

Schizophrenia (SCZ) is one of the most heritable human diseases, with heritability (or disease risk due to genetic factors) estimates ranging from 0.6 to 0.8 (1). However, individual genetic loci account for a relatively small portion of the phenotypic variance in SCZ (2). Therefore, increasing the sample size and application of refined statistical methods are required for identification of genes affecting disease risk in genome wide association studies (GWAS). Here, we apply our recently developed covariate-modulated local false discovery rate (cmfdr) method (3) to the current Psychiatric Genomic Consortium (PGC) SCZ sample (4).

Consistent with the findings from the PGC paper (4), we found gene loci spanning across multiple biological themes including the major histocompatibility complex, axonal guidance, mitochondrial energy metabolism, and others. Of particular interest is the presence of a large number of genes coding for elements of different neurotransmitter systems – glutamatergic, dopaminergic, serotonergic, GABAergic, cholinergic, opioid, purinergic – and ion channels for all four major ions determining the membrane potential: Na⁺, K⁺, Ca²⁺, and Cl⁻. This begs the question of whether these hits reflect independent mechanisms, or are tied together through common biological pathways and functions.

Evidence for coupling across many of these molecules has previously been demonstrated by Paul Greengard and collaborators in the neostriatum, following the discovery of the protein named DARPP-32 and its role as a convergence node for integration of “slow” and “fast” neurotransmission (5). Motivated by this concept, we have examined the gene loci identified by our analysis for the presence of putative elements of this “neurotransmitter integration network” (Fig. 1).

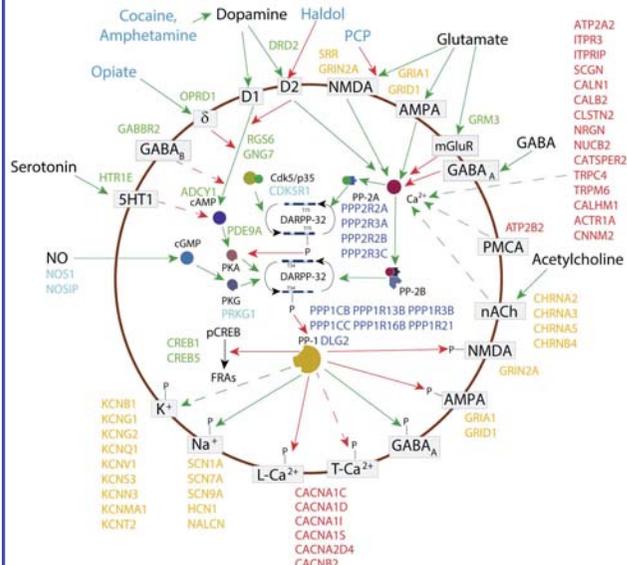


Fig. 1. Overlap of the present results with Greengard's neurotransmission integration scheme. Only a subset of the identified genes is shown. Red arrows indicate inhibition; green arrow indicates stimulation. Dashed arrows indicate "known function, but not experimentally proven". Genes are color-coded according to the categories in Table 1. Adapted from (5).

- 1 Cardno, A. G. et al. Arch Gen Psychiatry (1999).
- 2 Lee, S. H. et al. Nature genetics (2012).
- 3 Schork, A. J. et al. PLoS genetics (2013).
- 4 Schizophrenia Working Group of the Psychiatric Genomics Consortium, Nature (2014).
- 5 Greengard, P. Science (2001).

