Genome-wide association studies (GWAS) en la investigación neuropsiquiátrica

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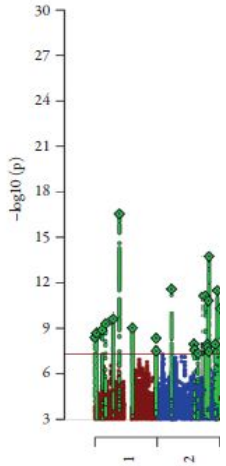


Figure 13.2 Manhattan plot adapted from S
represents either a directly genotyped or
displays the statistical significance as the
(5×10^{-8}). SNPs in green are in LD with

Table 33.1 GENOME-WIDE ASSOCIATION STUDIES OF ANXIETY DISORDERS

PHENOTYPE	AUTHOR (YEAR)	SAMPLE SIZE (GWAS) CASE	CONTROL	ARRAY	GENE (LOCATION)	SNP	P	OR
PD	Otowa et al. (2009)	200	200	Affymetrix 500K	*TMEM16B* (12p13)	rs12579350	3.73×10^{-9}	22.1
PD	Erhardt et al. (2011)	216	222	Illumina 300K	*TMEM132D* (12p24)	rs7309727	7.73×10^{-7}	2.2
PD	Otowa et al. (2012)	718	1,717	Affymetrix 500K, 6.0	*BDRKB2* (14q32)	rs10144552	4.43×10^{-6}	1.31
PD	Kawamura et al. (2013)	535	1,520	Affymetrix 6.0	CNV duplication (16p11.2)	-	3.5×10^{-6}	2.35
Phobic anxiety	Walter et al. (2013)	11,127		Affymetrix 6.0	(chr 13)	rs4911015	7.38×10^{-7}	-
GAD, PD, SAD, AG, SP	Otowa et al. (2016)	7016	14,745	Affymetrix 6.0, 500K, Illumina 1M Omini, 610, 550K, 370K, 317K, Cyto SNP12 v2	*LOC152225* (3q12.3)	rs1709393	1.65×10^{-8}	0.86
		18,186 (factor score analysis)			*CAMKMT* (2p21)	rs1067327	2.86×10^{-7}	-
OCD	Stewart et al. (2012)	1,465	5,557	Illumina Human 610, 550K	*DLGAP1* (18p11.31)	rs11081062	2.49×10^{-6}	-
		400 trios			*BTBD3* (20p12.2)	rs6131295	3.84×10^{-8}	1.96
OCD	Mattheisen et al. (2015)	1,406 (1,065 families)	1,489 (1,065 families)	Illumina HumanOmniExpress	*PTPRD* (9p23)	rs4401971	4.13×10^{-7}	-
			1,984	Illumina HumanOMNI1-QUAD				
PTSD	Logue et al. (2012)	295	196	Illumina OMNI 2.5–8	*RORA* (15q22.2)	rs8042149	2.5×10^{-8}	2.1
PTSD	Xie et al. (2013)	300	1,278	Illumina HumanOmni1-Quad	*TLL* (7p12)	rs406001	3.97×10^{-8}	-
PTSD	Guffanti et al. (2013)	94	319	Illumina HumanOmniExpress	*AC068718.1* (chr2)	rs10170218	5.10×10^{-8}	2.89
PTSD	Wolf et al. (2014)	293	191	HumanOmni2.5-8	*ADCY8* (8q24.22)	rs263232	6.12×10^{-7}	-
PTSD	Ashley-Koch et al. (2015)	710	998	Illumina HumanHap650, Human1M-Duo, HumanOmni2.5	*AK092087* (chr15)	rs12232346	2.14×10^{-6}	-
PTSD	Almli et al. (2015)	63	84	Illumina HumanOmniExpress	*DTHD1* (4p15)	rs717947	1.28×10^{-8}	-
PTSD	Nievergelt et al. (2015)	940	2,554	Illumina HumanOmniExpressExome	*PRTFDC1* (10p12.1)	rs6482463	2.04×10^{-7}	1.47
PTSD	Stein et al. (2016)	3167	4,607	Illumina HumanOmniExpress Exome, Illumina PsychChip	*ANKRD55* (5q11.2) in AA	rs159572	2.34×10^{-8}	1.64
					ZNF626 (chr 19) in EA	rs11085374	4.59×10^{-8}	0.77
GAD symptoms	Dunn et al. (2016)	12,282 (Hispanic/Latino adults)		HumanOmni2.5-8v.1-1	*THBS2* (6q27)	rs78602344	4.18×10^{-8}	-

