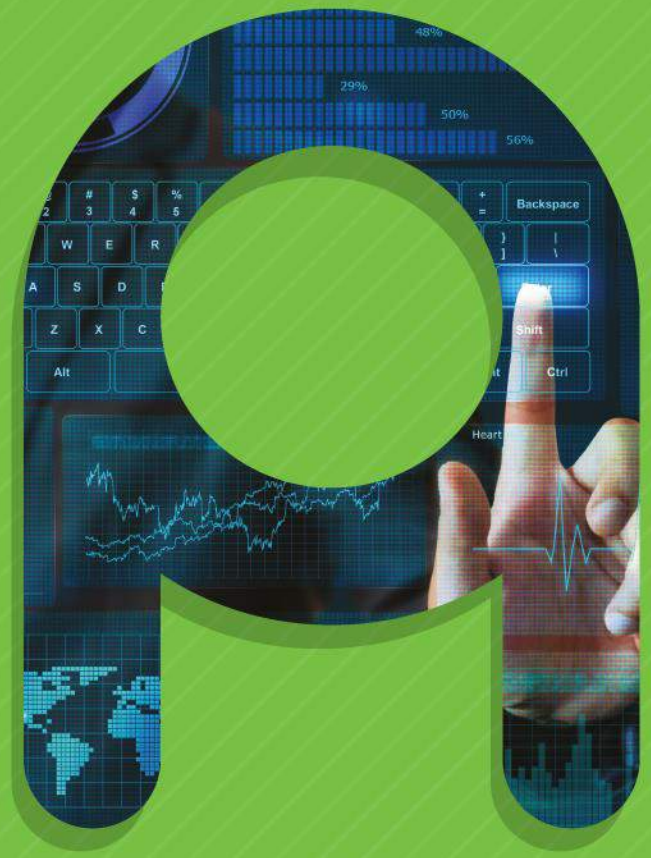

Genómica Funcional de Epileptogénesis en Modelos Animales y Humanos

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Chapter 30

Genetics of epilepsy

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Abstract

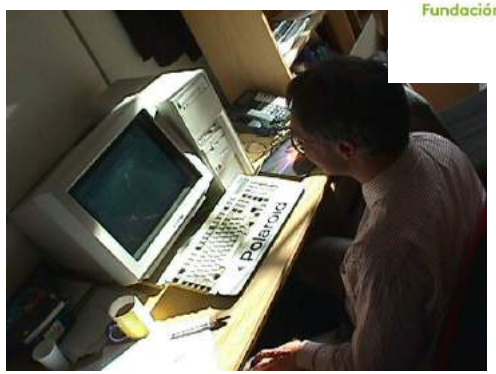
Discovery of nearly 200 genes implicated in epilepsy and insights into the molecular and cellular pathways involved are transforming our knowledge of the causes, classifications, diagnosis, and in some cases, treatments for individuals with chronic seizure disorders. Numerous disorders once considered "idiopathic" are now recognized as genetic conditions. Despite these remarkable advances, the cause of epilepsy for most individuals is unknown. We present a clinical approach to patients with epilepsy, presenting an algorithm for clinical and genetic testing, and review genes implicated in epilepsy and their associated syndromes.

Nolan D, Fink J. Genetics of epilepsy. Handb Clin Neurol. 2018;148:467-491.

From Data Generation to Data Analysis









Mitropoulos K, Al Jaibeji H, **Forero DA**, Laissue P, Wonkam A, Lopez-Correa C, Mohamed Z, Chantratita W, Lee MT, Llerena A, Brand A, Ali BR, Patrinos GP. **Success stories in genomic medicine from resource-limited countries**. Hum Genomics. 2015 Jun 18;9:11.

