumakiri C et al. 1999*
Personality traits	*Du L et al. 2000*
Personality traits	*Retz W et al. 2002*
Affective disorder	*Lenzinger E et al. 1999*
Major depression	*Ogilvie AD et al. 1996*
Major depression	*Yu YW et al. 2002*
Depression	*Neumeister A et al. 2002*
Bipolar affective disorder	*Heiden A 2000*
Bipolar and unipolar disorder	*Serretti A et al. 2001*
Bipolar disorder	*Mynett-Johnson L 2000*
Bipolar disorder	*Liu W et al. 1998*
Major and bipolar depressives	*Serretti A et al. 2001*
Schizophrenia	*Malhotra AK et al. 1998*
Smoking	*Ishikawa H et al. 1999*
Suicide	*Joiner TE Jr et al. 2002*
Suicide	*Baca-Garcia E et al. 2002*
Violent suicidal behavior	*Courtet P et al. 2001*
Violent suicide	*Bondy B et al. 2000*
Pathological gambling	*Perez de Castro I et al., 1999*
Harm avoidance behaviour	*Ricketts MH et al. 1998*

NO CONCLUSIVE RESULTS

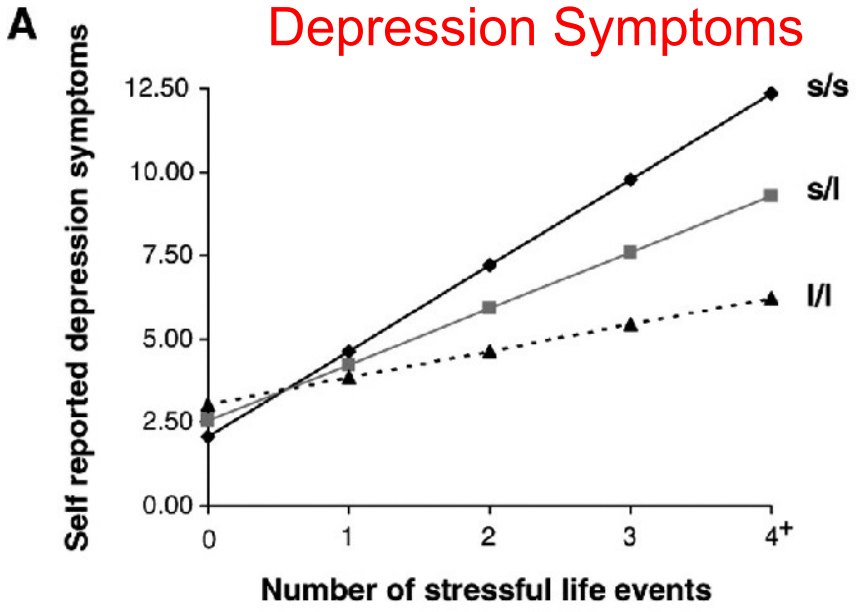
A. Caspi

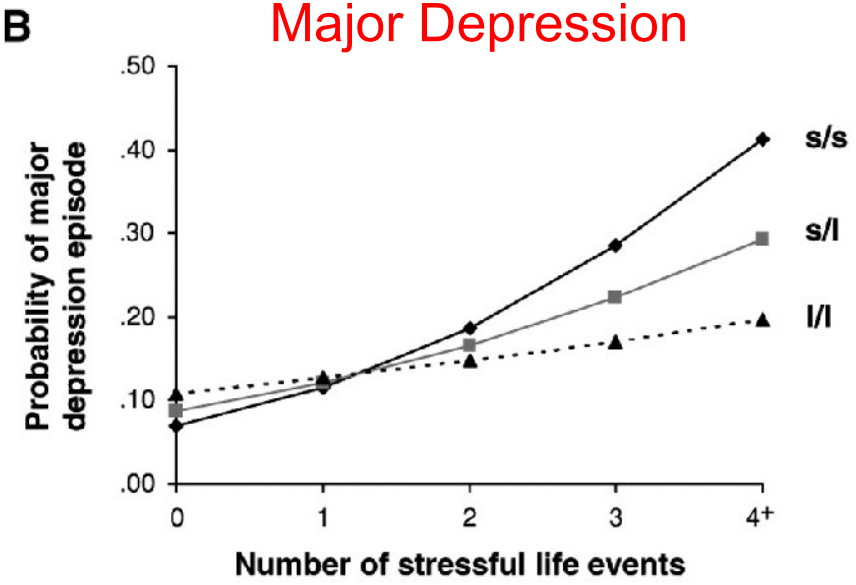
Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

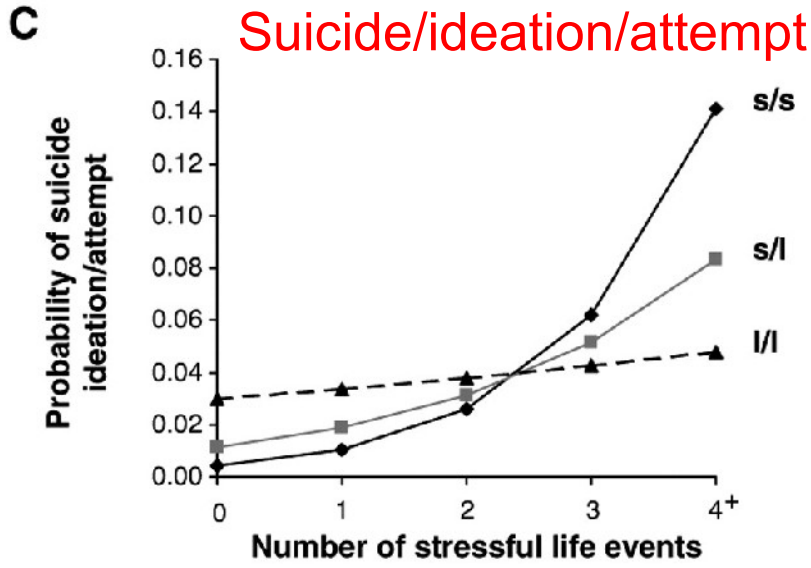
Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2*]
Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2]
Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3]
Antony Braithwaite,[4] Richie Poulton[3]

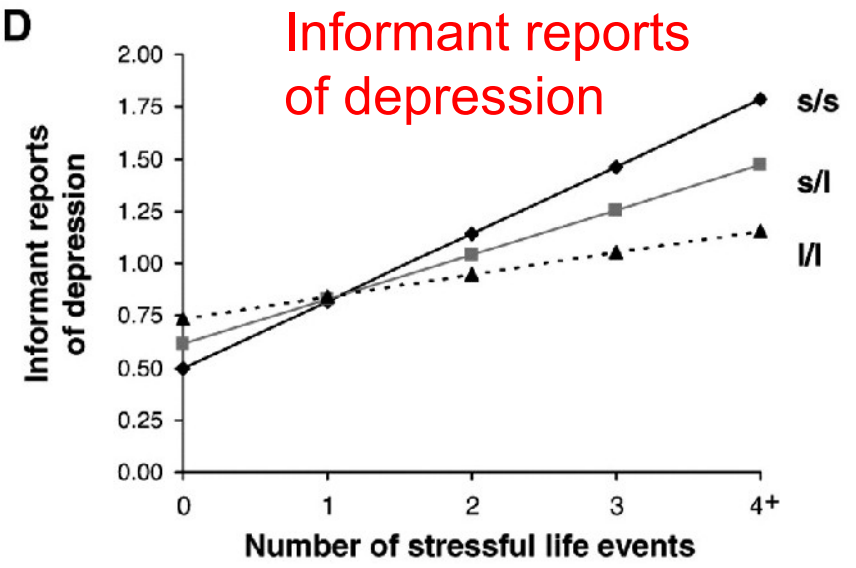
18 JULY 2003 VOL 301 SCIENCE www.sciencemag.org

Number of citations = 2.673 < 9 years)