GWAS: genome-wide association study; OR: odds ratio; CNV: copy number variation; chr: chromosome; EA: European American; AA: African American.

PD: panic disorder; GAD: generalized anxiety disorder; AG: agoraphobia; SAD: social anxiety disorder; SP: specific phobia; OCD: obsessive-compulsive disorder; PTSD: posttraumatic stress disorder.

ext Nestler's Neurobiology of Mental Illness, edited by Dennis S. Charney, et al., Oxford University Press USA - OSO, 2018

Table 13.3 STUDIES REPORTING GWAS IN BIPOLAR DISORDER IN EUROPEAN SAMPLES

TION	YEAR	PRIMARY OR STAGE 1 CASES	CONTROLS	GWS	REPLICATION OR STAGE 2[a] CASES	CONTROLS	GWS
	2007	1,868	2,938	–	NA	NA	NA
	2008	461	563	–	772	876	+
	2008	1,461	2,008	–	NA	NA	NA
	2009	1,098	1,267	–	4,387	6,209	+
	2009	2,076	1,676		3,683	14,507	

Table 24.1 GENOME-WIDE SIGNIFICANT GWAS FINDINGS FOR MAJOR DEPRESSION

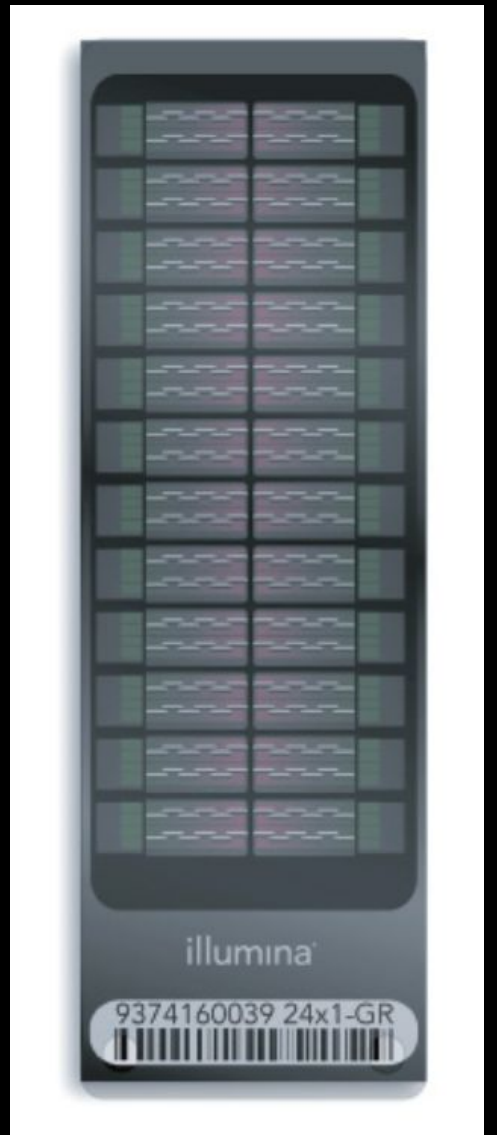
SNP	CHR	POSITION	P-VALUE (UNADJ)	GENE CONTEXT
PGC				
(None)				
Hek et al.				
rs40465	5	103981726	4.78 E-8	—
CONVERGE				
rs35936514	10	126244970	6.45E-12	LHPP
rs12415800	10	69624180	2.5E-10	SIRT1,-20246; DNAJC12,-26411
Okbay et al.				—
rs7973260	12	118375486	1.78E-09	KSR2
rs62100776	18	50754633	8.45E-09	DCC
rs6992714	8	64628120	9.32E-08	LOC286184,-53867
23andMe				
rs10514299	5	87663610	9.99E-16	TMEM161B*,-98945; LOC100505894; LINC00461,172986; MIR9-2,299060; MEF2C,350447
rs1518395	2	58208074	4.32E-12	VRK2,-65702
rs2179744	22	41621714	6.03E-11	L3MBTL2; (ACO2*,-243414)
rs11209948	1	72811904	8.38E-11	NEGR1,-63627
rs454214	5	88003403	1.09E-09	TMEM161B*,-438738; LOC100505894,270912; LINC00461,-22783; MIR9-2,-40646; MEF2C (eQTL),10654
rs301806	1	8482078	1.90E-09	RERE
rs1475120	6	105389953	4.17E-09	HACE1,-82159; LIN28B*,-14969
rs10786831	10	106614571	8.11E-09	SORCS3
rs12552	13	53625781	8.16E-09	OLFM4
rs6476606	9	37005561	1.20E-08	PAX5
rs8025231	15	37648402	1.23E-08	MEIS2,-254902; TMCO5A,-579054
rs12065553	1	80793118	1.32E-08	—
rs1656369	3	158280085	1.34E-08	RSRC1*,17509; MLF1,-8867
rs4543289	5	164484948	1.36E-08	
rs2125716	12	84941429	3.05E-08	SLC6A15*,311837
rs2422321	1	73293393	3.18E-08	NEGR1,-545116
rs7044150	9	2982931	4.31E-08	PUM3(KIAA0020),-138801; RFX3,241715