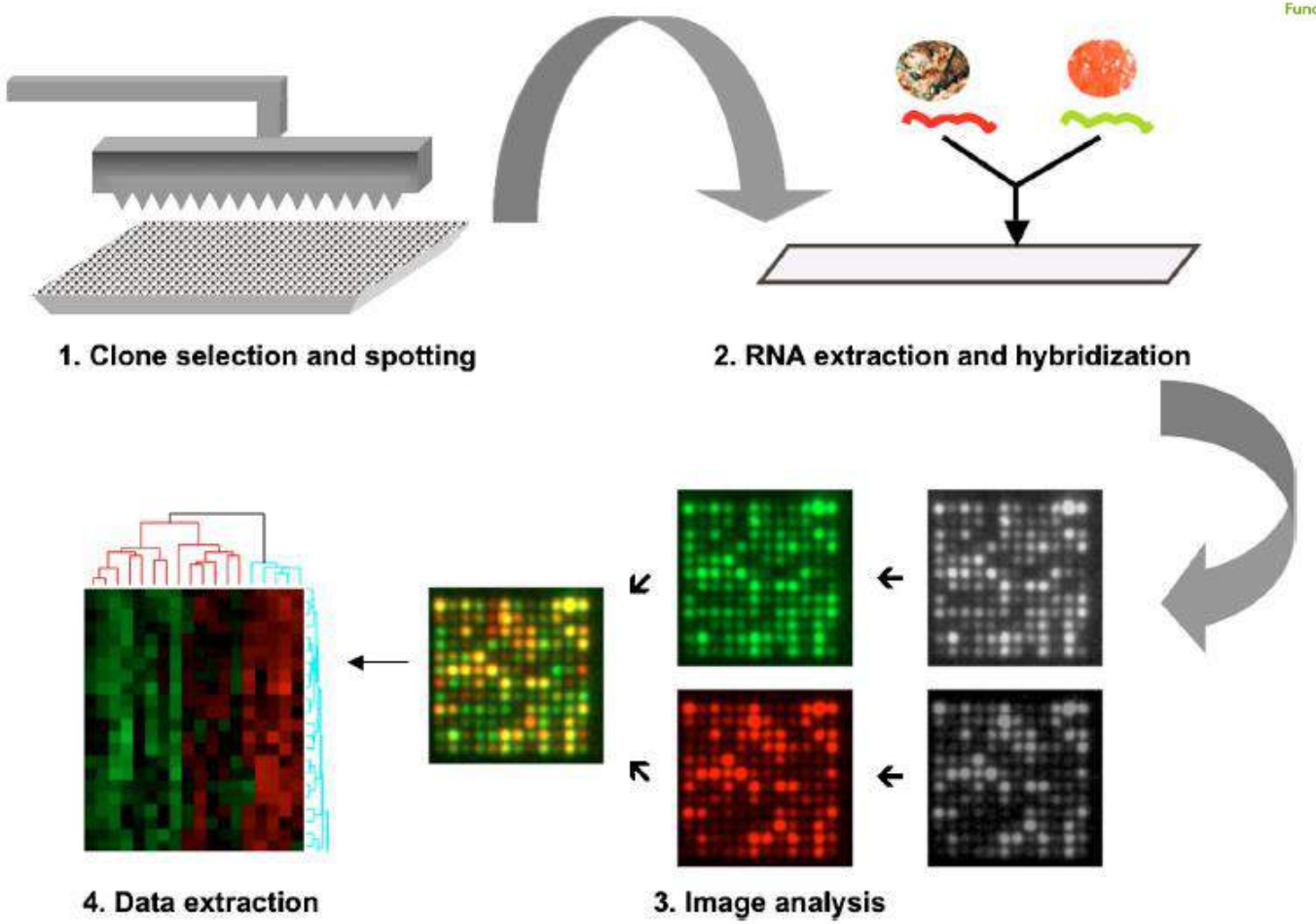


Fig. 1. Microarray technology: From bedside to bench and back again. (1) Clones or oligonucleotides are selected and robotically spotted onto a glass slide or nylon filter. (2) RNA is extracted from cells or tissues of interest and labeled either with cy3 or cy5 (glass slides) or with P^{33} (nylon filters) and hybridized. (3) Images are analyzed using programs such as ArrayPro or IPLAB. (4) Data is clustered and information extracted using bioinformatics.

Weeraratna AT, Nagel JE, de Mello-Coelho V, Taub DD. **Gene expression profiling: from microarrays to medicine**. J Clin Immunol. 2004 May;24(3):213-24.

PLOS COMPUTATIONAL BIOLOGY

EDITORIAL

Ten simple rules for carrying out and writing meta-analyses

Diego A. Forero[1,2]*, Sandra Lopez-Leon[3], Yeimy González-Giraldo[4], Pantelis G. Bagos[5]

Forero DA, Lopez-Leon S, González-Giraldo Y, Bagos PG.
Ten simple rules for carrying out and writing meta-analyses.
PLoS Computational Biology (Q1) 2019 May 16;15(5):e1006922.