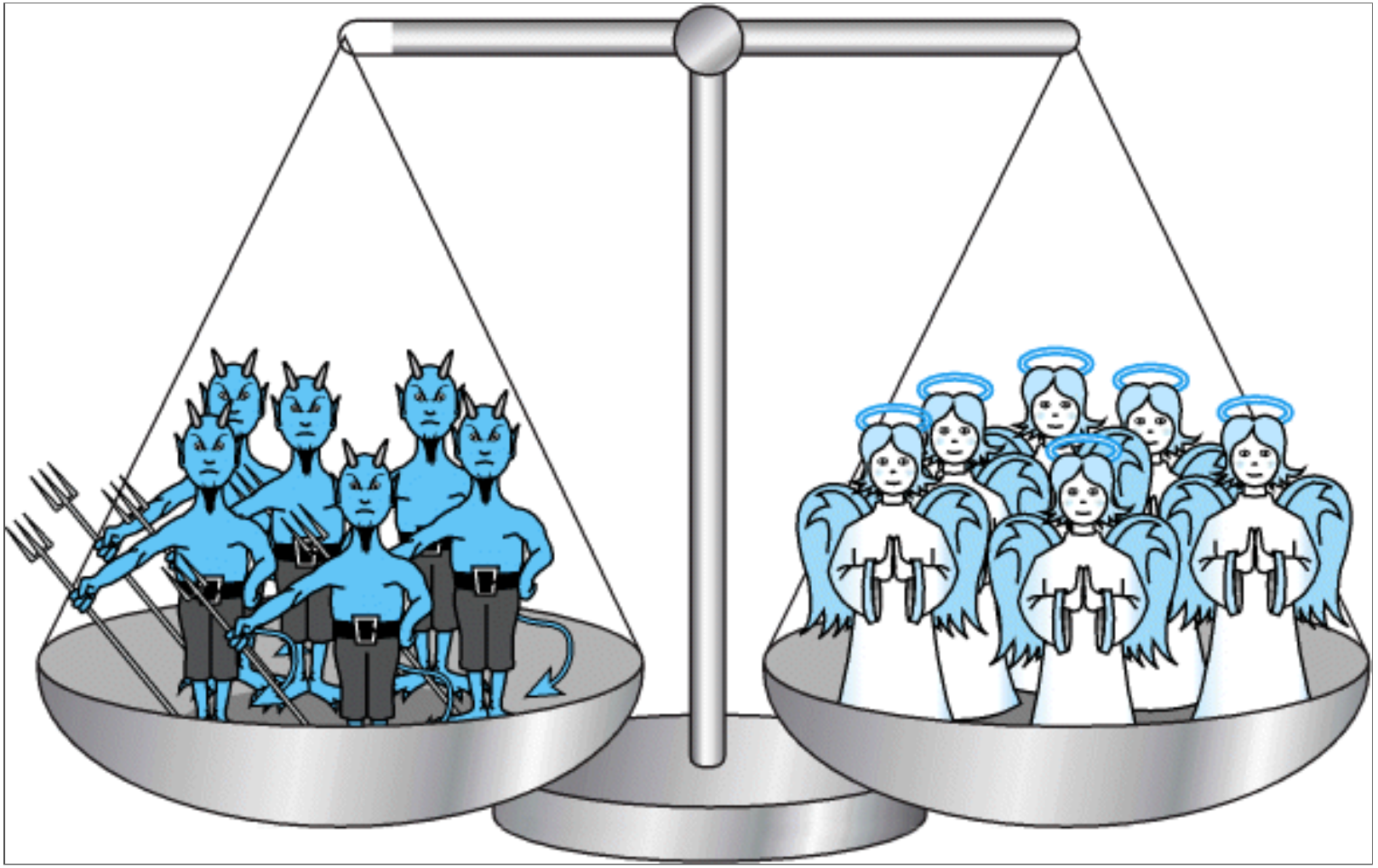






Caspi et al Science, vol 301; 0 2003

Is the "Short" variant always a bad/risk factor?

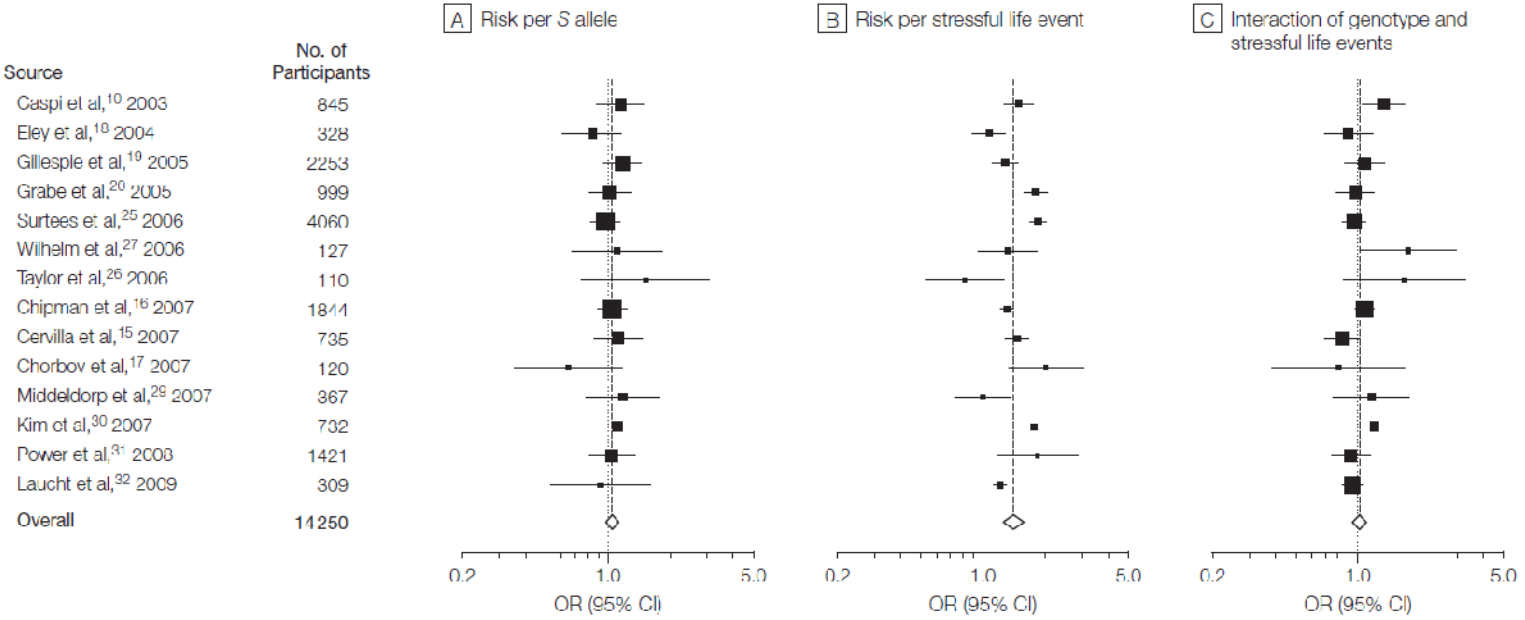


SS= BAD BOY

LL = GOOD BOY

2009

Figure 2. Logistic Regression Analyses of Risk of Depression for 14 Studies



..no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with an elevated risk of depression

Risch et al JAMA 2009; 301, 462-71

The positive results for the 5-HTTLPR SLE interactions in logistic regression models are compatible with chance findings.

Munafo et al Biological psychiatry 2009; 65: 211-19

¡¡¡ **INNOCENT !!!**

14 studies included

2010

META-ANALYSIS

ONLINE FIRST

The Serotonin Transporter Promoter Variant (5-HTTLPR), Stress, and Depression Meta-analysis Revisited

Evidence of Genetic Moderation

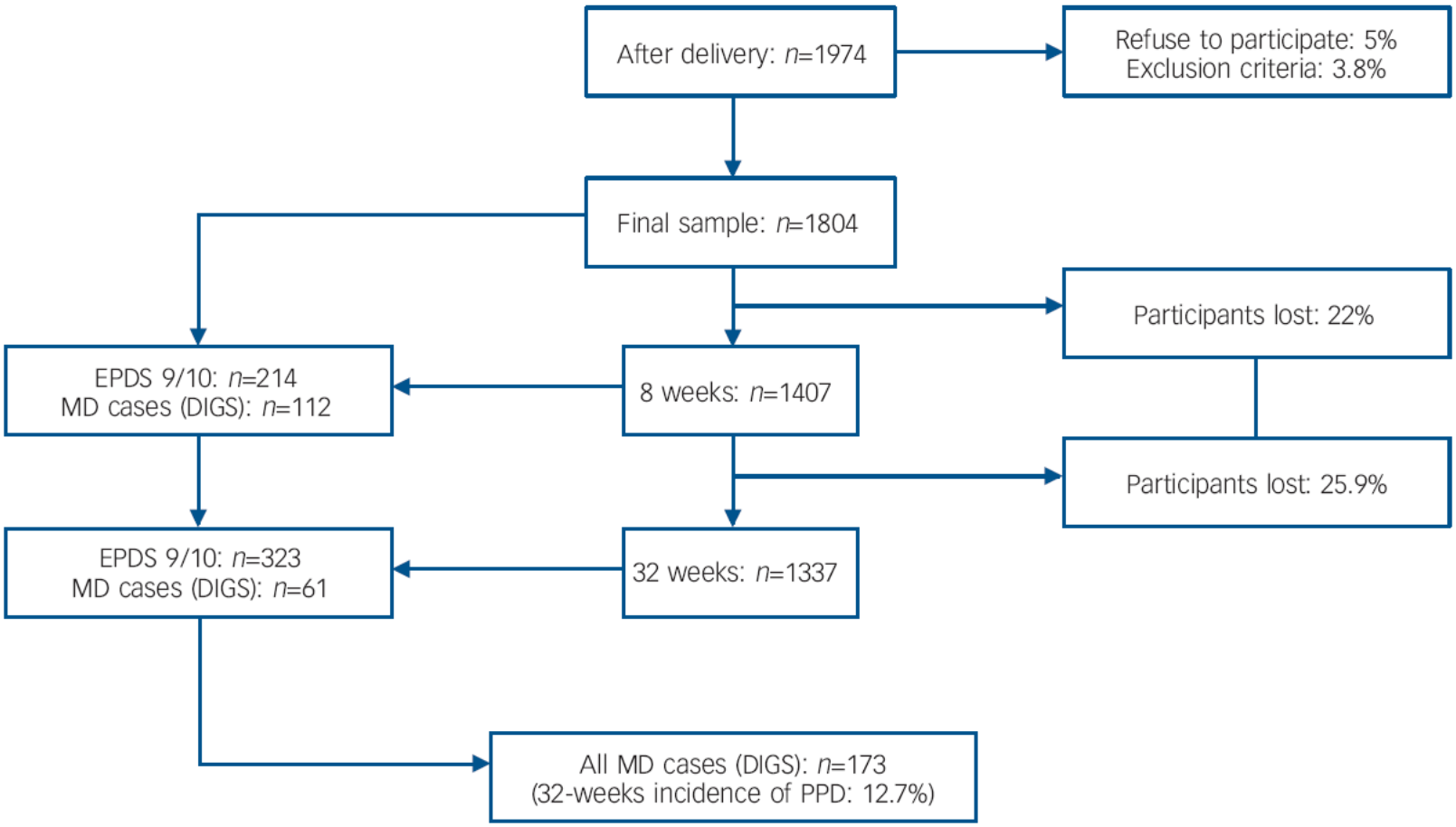
Katja Karg, BSc; Margit Burmeister, PhD; Kerby Shedden, PhD; Srijan Sen, MD, PhD