La mayoría de las enfermedades neuropsiquiátricas son poligénicas.

Cientos de genes de riesgo, por si solos, no tienen un efecto significativo en el desarollo de la enfermedad mental.

Genome-wide association studies (GWAS)

- Se examina el genoma de diferentes individuos en busca de marcadores genéticos (SNPs).
- Si hay una diferencia consistente dentro del grupo experimental, puede que haya una asociación entre ese gen y la enfermedad.
- Una forma objetiva y libre de hipótesis para estudiar la genética detrás de las enfermedades mentales.



Estudios GWAS para la esquizofrenia

Schizophrenia risk from complex variation of complement component 4

Aswin Sekar[1,2,3], Allison R. Bialas[4,5], Heather de Rivera[1,2], Avery Davis[1,2], Timothy R. Hammond[4], Nolan Kamitaki[1,2], Katherine Tooley[1,2], Jessy Presumey[5], Matthew Baum[1,2,3,4], Vanessa Van Doren[1], Giulio Genovese[1,2], Samuel A. Rose[2], Robert E. Handsaker[1,2], Schizophrenia Working Group of the Psychiatric Genomics Consortium*, Mark J. Daly[2,6], Michael C. Carroll[5], Beth Stevens[2,4] & Steven A. McCarroll[1,2]

Figure 13.2 Manhattan plot adapted from Schizophrenia Working Group of the Psychiatric Genomics Consortium, *Nature* 511:421–427. Each point represents either a directly genotyped or imputed SNP. SNPs are plotted on the x-axis starting from chromosome 1 to chromosome 22. The y-axis displays the statistical significance as the $-\log_{10} P$ value of the association results for each SNP. The red line shows the genome-wide significance level (5×10^{-8}). SNPs in green are in LD with the index SNPs (diamonds) which represent independent genome-wide significant associations.

GWAS: Limitaciones

- Debido a los estrictos estándares estadísticos, los GWAS requieren de una gran muestra para obtener resultados significativos.
- Muchos de los SNPs que se encuentran en el genoma se encuentran en regiones no codificantes.