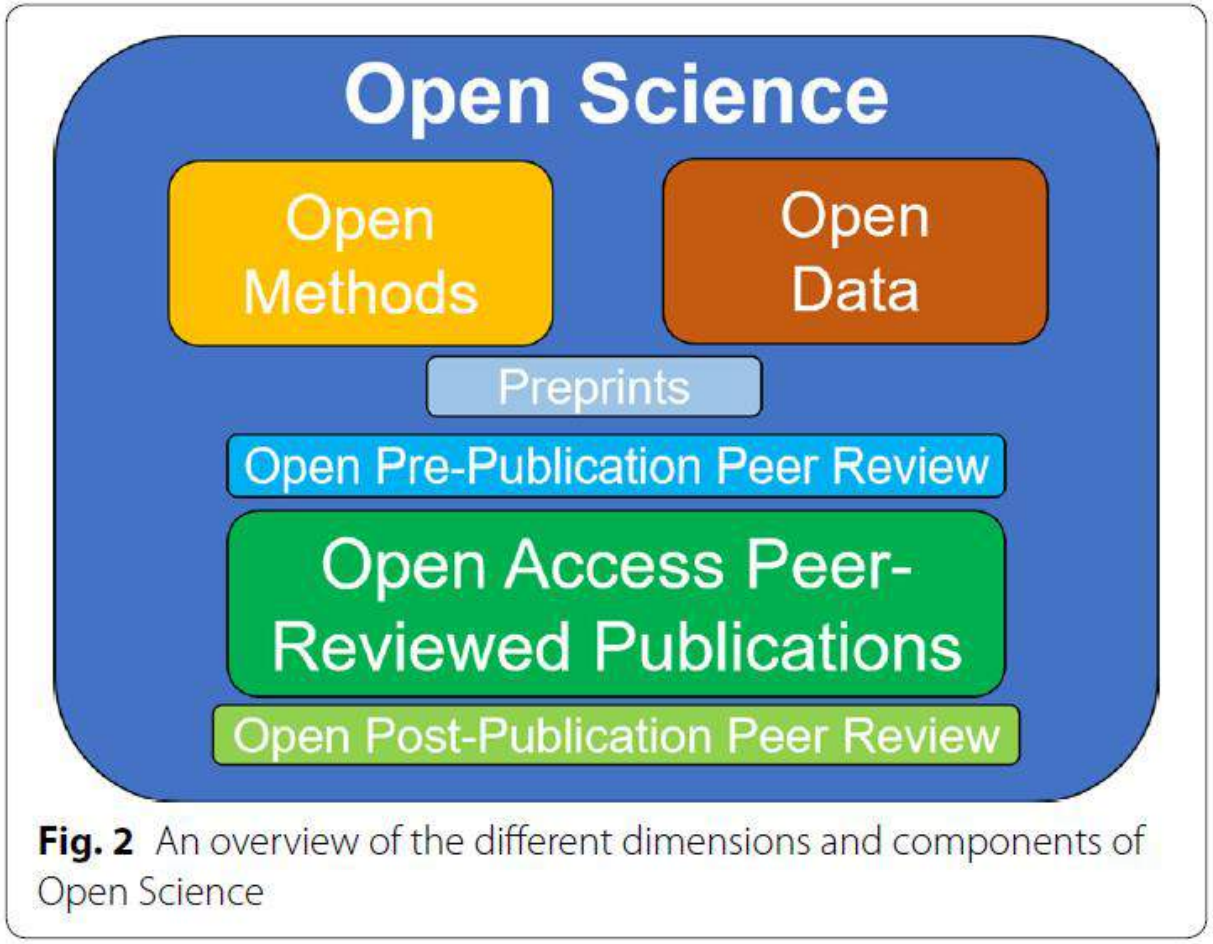


Fig. 2 An overview of the different dimensions and components of Open Science

Forero DA, Lopez-Leon S, Perry G. **A brief guide to the science and art of writing manuscripts in biomedicine**. J Transl Med. 2020 Nov 10;18(1):425.

Cellular and Molecular Neurobiology (2021) 41:1579–1587
https://doi.org/10.1007/s10571-020-00927-x

ORIGINAL RESEARCH

Functional Genomics of Epileptogenesis in Animal Models and Humans

Diego A. Forero[1,2]

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Abstract
It has been estimated that epilepsies are among the top five neurological diseases with the highest burden of disease. In recent years, genome-wide expression studies (GWES) have been carried out in experimental models of epilepsy and in samples from human patients. In this study, I carried out meta-analyses and analyses of convergence for available GWES for epileptogenesis in humans and in mouse, rat, zebrafish and fruit fly models. Multiple lines of evidence (such as genome-wide association data and known druggable genes) were integrated to prioritize top candidate genes for epileptogenesis and a functional enrichment analysis was carried out. Several top candidate genes, which are supported by multiple lines of genomic evidence, such as *GRIN1, KCNAB1* and *STX1B*, were identified. Druggable genes of potential interest (such as *GABRA2, GRIK1, KCNAB1 and STX4*) were also identified. An enrichment of genes regulated by the MEF2 and SOX5 transcription factors and the miR-106b-5p and miR-101-3p miRNAs was found. The current work is the first meta-analysis and convergent analysis of GWES for epileptogenesis in humans and in multiple animal models, integrating results from several genomic studies. Novel candidate genes and pathways for epileptogenesis were identified in this analysis.