Conclusion: Contrary to the results of the smaller earlier meta-analyses, we find strong evidence that the studies published to date support the hypothesis that 5-HTTLPR moderates the relationship between stress and depression.

54 studies included

Kang Arch Gen Psychiatry 2010

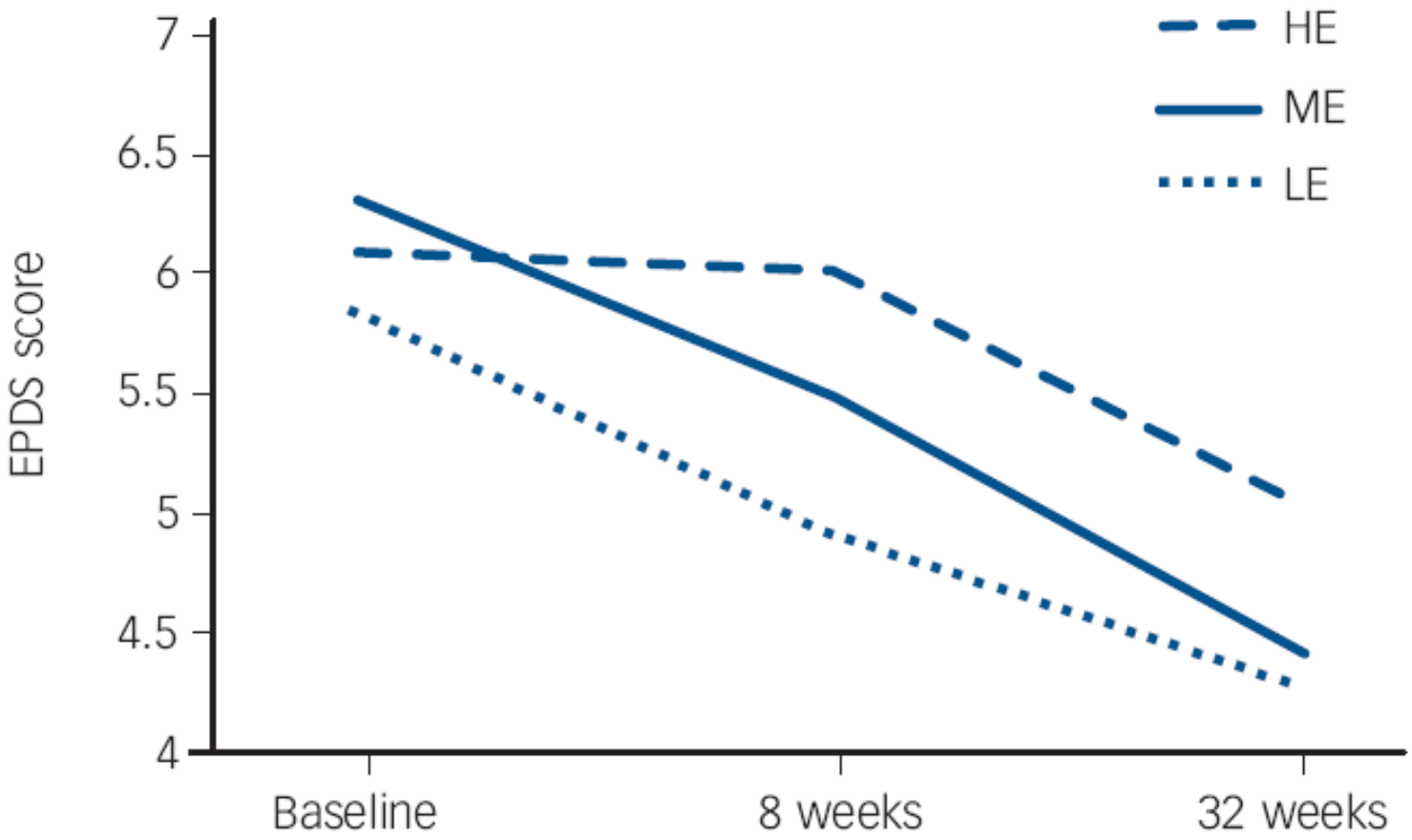
Postpartum Depression Multicentric Genetic Study



Sanjuan J et al Brit J Psychiatry Nov 2008

Mood changes after delivery: role of the serotonin transporter gene

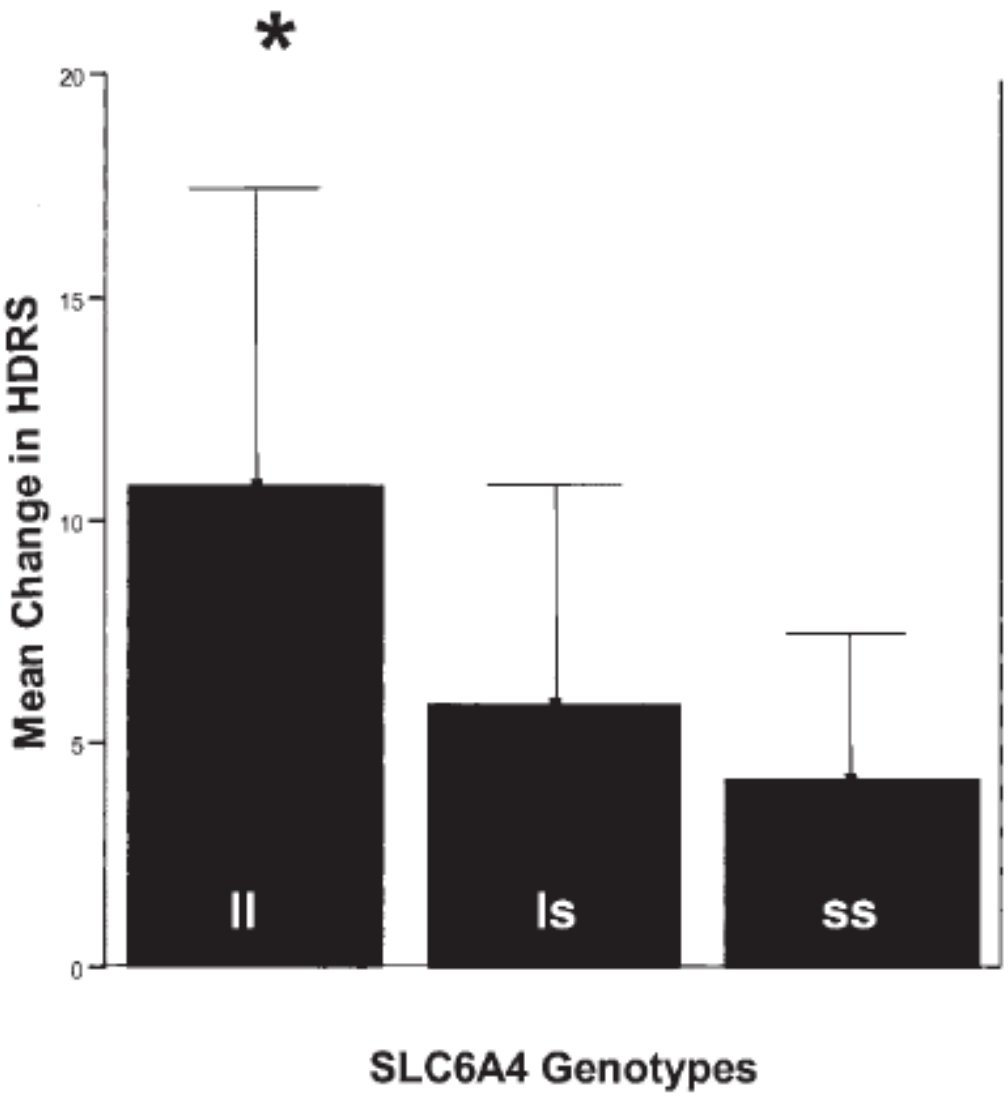
J. Sanjuan, R. Martin-Santos, L. Garcia-Esteve, J. M. Carot, R. Guillamat, A. Gutierrez-Zotes, I. Gornemann, F. Canellas, E. Baca-Garcia, M. Jover, R. Navines, V. Valles, E. Vilella, Y. de Diego, J. A. Castro, J. L. Ivorra, E. Gelabert, M. Guitart, A. Labad, F. Mayoral, M. Roca, M. Gratacos, J. Costas, J. van Os and R. de Frutos



