

Supplemental Data

Exome Sequencing Followed by Large-Scale Genotyping

Fails to Identify Single Rare Variants of Large Effect

in Idiopathic Generalized Epilepsy

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Table S3. Reactome Pathway Analysis Results: Top 20 Most Significantly Enriched Pathways in IGE

Unadjusted Probability of Seeing N or More Genes in This Pathway by Chance	Number of Genes in Your Query that Map to This Pathway	Total Number of Genes Involved in This Pathway	Name of This Pathway	Gene Symbols Mapping to This Pathway
6.80E-05	9	29	ABC-family proteins mediated transport	<i>CFTR, ABCA8, ABCG4, ABCA4, ABCC3, ABCC2, ABCB5, ABCC11, ABCC9</i>
3.70E-04	44	396	Transmembrane transport of small molecules	<i>SLCO2A1, SLC1A7, TF, SLC18A1, CFTR, SLC5A2, SLC14A2, NUP133, GABRB2, ATP10D, ABCB5, ATP4B, SLC3A1, SLC2A10, SLC6A19, SLC5A9, ABCA8, ABCG4, SLC35C1, NUP188, SLC47A1, NUP205, SLC30A6, ATP6V1E1, SLC7A6, SLC22A1, SLC7A3, ATP10A, SLC20A2, ADCY7, ABCC2, ATP1A1, SLC17A5, ATP8B1, NUP153, NUP160, SLC27A6, ABCA4, ABCC3, SLC39A6, SLCO1A2, ABCC11, ABCC9, HMOX2</i>
4.10E-04	5	11	The ABCC family mediates organic anion transport	<i>ABCC3, CFTR, ABCC2, ABCC9, ABCC11</i>
1.50E-03	17	116	Metabolism of carbohydrates	<i>ENO3, GYS2, PHKG2, PYGB, GALE, PRPS1, NUP133, GAPDHS, TREH, SI, LCT, NUP153, NUP160, ENO2, NUP188, PGAM2, NUP205</i>
2.20E-03	5	15	Class C/3 (Metabotropic glutamate/pheromone receptors)	<i>GRM7, GABBR2, TAS1R2, CASR, GRM3</i>
2.60E-03	3	5	Digestion of dietary carbohydrate	<i>TREH, SI, LCT</i>
2.60E-03	3	5	Shc1 binds phosphorylated ERBB2:ERBB3 heterodimers	<i>ERBB3, ERBB2, NRG1</i>
2.60E-03	3	5	Binding of PI3K subunit p85 (PIK3R1) to ERBB2:P-ERBB3 heterodimer	<i>ERBB3, ERBB2, NRG1</i>
2.60E-03	3	5	GRB7 binds phosphorylated heterodimer of ERBB2 and ERBB3	<i>ERBB3, ERBB2, NRG1</i>
2.60E-03	3	5	GRB7 events in ERBB2 signaling	<i>ERBB3, ERBB2, NRG1</i>
2.60E-03	3	5	RNF41 binds neuregulin-activated ERBB3	<i>ERBB3, ERBB2, NRG1</i>
4.30E-03	4	11	Trans-autophosphorylation of p-Y877-ERBB2 heterodimers	<i>ERBB3, EGF, ERBB2, NRG1</i>
4.30E-03	4	11	Trans-autophosphorylation of ERBB2 heterodimers	<i>ERBB3, EGF, ERBB2, NRG1</i>
4.40E-03	2	2	GABA synthesis	<i>GAD1, GAD2</i>
4.40E-03	2	2	Synthesis of GABA by GAD2	<i>GAD1, GAD2</i>
4.40E-03	2	2	GPR77 binds anaphylatoxins and their desArginated derivatives	<i>GPR77, C5</i>
4.40E-03	2	2	Both hexosaminidase A and B can cleave GalNAc from globoside	<i>HEXB, HEXA</i>
5.00E-03	3	6	PIP2 to PIP3 conversion by PI3K bound to phosphorylated heterodimer of ERBB2 and ERBB3	<i>ERBB3, ERBB2, NRG1</i>
5.00E-03	3	6	Recruitment of PI3K subunit p110 (PIK3CA) by PIK3R1 bound to phosphorylated heterodimer of ERBB2 and ERBB3.	<i>ERBB3, ERBB2, NRG1</i>
6.10E-03	4	12	SHC1 phosphorylation by ERBB2 heterodimers	<i>ERBB3, EGF, ERBB2, NRG1</i>