Keywords Transcriptomics · Genomics · Neurological diseases · Epilepsies · Functional genomics

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Q1, Factor de impacto: 5.046, de la editorial Springer Nature

Table 1 Details of GWES included

Organism	Author	NCBI GEO	Design	Platform	PMID
Human	Helbig (2008)	GSE7486	Lymphoblastoid cell lines from patients with idiopathic absence epilepsies	Affymetrix Human Genome U133 Plus 2.0 Array	18435749
Mouse	Kalozoumi (2018)	GSE88992	Hippocampi from mice treated with kainate	Affymetrix Mouse Genome 430 2.0 Array	30114263
Mouse	Losing (2017)	GSE100202	Hippocampi from mice treated with pilocarpine	Affymetrix Mouse Gene 1.0 ST Array	28716058
Mouse	Kedmi (2007)	GSE6614	Brains from mice with nicotine-induced seizures	Affymetrix Murine Genome U74A Version 2 Array	17456735
Rat	Wilson (2005)	GSE1834	Hippocampi from rats treated with kainate	Affymetrix Rat Genome U34 Array	15800381
Rat	Okamoto (2010)	GSE14763	Hippocampi from rats treated with pilocarpine	GE Healthcare/Amersham Biosciences CodeLink™ Rat Whole Genome Bioarray	20377889
Rat	McClelland (2014)	GSE22894	CA1 from rats treated with kainate	Illumina ratRef-12 v1.0 expression beadchip	25117540
Zebrafish	Grone and Baraban 2015	GSE43312	Larvae from Scn1a mutant zebrafish	Agilent-026437 D. rerio Oligo Microarray V3	(–)
Drosophila	Singh (2011)	GSE10988	Heads from drosophila treated with levetiracetam and Pentylenetetrazole	CDMC_Drosophila_12k1	21503142

PMID PubMed identifier, *NCBI GEO* NCBI GEO database identifier

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Table 2 Main candidate genes

Gene	Evidence	Gene	Evidence	Gene	Evidence	Gene	Evidence
ADCY7	Mm-GW	*FUS*	Mm-GW	*LXN*	Hs-Mm-Rn	*S100A4*	Mm-Rn-Dr
ANXA5	Mm-Rn-Dr	*GABRA2*	Mm-GW	*MAPK6*	Mm-Rn-Dr	*SCN1A*	Mm-GW
ATP1B2	Hs-Mm-Dr-Dm	*GALNT3*	Mm-GW	*MCM6*	Hs-Mm-Rn	*SCN3A*	Mm-GW
ATP2B2	Mm-Rn-Dr	*GATM*	Hs-Mm-Rn	*MRPL10*	Hs-Dr-GW	*SEC61A1*	Mm-Rn-Dr
ATXN1	Mm-GW	*GJA1*	GW-Mm-Dr	*MYC*	Mm-Rn-Dr	*SEC61B*	Hs-Mm-Rn-Dr
BCKDK	GW-Mm-Dr	*GLS*	Hs-Dr-GW	*MYO5B*	Mm-Rn-Dr	*SERPINE1*	Mm-Rn-Dr
BOK	Mm-Rn-Dr	*GNAQ*	Hs-Mm-Dm	*NAB1*	Hs-Mm-GW	*SMAD1*	Hs-Mm-Rn
BRD7	Mm-GW	*GPD1*	Hs-Mm-Dm	*NDUFS2*	Hs-Mm-Dm	*SOX11*	Mm-Rn-Dr
CADPS	Hs-Mm-Rn	*GRIK1*	Mm-GW	*NFE2L1*	Mm-GW	*STAM2*	Hs-Mm-Dm
CALM2	Mm-Rn-Dr	*GRIN1*	Hs-Mm-Rn	*NINJ1*	Hs-Mm-Rn	*STAT3*	Hs-Mm-Rn
CAPZA2	Hs-Mm-Rn	*GTPBP1*	Hs-Mm-Dr-Dm	*NOL6*	Hs-Dr-Dm	*STX1B*	Mm-GW
CBX1	GW-Mm-Dr	*HAND2*	Hs-Mm-Dr-Dm	*NPEPPS*	Mm-GW	*SUMO3*	Hs-Dr-Dm
CCL2	Mm-Rn-Dr	*HEATR3*	GW-Dr	*NTRK2*	Hs-Mm-Rn	*TBX21*	GW-Dr
CDO1	Hs-Mm-Rn	*HK2*	Mm-Rn-Dr	*OLFM1*	Hs-Mm-Rn-Dr	*THRA*	Mm-Rn-Dr
CLIC4	Hs-Mm-Dr-Dm	*HOXB5*	GW-Dr	*P4HB*	Hs-Mm-Rn-Dr	*TMPO*	Hs-Mm-Rn-Dr
CPD	Hs-Mm-Dm	*HOXB9*	Mm-GW	*PENK*	Hs-Mm-Rn	*TPM2*	Hs-Mm-Dm
CYP7B1	Hs-Mm-Rn	*INPP1*	Mm-GW	*PHKG2*	Mm-GW	*TPM3*	Hs-Mm-Dr-Dm
DGKA	Mm-Rn-Dr	*ITGAX*	Mm-GW	*PLCD1*	Mm-Rn-Dr	*TPM4*	Hs-Mm-Dr-Dm
EEF2K	Mm-Rn-Dr	*ITGB1*	Mm-Rn-Dr	*PNPO*	Mm-GW	*TPSB2*	Hs-Dr-Dm
F3	Mm-Rn-Dr	*ITSN2*	GW-Dr	*PPP3CA*	Hs-Mm-Rn	*USP21*	Hs-Mm-Dm
FAM173A	Hs-Mm-Dm	*KCNAB1*	Mm-GW	*PTGFRN*	Hs-Mm-Rn	*VIM*	Hs-Mm-Rn-Dr
FBRS	Mm-GW	*KCNC1*	Hs-Mm-Rn	*PTPN1*	Hs-Mm-Rn	*VKORC1*	Mm-GW
FBXL19	GW-Dr	*KPNB1*	Mm-GW	*PTPN2*	Hs-Mm-Rn	*VSNL1*	Hs-Mm-Rn
FKBP1B	Mm-GW	*LOXL1*	Hs-Mm-Rn	*PTPRF*	Hs-Mm-Rn-Dr	*XPO7*	Hs-Mm-Rn