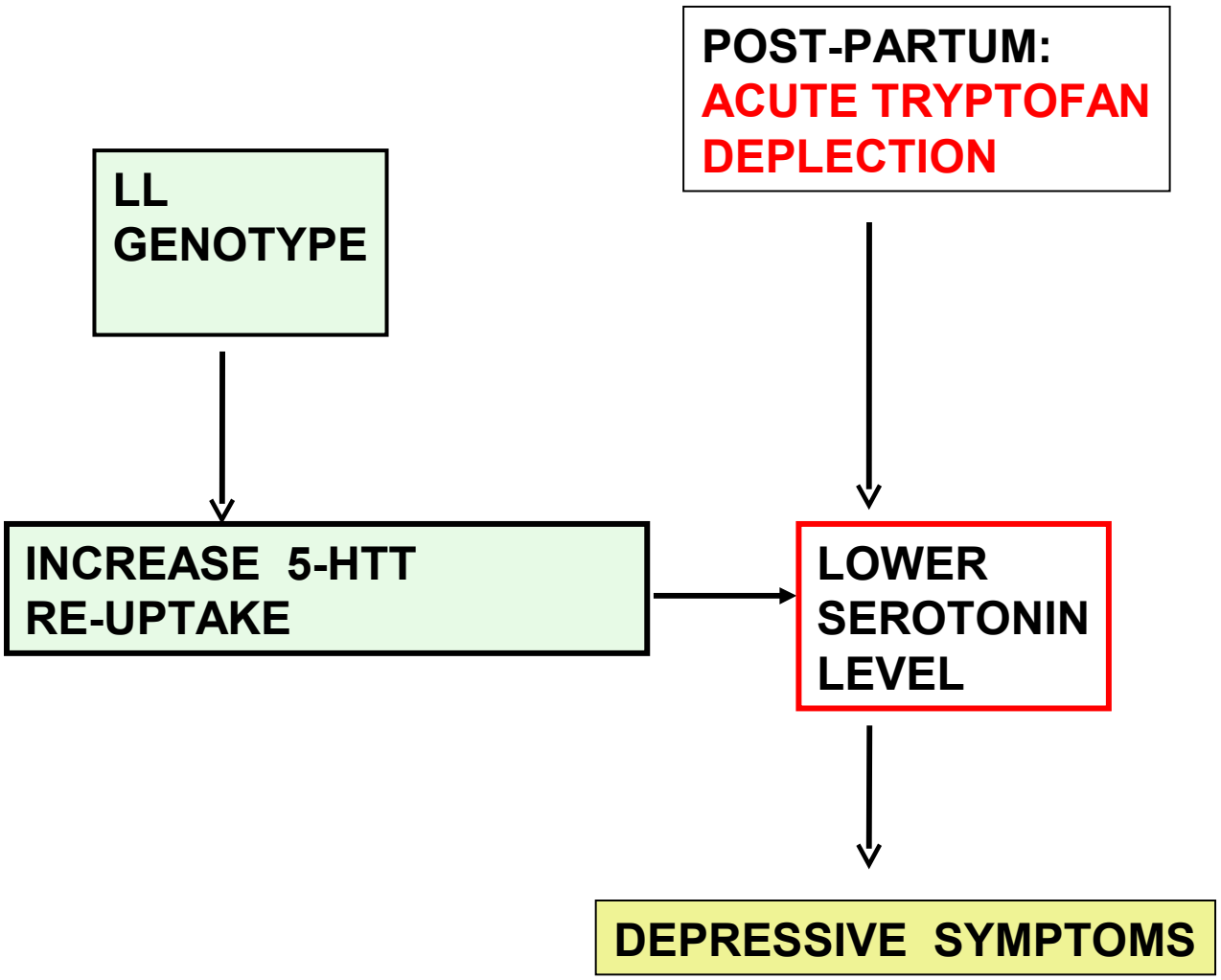
Sanjuan J et al Brit J Psychiatry Nov 2008

Associatic ... romoter region pol ... ng tryptophar ...

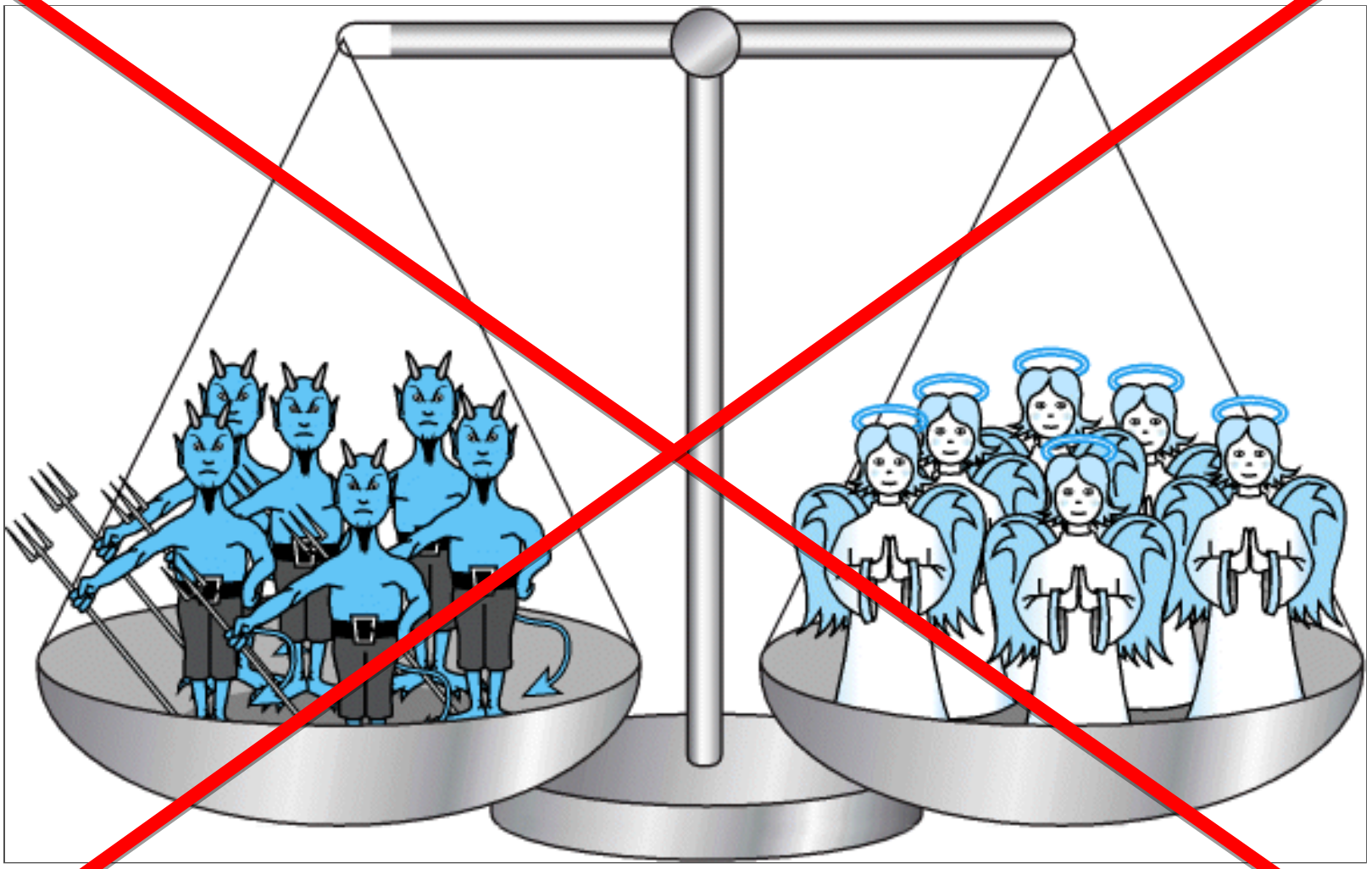
FA Moreno[1], DC ... elgado[4]



POSTPARTUM A DIFFERENT GENETIC WAY TO DEPRESSION?



Sanjuan J et al Brit J Psychiatry Nov 2008



SS= BAD BOY

LL = GOOD BOY

WHEN DOES A LIFE EVENT BECOME A RISK FACTOR FOR DEPRESSION?