Table S4. List of Regions Implicated as IGE Link Loci through Linkage Studies

Region or Gene Implicated by a Linkage Study	Study/PubmedID
10p11.2	Kinirons P et al. Am J Med Genet A. 2008 Mar 1;146A(5):578-84. PMID:18241056
10q25.2-26.11	Puranam RS et al. Ann Neurol. 2005 Sep;58(3):449-58. PMID:16130088
9q32-33	Baykan B et al. Epilepsia. 2004 May;45(5):479-87. PMID:15101829
8q24	Plaster NM et al. Neurology. 1999 Oct 12;53(6):1180-3. PMID:10522869
8q24	Fong GC et al. Am J Hum Genet. 1998 Oct;63(4):1117-29. PMID:9758624
8p23-p21	Baulac S et al. Arch Neurol. 2008 Jul;65(7):943-51. PMID:18625863
8p12	Durner M et al. Am J Hum Genet. 1999 May;64(5):1411-9. PMID:10205274
6p21.32	Pal DK et al. Am J Hum Genet. 2003 Aug;73(2):261-70. Epub 2003 Jun 25. PMID:12830434
<i>EFHC1</i>	Suzuki T et al. Neurosci Lett. 2006 Sep 11;405(1-2):126-31. Epub 2006 Jul 28. PMID:16876319
<i>EFHC1</i>	Suzuki T et al. Biochem Biophys Res Commun. 2001 Nov 2;288(3):626-36. PMID:11676489
<i>GABRA1</i>	Cossette P et al. Nat Genet. 2002 Jun;31(2):184-9. Epub 2002 May 6. PMID: 11992121
5q13.3-5q23.1	Durner M et al. Ann Neurol. 2001 Mar;49(3):328-35. PMID:11261507
3q26	Sander T et al. Hum Mol Genet. 2000 Jun 12;9(10):1465-72. PMID:10888596
3q13.2-21.2	Kapoor A et al. Ann Neurol. 2008 Aug;64(2):158-67. PMID:18756473
3p23-p14	Chioza BA et al. Epilepsy Res. 2009 Dec;87(2-3):247-55. Epub 2009 Oct 17. PMID:19837565
3p22.3-22.2	Blair MA et al. Epilepsia. 2011 May;52(5):993-9. doi: 10.1111/j.1528-1167.2011.03059.x. Epub 2011 Apr 11. PMID:21480884
3p14.2-p12.1	Zara F et al. Neurology. 1998 Aug;51(2):493-8. Erratum in: Neurology 1998 Nov;51(5):1520. PMID:9710024
2q36.3-37.1	Klein KM et al. Epileptic Disord. 2008 Mar;10(1):13-8. PMID:18367426
2q36	Sander T et al. Hum Mol Genet. 2000 Jun 12;9(10):1465-72. PMID:10888596
2q33-q36	Ratnapriya R et al. Hum Genet. 2010 Aug;128(2):123-30. Epub 2010 May 14. PMID:20467754
2q24.1	Layouni S et al. Epilepsy Res. 2010 Jun;90(1-2):33-8. Epub 2010 Apr 7. PMID:20378313
2q23.3	Layouni S et al. Epilepsy Res. 2010 Jun;90(1-2):33-8. Epub 2010 Apr 7. PMID:20378313
23-q31	Lopes-Cendes I et al. Am J Hum Genet. 2000 Feb;66(2):698-701. PMID:10677328
19q13.1	Wallace RH et al. Nat Genet. 1998 Aug;19(4):366-70. PMID:9697698
18q12.2-18q21.32	Durner M et al. Ann Neurol. 2001 Mar;49(3):328-35. PMID:11261507
15q13.3	Elmslie FV et al. Am J Hum Genet. 1996 Sep;59(3):653-63. PMID:8751867
14q23	Sander T et al. Hum Mol Genet. 2000 Jun 12;9(10):1465-72. PMID:10888596
11q22.1-23.3	Yang MS et al. Neurosci Lett. 2003 Aug 7;346(3):133-6. PMID:12853102
5p14.1	Durner M et al. Ann Neurol. 2001 Mar;49(3):328-35. PMID:11261507