Hs GWES in humans, *Mm* meta-analysis of GWES in mice, *Rn* convergence of GWES in rats, *Dm* GWES in fruit flies, *Dr* GWES in zebrafish, *GW* GWAS in humans

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Cellular and Molecular Neurobiology 2021 Oct;41(7):1579-1587.

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Table 3 Top druggable genes

Gene	Evidence	Gene	Evidence	Gene	Evidence
ADCY7	Mm	*HOXB5*	Dr	*PHKG2*	Mm
ATXN1	Mm	*HOXB9*	Mm	*PNPO*	Mm
BCKDK	Mm-Dr	*HSD3B7*	Hs	*PRSS36*	Dm
BRD7	Mm	*INPP1*	Mm	*PRSS53*	Dm
CBX1	Mm-Dr	*ITGAM*	Hs	*PTPRK*	Hs
CSRNP3	Hs	*ITGAX*	Mm	*PYCARD*	Hs
FBRS	Mm	*ITSN2*	Dr	*SCN1A*	Mm
FBXL19	Dr	*KCNAB1*	Mm	*SCN3A*	Mm
FKBP1B	Mm	*KPNB1*	Mm	*SP2*	Hs
FUS	Mm	*KRTAP19-1*	Hs	*SP6*	Hs
GABRA2	Mm	*KRTAP19-3*	Hs	*STAT1*	Hs
GALNT3	Mm	*MRPL10*	Hs-Dr	*STX1B*	Mm-Dm
GJA1	Mm-Dr	*NAB1*	Hs-Mm	*STX4*	Dm
GLS	Hs-Dr	*NFE2L1*	Mm	*TBX21*	Dr
GRIK1	Mm	*NPEPPS*	Mm	*VKORC1*	Mm
HEATR3	Dr	*PAPD5*	Hs	*VRK2*	Hs-Dm
HIBCH	Hs	*PFN4*	Hs	*ZNF629*	Hs

Hs GWES in humans, *Mm* meta-analysis of GWES in mice, *Rn* convergence of GWES in rats, *Dm* GWES in fruit flies, *Dr* GWES in zebrafish