BEREAVENT

DIVORCE

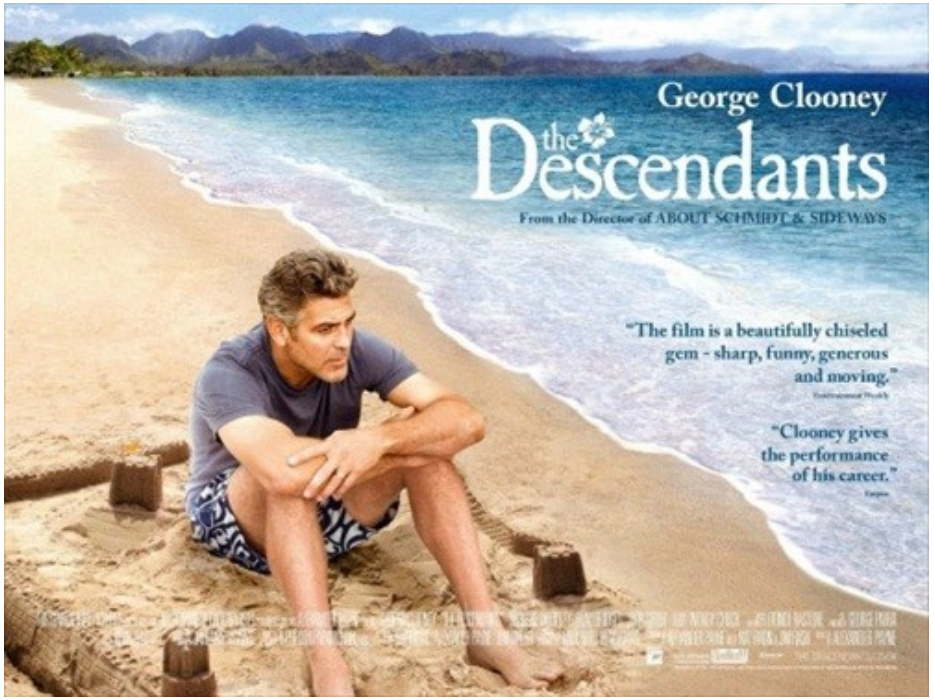
JOB LOSS

MALTREATMENT

Meaning of Life Events - Adulthood

Table 4. Studies Included in the Stressful Life Events Group Meta-Analysis

Source, Year	Total No. of Participants	1-Tailed *P* Value	Fisher *P* Value After Study Exclusion
Caspi et al,[1] 2003	845	.010	.054
Eley et al,[72] 2004	374	.258	.034
Kendler et al,[19] 2005	549	.007	.047
Jacobs et al,[20] 2006	374	.020	.040
Sjöberg et al,[21] 2006	198	.472	.032
Surtees et al,[74] 2006	4175	.500	.014
Taylor et al,[63] 2006	110	.028	.034
Wilhelm et al,[75] 2006	127	.118	.034
Zalsman et al,[64] 2006	79	.342	.033
Cervilla et al,[76] 2007	737	.014	.050
Chipman et al,[61] 2007	2094	.292	.039
Chorbov et al,[77] 2007	236	.99995	.025
Dick et al,[35] 2007	956	.004	.062
Kim et al,[78] 2007	732	.039	.046
Mandelli et al,[15] 2007	670	.011	.049
Middeldorp et al,[79] 2007	367	.500	.032
Scheid et al,[16] 2007	568	.080	.040
Lazary et al,[38] 2008	567	.002	.050
Power et al,[80] 2010	1421	.620	.026
Araya et al,[34] 2009	4334	.500	.013
Coventry et al,[42] 2010	3243	.500	.021
Bukh et al,[43] 2009	290	.035	.037
Laucht et al,[62] 2009	309	.500	.032
Ritchie et al,[82] 2009	942	.539	.030
Wichers et al,[83] 2009	502	.380	.033
Zhang et al,[45] 2009	792	.998	.016
Hammen et al,[13] 2010	346	.376	.034
Goldman et al,[50] 2010	984	.020	.055
Total	**26 921**		
Average sample size	961		.03



BEREAVEMENT = Life Event = 5 points

INFIDELITY = Life Event = 5 points

TOTAL 10 points

???????

Kang Arch Gen Psychiatry 2010

CONCLUSIONES (PROVISIONALES) ESTUDIOS DE INTERACCIÓN G X E

-No hay polimorfismos buenos y malos en variantes comunes

-Dificultad para definir cuales son los factores de riesgo ambiental

-Necesidad de modelos matemáticos que permitan analizar combinaciones de miles de variables