Table S5. Genes with Multiple Rare Candidate Epilepsy Variants

Gene	Number of Unique Variants in Gene that Are Present in at Least One IGE Case and Absent in Control Cohorts (Including NHLBI Cohort)	Number of IGE Patients Harboring One of the Rare Candidate Variants
<i>MYO15A</i>	3	6
<i>USH2A</i>	5	6
<i>NUP205</i>	5	5
<i>HECTD1</i>	3	4
<i>HEXA</i>	2	4
<i>LAMC2</i>	3	4
<i>UTRN</i>	2	4
<i>MXRA5</i>	2	3
<i>UNC45B</i>	2	3
<i>ABCC11</i>	2	3
<i>ANXA1</i>	3	3
<i>CCDC77</i>	3	3
<i>CYP2C9</i>	2	3
<i>SCN7A</i>	2	3
<i>SLC27A5</i>	2	3
<i>TDRD6</i>	3	3
<i>UROS</i>	2	3
<i>ATP10D</i>	2	3
<i>C12orf63</i>	2	3
<i>C14orf155</i>	2	3
<i>CNDP2</i>	2	3
<i>DEPDC1B</i>	2	3
<i>DNAH8</i>	2	3
<i>DZIP3</i>	3	3
<i>KIAA0100</i>	2	3
<i>KLF3</i>	2	3
<i>LAMA3</i>	3	3
<i>MDN1</i>	2	3
<i>PIK3R3</i>	3	3
<i>PIWIL3</i>	3	3
<i>PLCE1</i>	3	3
<i>PROX1</i>	2	3
<i>SPECC1L</i>	2	3
<i>SPEN</i>	3	3
<i>VWF</i>	2	3
<i>FAAH2</i>	2	2
<i>UBQLN2</i>	2	2
<i>ATXN7</i>	2	2
<i>KIAA0556</i>	2	2
<i>ARID4A</i>	2	2
<i>C1orf164</i>	2	2
<i>CEACAM5</i>	2	2
<i>CSMD2</i>	2	2

<i>DNAH7</i>	2	2
<i>DSP</i>	2	2
<i>EMILIN2</i>	2	2
<i>FICD</i>	2	2
<i>HIVEP1</i>	2	2
<i>KIAA0922</i>	2	2
<i>KIAA1632</i>	2	2
<i>LRBA</i>	2	2
<i>MYH6</i>	2	2
<i>MYOM1</i>	2	2
<i>OIT3</i>	2	2
<i>PCDH9</i>	2	2
<i>PHF3</i>	2	2
<i>PKHD1</i>	2	2
<i>PLXNA3</i>	2	2
<i>PPL</i>	2	2
<i>PPP1R13L</i>	2	2
<i>RNF123</i>	2	2
<i>RPE65</i>	2	2
<i>RPUSD2</i>	2	2
<i>SLC16A4</i>	2	2
<i>SLC18A1</i>	2	2
<i>SPHKAP</i>	2	2
<i>STON1- GTF2A1L</i>	2	2
<i>TULP4</i>	2	2
<i>VPS13D</i>	2	2
<i>ABCB5</i>	2	2
<i>ABCC3</i>	2	2
<i>AKAP8</i>	2	2
<i>ALPK3</i>	2	2
<i>ARL6</i>	2	2
<i>ATBF1</i>	2	2
<i>ATP10A</i>	2	2
<i>ATXN1</i>	2	2
<i>BSN</i>	2	2
<i>CILP</i>	2	2
<i>CNTNAP2</i>	2	2
<i>DNAH3</i>	2	2
<i>DNAH5</i>	2	2
<i>DOCK8</i>	2	2
<i>EPHB4</i>	2	2
<i>FAM83H</i>	2	2
<i>FAT2</i>	2	2
<i>FCGBP</i>	2	2
<i>FGD6</i>	2	2
<i>GCN1L1</i>	2	2
<i>GPNMB</i>	2	2

<i>GPR177</i>	2	2
<i>GSS</i>	2	2
<i>HMCN1</i>	2	2
<i>HSPA4L</i>	2	2
<i>KIAA1109</i>	2	2
<i>MAP2</i>	2	2
<i>MARVELD2</i>	2	2
<i>MX1</i>	2	2
<i>MYOM2</i>	2	2
<i>NR1I2</i>	2	2
<i>OR4B1</i>	2	2
<i>PLCB3</i>	2	2
<i>PLEKHA6</i>	2	2
<i>PLXNA2</i>	2	2
<i>PTPRD</i>	2	2
<i>SALL4</i>	2	2
<i>SH3PXD2B</i>	2	2
<i>SILV</i>	2	2
<i>SPG11</i>	2	2
<i>STOX1</i>	2	2
<i>TRAK2</i>	2	2
<i>TXNDC3</i>	2	2
<i>XKR8</i>	2	2
<i>ZBED4</i>	2	2
<i>ZNF592</i>	2	2