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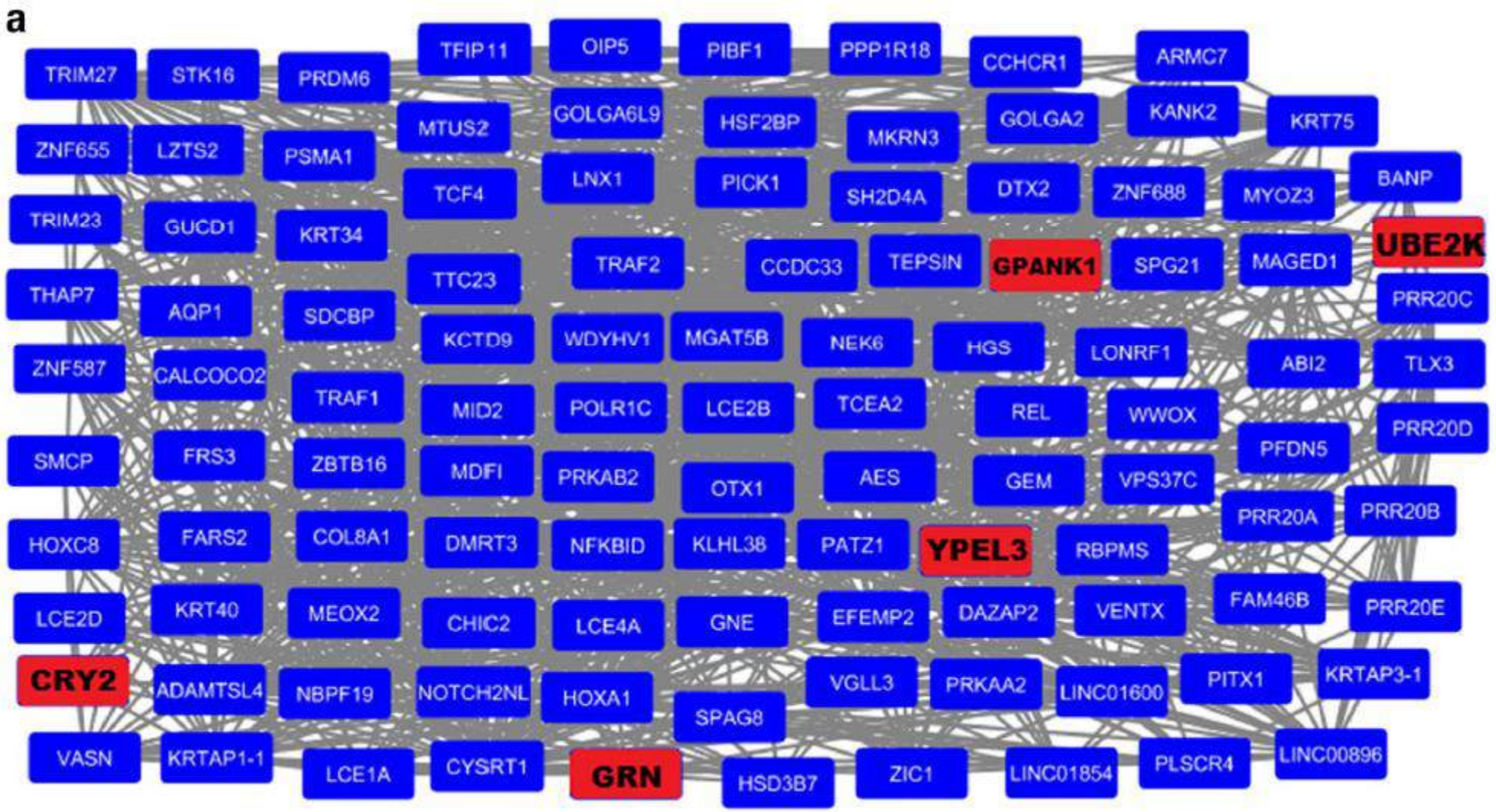

Fig. 1 a Protein–protein interaction network for top genes found in a CFG analysis of epileptogenesis in humans and animal models. A highly connected subnetwork is shown and top genes are highlighted in red.