MENU

1-Heredabilidad de las enfermedades psiquaitricas

2.Datos generales genetica molecular

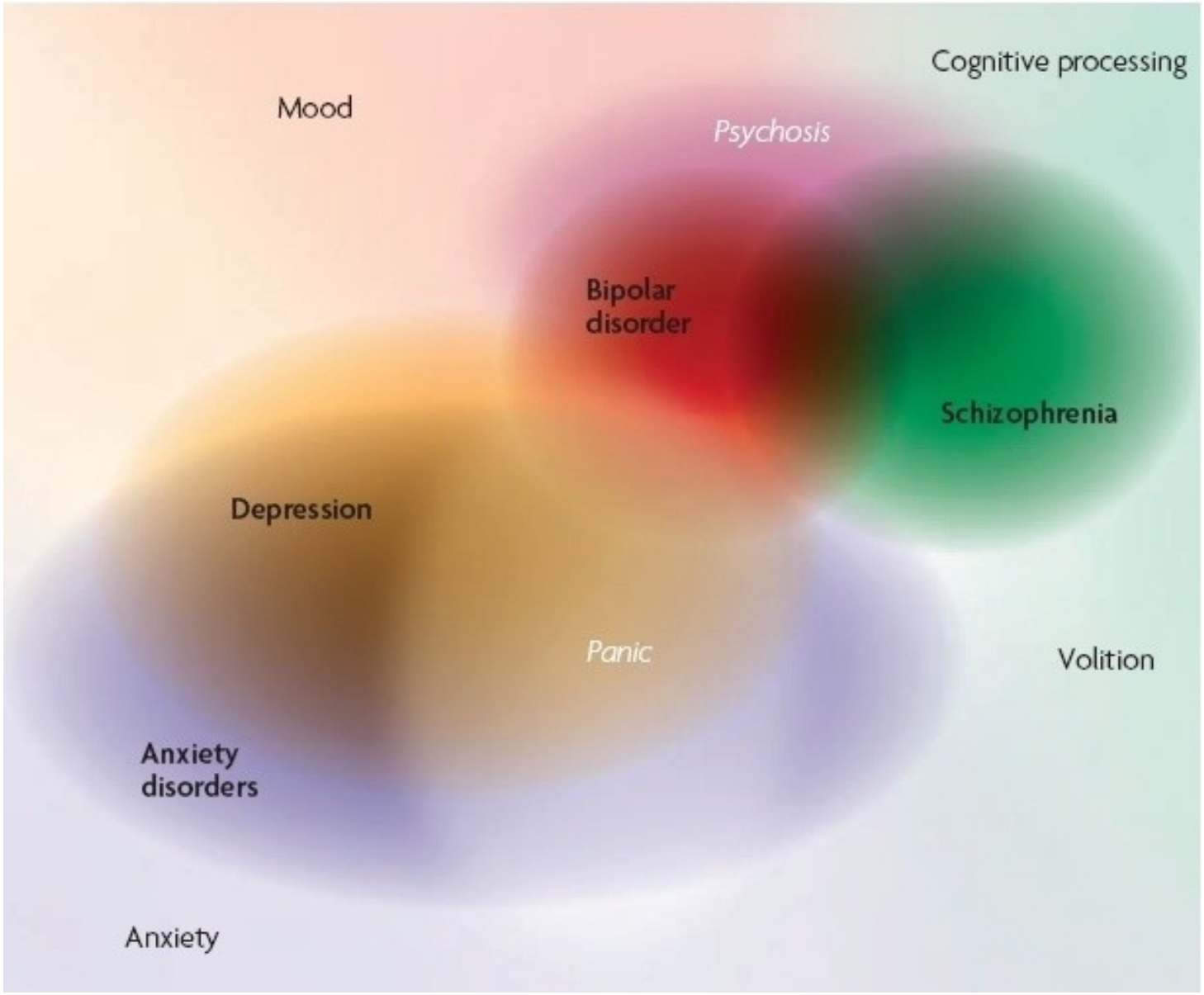
-Estudios de todo el genoma amplio

-Cambios en expresión génica

3-Interacción genético-ambiental

5-Futuro- Practica Clinica

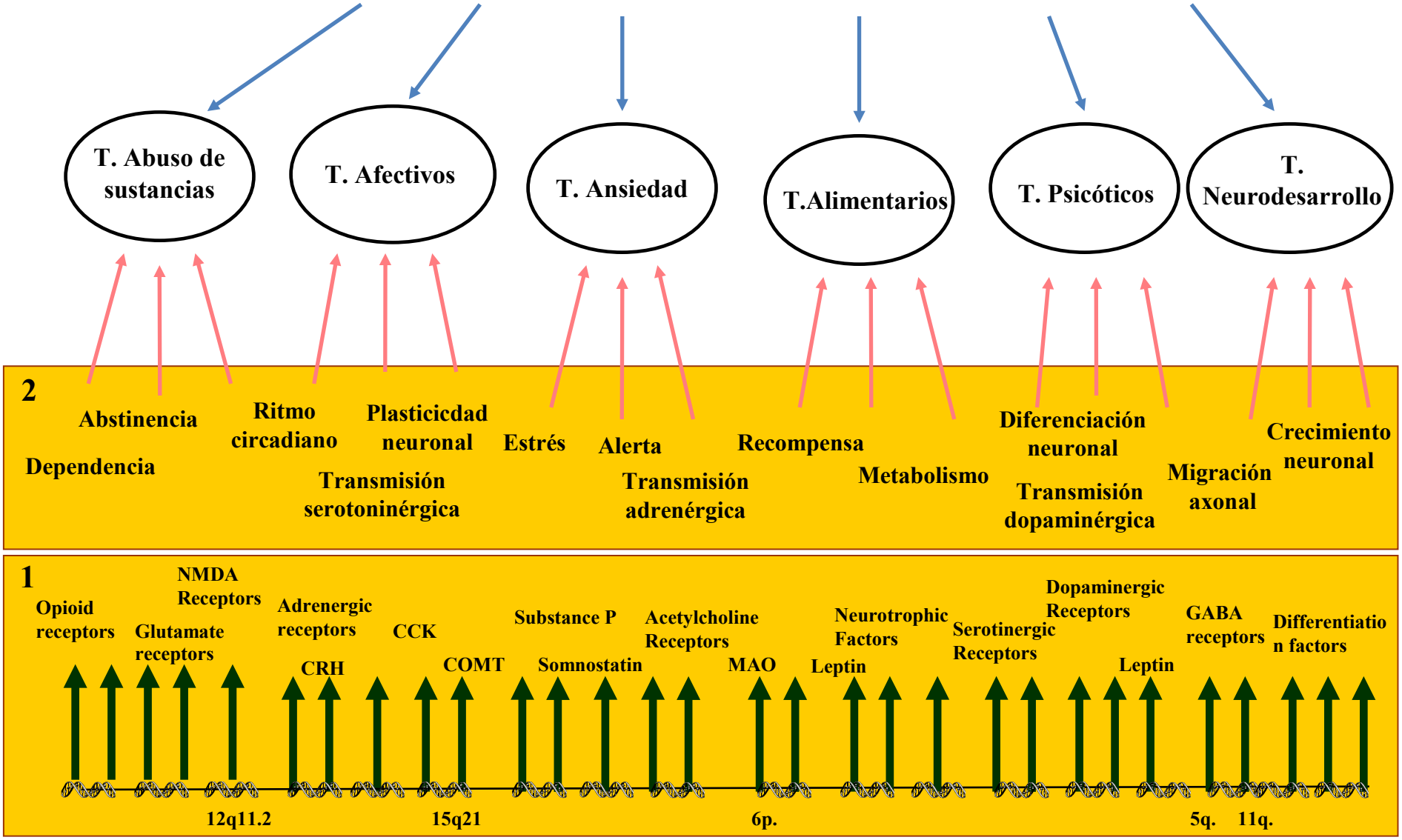
SOLAPAMIENTO DE TRASTORNOS MENTALES



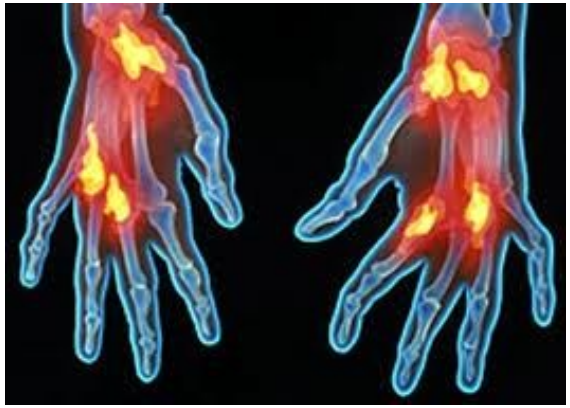
Burmeister et al Nat Rev Genet 2008, 9: 527-40

AMPLIANDO EL FENOTIPO

TRASTORNOS PSIQUIÁTRICOS

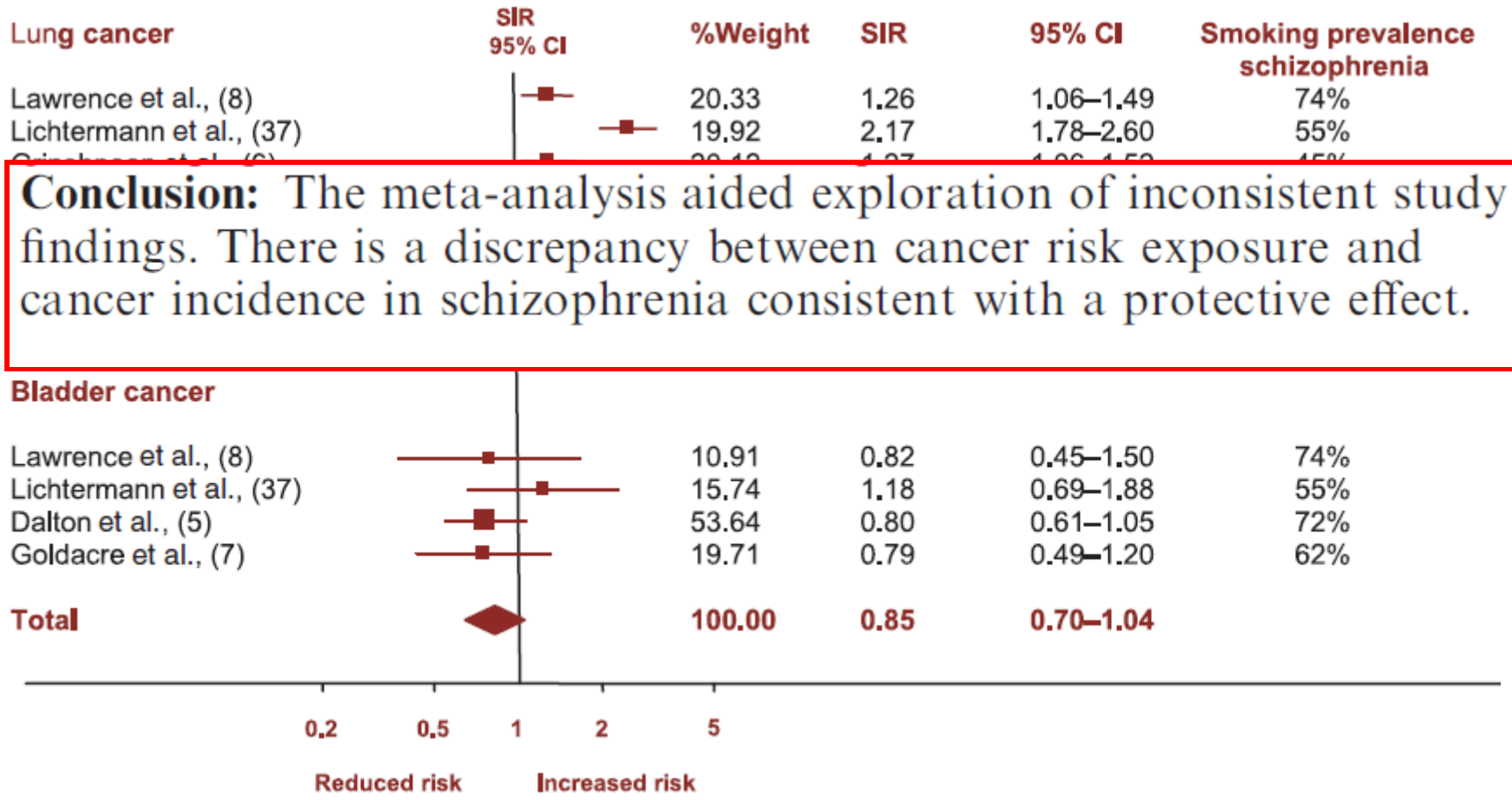


¿ES LA ESQUIZOFRENIA UN FACTOR DE PROTECCIÓN DE ALGUNAS ENFERMEDADES INMUNOLOGICAS ARTRITITIS REUMATOIDE?



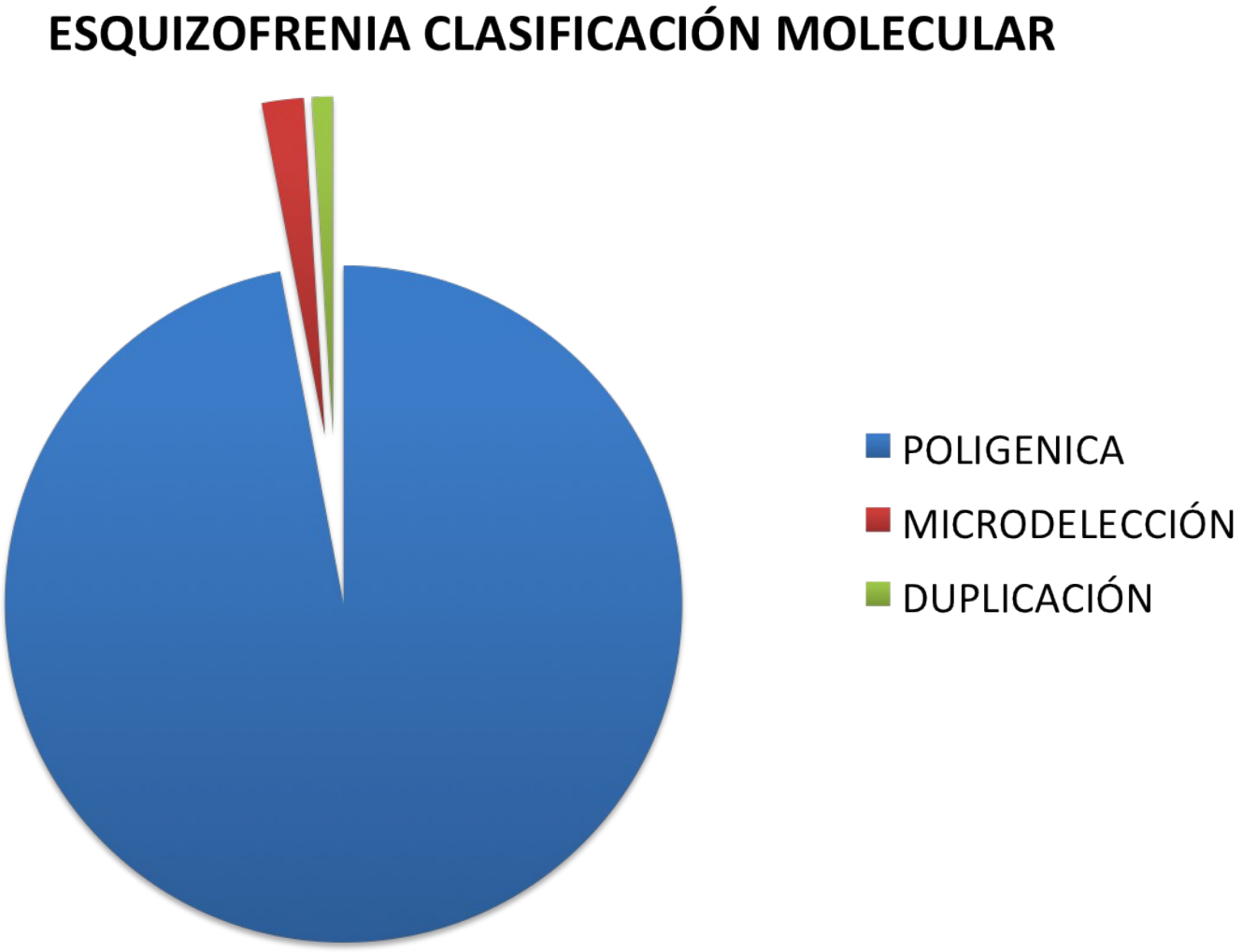
CANCER Y ESQUIZOFRENIA

Cancer incidence in patients with schizophrenia and their first-degree relatives – a meta-analysis



Conclusion: The meta-analysis aided exploration of inconsistent study findings. There is a discrepancy between cancer risk exposure and cancer incidence in schizophrenia consistent with a protective effect.

RECORTANDO EL FENOTIPO



13 - 14 September 2011.

PHENOMENOLOGY – Frank Laroi

COGNITION – Flavie Waters

EMOTIONS - Andre Aleman

ELECTROPHYSIOLOGY – Judith Ford

NEUROBIOLOGY – Paul Shotbolt

NEUROIMAGING – Paul Allen

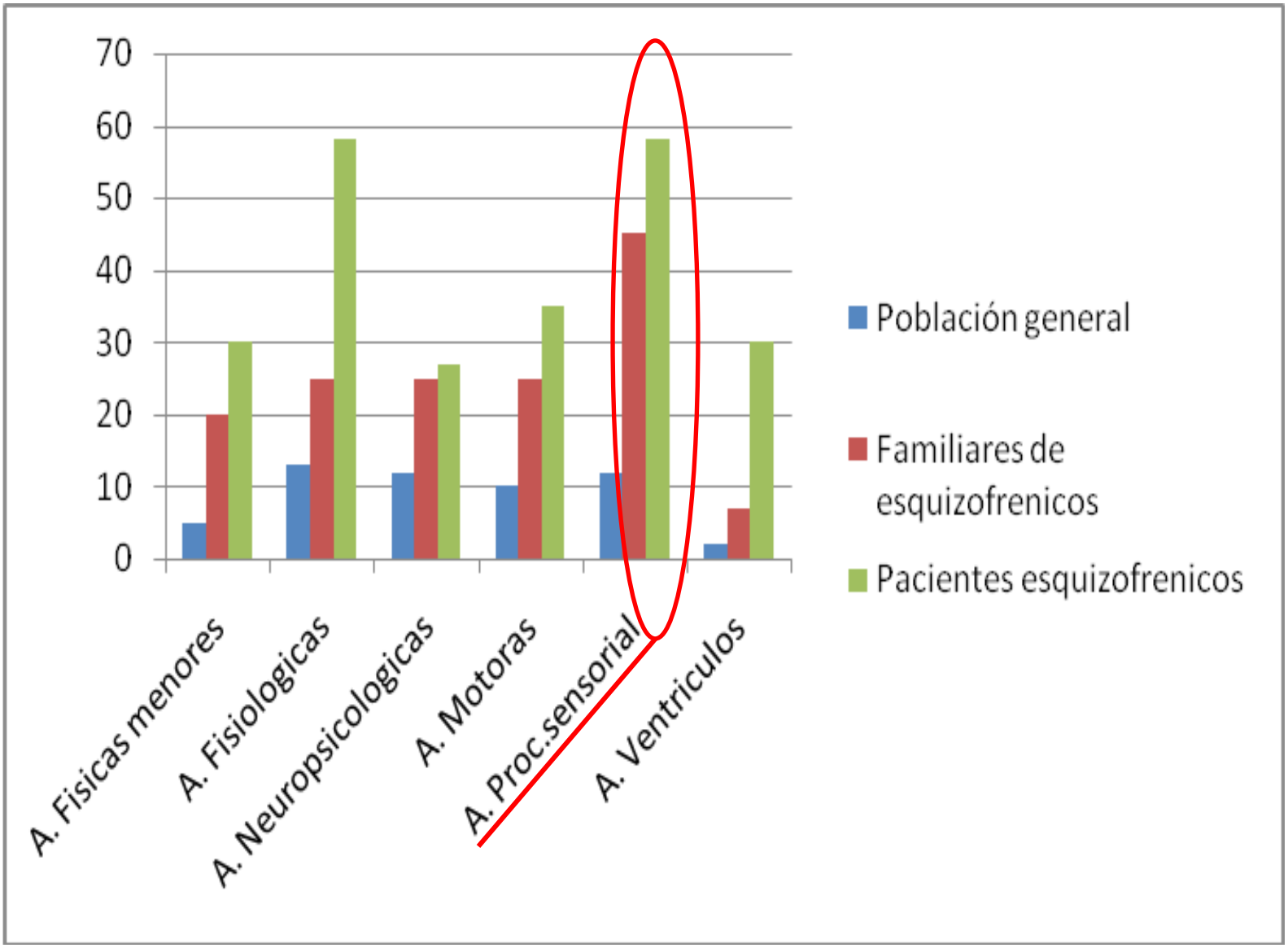
GENETICS - Julio Sanjuan

TREATMENT – Iris Sommer

VOCES EN LA CABEZA.COM

OUR GENETIC STUDIES OF HALLUCINATIONS IN PSYCHOSES

Author/year Journal	**Sample**	**Gene/ nº of SNPs**	**RESULTS**
Sanjuan et al 2004 Eur J. Psychiatry	Schizophrneic Auditory Hallucinations	CCK-AR 4 SNPs	Negative (Positive in persistant)
Toirac et al 2007 Psychiatric Genetics	Schizophrenic Auditory Hallucinations	**CCK-AR** 12 SNPs	**Positive**
Sanjuan et al 2005 J. NeuroPsychopharchology	Schizophrenic Auditory Hallucinations	**HTTLPR** 4 SNPs	**Positive**
Rivero et al 2006 Schizophrenia Research	Schizophrenic Auditory Hallucinations	ASPM 6 SNPs	Negative
Sanjuan et al 2005 Schizophrenia Research	Schizophrenic Auditory Hallucinations	FOXP2 3 SNPs	Negative
Tolosa et al 2008 Schizophrenia Research	Schizophrneic Auditory Hallucinations	HAR1 10 SNPs	Negative **(positive In Auditory Hallucinations)**
Carrera et al 2008 Am J Med Gen	Schizophrneic	**MAOB** **50 SNPs**	**POSITIVE**
Sanjuan et al 2006 Psychiatric Genetics	Schizohrenic Auditory Hallucinations	**FOXP2** **10 SNPs**	**Positive**