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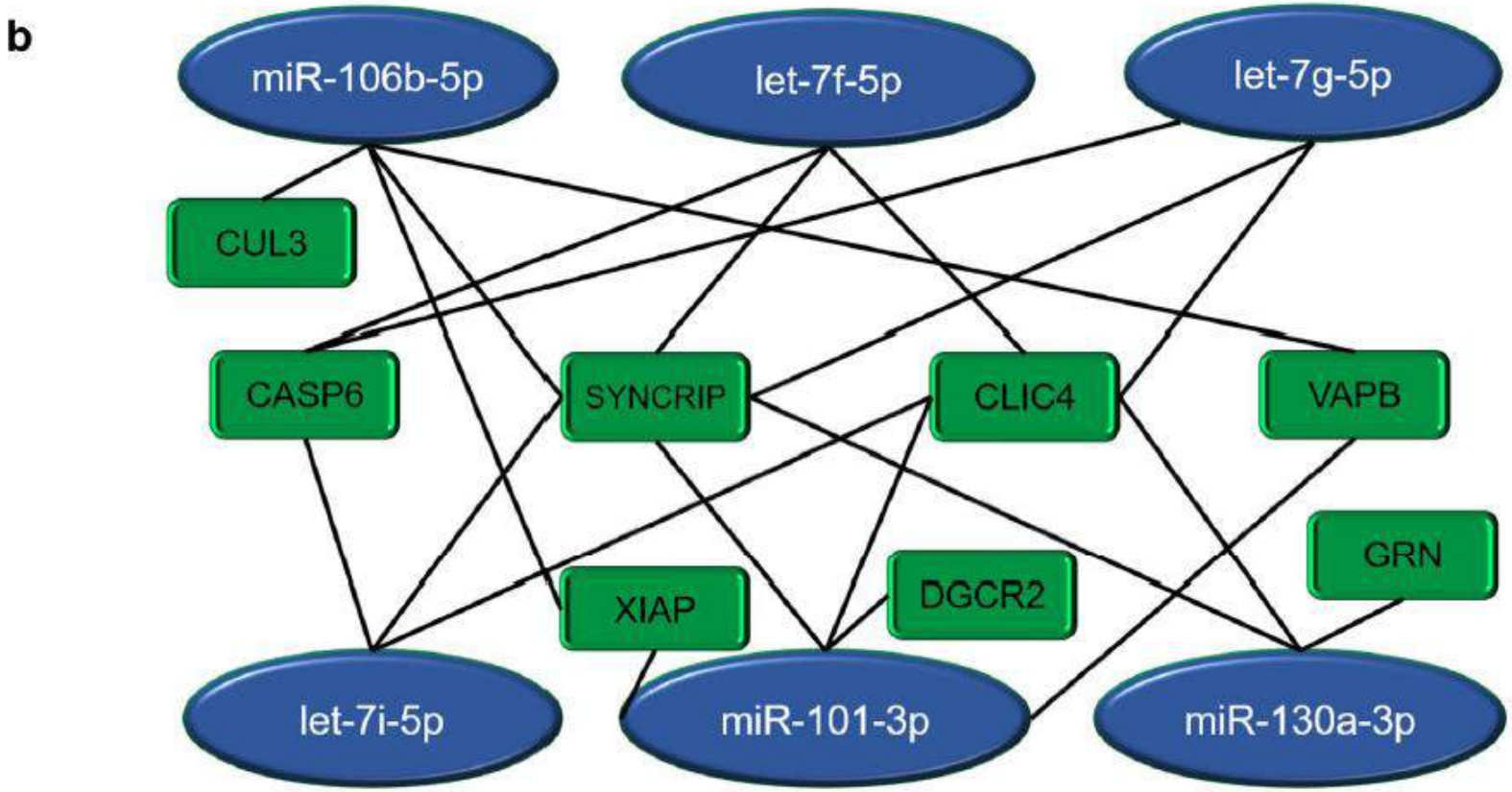

Fig. 1 b Overview of interactions between miRNAs found dysregulated in human patients and top genes identified in a CFG analysis of epileptogenesis in humans and animal models. Experimentally validated miRNA-mRNA interactions were retrieved from TarBase 8.0

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Table 4 Functional enrichment analysis of top candidate genes for epileptogenesis in humans and mouse models

Category	Term	*p* value	FDR
GO_BP	Positive regulation of transcription from RNA polymerase II promoter	1.4E−8	2.6E−5
GO_BP	Negative regulation of transcription from RNA polymerase II promoter	5.7E−8	1.0E−4
GO_BP	Negative regulation of apoptotic process	2.3E−6	4.1E−3
GO_BP	Apoptotic process	6.7E−6	1.2E−2
GO_CC	Nucleoplasm	8.3E−13	1.2E−9
GO_CC	Cytosol	6.9E−9	9.9E−6
GO_CC	Extracellular exosome	1.8E−7	2.6E−4
GO_CC	Cytoplasm	6.5E−7	9.4E−4
GO_CC	Focal adhesion	1.2E−5	1.8E−2
GO_MF	Protein binding	1.4E−19	2.1E−16
GO_MF	Protein heterodimerization activity	7.4 E−6	1.1 E−2
GNF	Whole Brain	1.4 E−8	1.5 E−5
GNF	Globus pallidus	5.2 E−7	5.5 E−4
GNF	Subthalamic nucleus	9.5 E−6	1.0 E−2

GO_BP gene ontology, biological process, *GO_CC* gene ontology, cellular component, *GO_MF* gene ontology, molecular function, *GNF* human gene expression atlas 2

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Table 5 Transcription factors found as enriched in top candidate genes for epileptogenesis in humans and mouse models

TF	#	p	FDR	TF	#	p	FDR	TF
MEF2	400	7.7E−13	9.4E−10	MRF2	275	2.5E−7	3.0E−4	HMX1
CREBP1	281	1.7E−12	2.1E−9	IRF1	153	2.6E−7	3.2E−4	IK1
SOX5	280	7.3E−12	9.0E−9	PAX4	396	2.7E−7	3.3E−4	GCNF
SRY	250	1.3E−11	1.5E−8	USF	310	2.7E−7	3.4E−4	FAC1
NKX61	253	1.5E−10	1.9E−7	NKX22	244	3.0E−7	3.7E−4	CEBP
CEBPB	310	1.6E−10	2.0E−7	NKX25	332	3.0E−7	3.7E−4	GFI1
MYB	261	2.3E−10	2.8E−7	CHOP	260	3.0E−7	3.7E−4	SOX9
FOXO4	300	2.0E−9	2.4E−6	PAX6	289	3.5E−7	4.3E−4	HNF1
FOXO1	239	2.7E−9	3.3E−6	OCT1	441	4.3E−7	5.3E−4	COUP
STAT	209	2.9E−9	3.6E−6	PBX1	304	4.4E−7	5.4E−4	GR
HFH1	253	6.1E−9	7.5E−6	E2F	302	4.6E−7	5.6E−4	MZF1
ATF6	257	2.0E−8	2.4E−5	E4BP4	239	4.6E−7	5.7E−4	HOXA9
POU3F2	318	2.6E−8	3.2E−5	IRF7	247	5.0E−7	6.2E−4	FOXJ2
TBP	205	7.3E−8	9.0E−5	AREB6	423	5.4E−7	6.7E−4	FREAC4
FREAC2	191	7.5E−8	9.1E−5	FREAC3	233	5.7E−7	7.0E−4	EN1
STAT1	225	9.2E−8	1.1E−4	SREBP1	315	7.0E−7	8.6E−4	RP58
CETS1P54	154	9.7E−8	1.2E−4	NKX3A	250	9.1E−7	1.1E−3	MEIS1
RSRFC4	259	9.9E−8	1.2E−4	HLF	223	9.3E−7	1.1E−3	AP4
STAT3	259	1.2E−7	1.5E−4	EVI1	411	1.1E−6	1.3E−3	CDC5
RREB1	218	1.3E−7	1.6E−4	HOXA3	228	1.1E−6	1.4E−3	NFKB
GATA1	411	1.4E−7	1.7E−4	CDP	313	1.3E−6	1.5E−3	CART1
FREAC7	265	1.6E−7	2.0E−4	NGFIC	173	1.5E−6	1.8E−3	MYCMAX

TF transcription factor, # number of genes, *p* value, *FDR* false discovery rate

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TF	#	p	FDR	TF	#	p	FDR
MEF2	246	1.5E−6	1.8E−3	NFKAPPAB	194	1.3E−5	1.6E−2
CREBP1	198	1.5E−6	1.9E−3	ISRE	233	1.3E−5	1.6E−2
SOX5	299	1.5E−6	1.9E−3	HSF1	169	1.5E−5	1.8E−2
SRY	254	1.7E−6	2.1E−3	BACH1	261	1.5E−5	1.8E−2
NKX61	387	1.8E−6	2.2E−3	HTF	278	1.6E−5	1.9E−2
CEBPB	239	2.0E−6	2.5E−3	AP1	304	1.7E−5	2.1E−2
MYB	239	2.3E−6	2.9E−3	PAX5	291	1.8E−5	2.2E−2
FOXO4	292	2.5E−6	3.0E−3	IK3	233	1.9E−5	2.3E−2
FOXO1	226	2.5E−6	3.1E−3	PPARG	403	1.9E−5	2.4E−2
STAT	275	2.6E−6	3.2E−3	AP1FJ	166	2.1E−5	2.5E−2
HFH1	258	2.7E−6	3.3E−3	RFX1	311	2.1E−5	2.6E−2
ATF6	265	4.8E−6	5.9E−3	BACH2	227	2.1E−5	2.6E−2
POU3F2	336	4.8E−6	5.9E−3	AML1	384	2.1E−5	2.6E−2
TBP	244	5.1E−6	6.2E−3	FOXO3	155	2.3E−5	2.8E−2
FREAC2	279	7.7E−6	9.4E−3	RORA2	247	2.5E−5	3.1E−2
STAT1	271	7.8E−6	9.5E−3	RORA1	235	2.6E−5	3.2E−2
CETS1P54	245	9.8E−6	1.2E−2	SRF	354	2.8E−5	3.4E−2
RSRFC4	327	9.9E−6	1.2E−2	MAZR	125	2.8E−5	3.5E−2
STAT3	239	1.0E−5	1.2E−2	GRE	247	2.9E−5	3.6E−2
RREB1	260	1.1E−5	1.3E−2	TST1	230	3.3E−5	4.1E−2
GATA1	250	1.1E−5	1.4E−2	TATA	279	3.5E−5	4.3E−2
FREAC7	321	1.1E−5	1.4E−2				

TF transcription factor, # number of genes, *p* value, *FDR* false discovery rate

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https://doi.org/10.1186/s13104-021-05817-z

BMC Research Notes

COMMENTARY Open Access

The importance of adherence to international standards for depositing open data in public repositories

Diego A. Forero[1,2*], Walter H. Curioso[3] and George P. Patrinos[4,5,6]

Forero DA, Curioso WH, Patrinos GP. **The importance of adherence to international standards for depositing open data in public repositories.** *BMC Res Notes. 2021 Nov 2;14(1):405.*

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