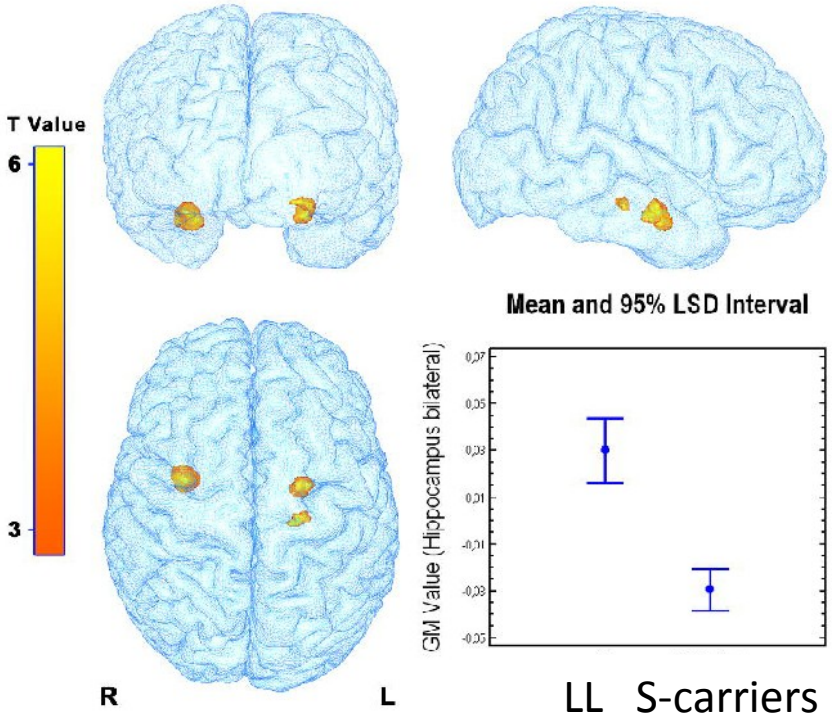


A.J. Allen et al. Schizophrenia Research 109 (2009) 24–37 (modificado)

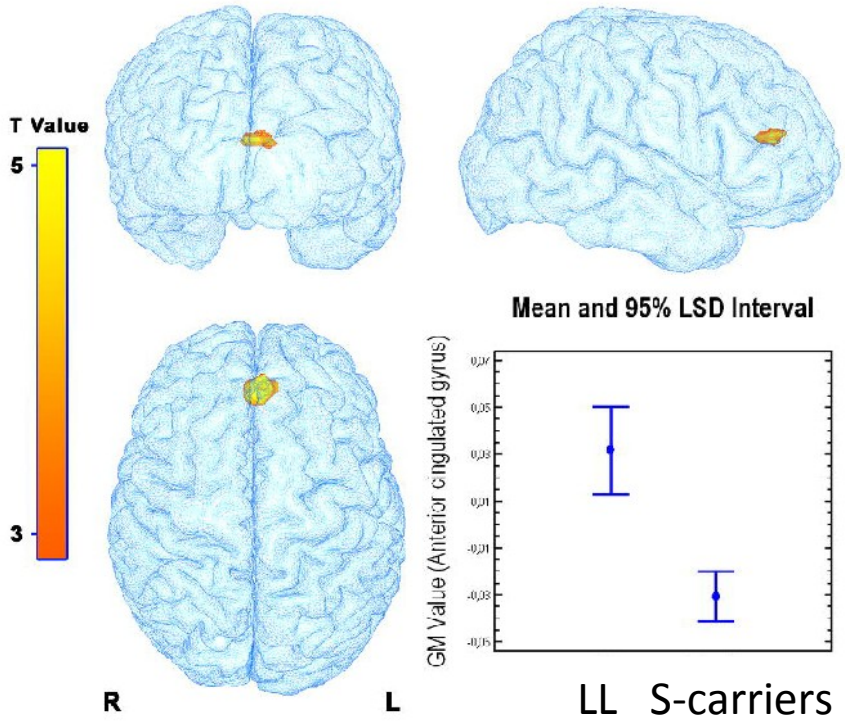
SLC6A4 gene: 5-HTTLPR and neuroimaging phenotypes

Effect of 5-HTTLPR on brain structure (VBM)

Controls



Patients



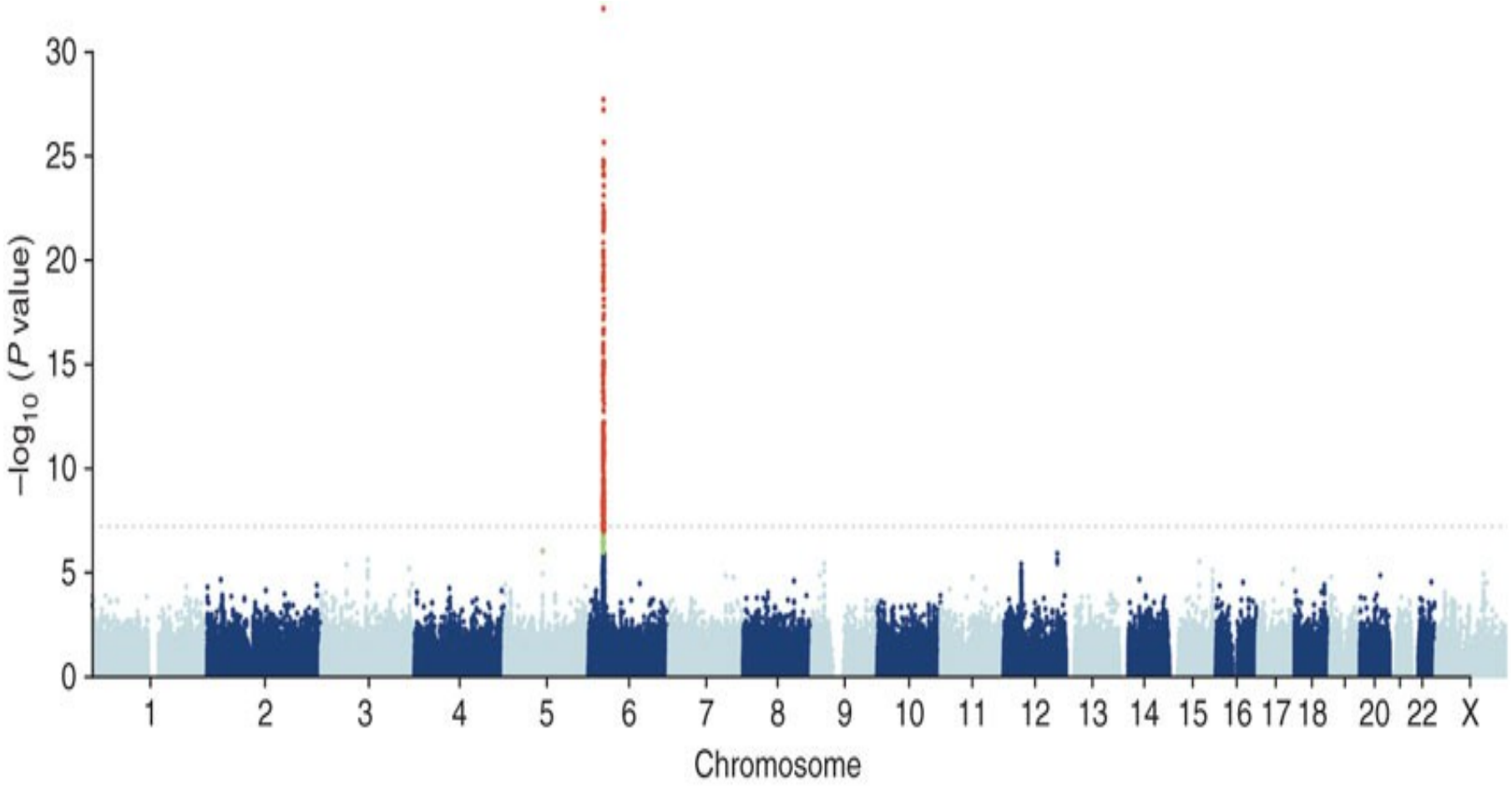
✓Hippocampus (bilateral)

✓ Parahippocampal gyrus (left)

✓Anterior cingulate gyrus

Rivero et al (under review)

GWAS of Drug-induced Liver Injury due to Flucloxacillin



Daly et al. Nature Genetics, 2009

FUTURO

1. MEJORAR LA DEFINICIÓN DEL FENOTIPO

2.PROYECTOS COLABORATIVOS INTERNACIONALES

3. MEJORAR INTEGRACIÓN BASICOS-CLINICOS

4. NECESIDAD DE NUEVAS IDEAS
HIPOTESIS FISIO-PATOLOGICAS

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Coordinator PI. J. Sanjuan

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Martinez MC. "

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