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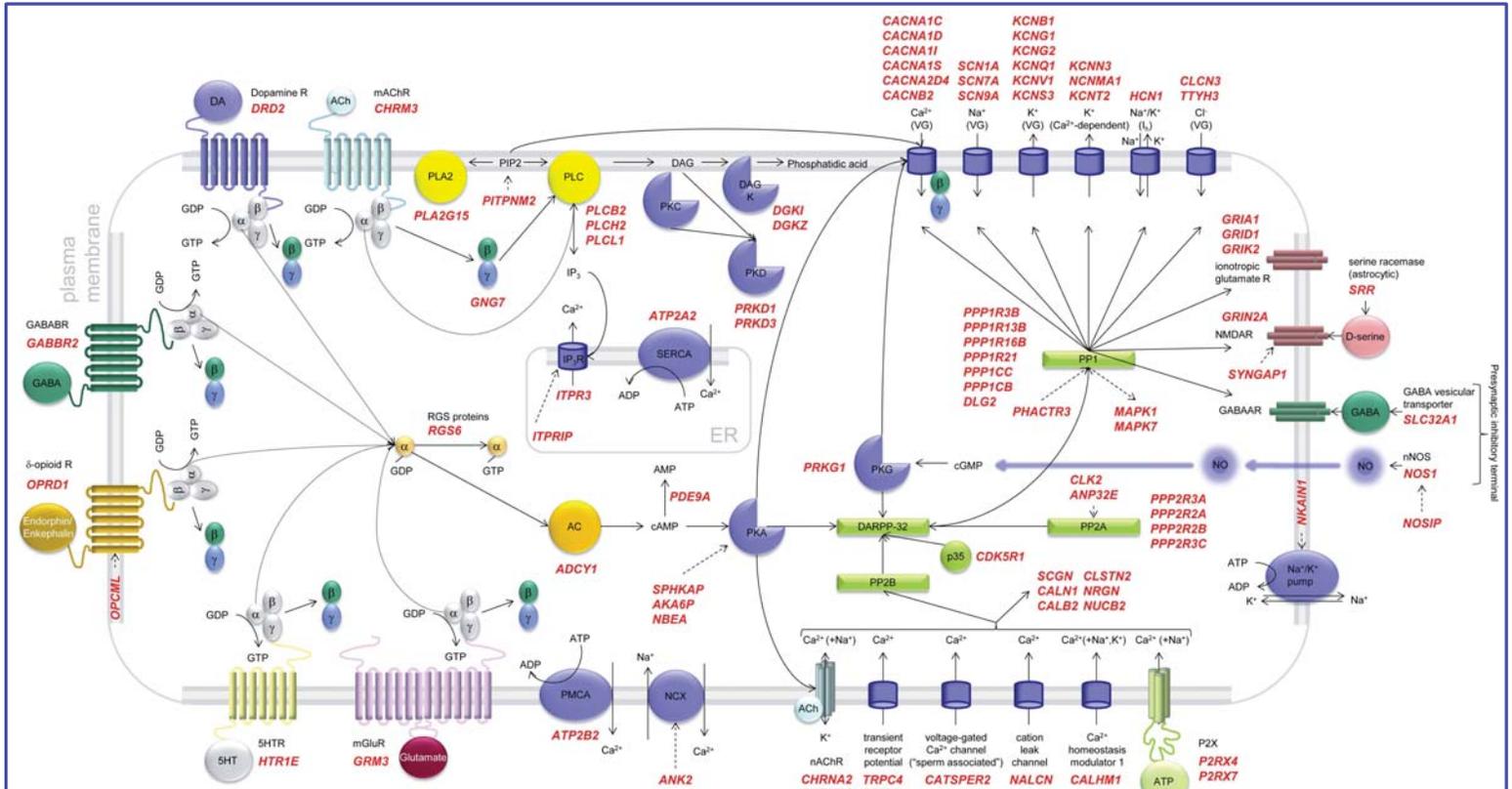


Fig. 2. Expanded version of Greengard's neurotransmission integration scheme shown in Fig. 1. The genes listed in Table 1 are shown in red. The b-arrestins/GRK pathway is not illustrated.

Candidate gene name	Genomic location	Description of the candidate gene	Candidate gene name	Genomic location	Description of the candidate gene	Candidate gene name	Genomic location	Description of the candidate gene
CACNA1C	12p13.3	VG Ca ²⁺ channel, I type, α1C	CHRNA2	2q24.3	cholinergic receptor, nicotinic, α2	ANKK1	10q24.3	ankyrin 1, cytoplasmic domain
CACNA1D	3p14.3	VG Ca ²⁺ channel, I type, α1D	CHRNA3	2q24.3	cholinergic receptor, nicotinic, α3	ANKK2	10q24.3	ankyrin 2, cytoplasmic domain
CACNA1E	22q13.1	VG Ca ²⁺ channel, I type, α1E	CHRNA4	11p15.5	cholinergic receptor, nicotinic, α4	ANKK3	10q24.3	ankyrin 3, cytoplasmic domain
CACNA1F	1q32	VG Ca ²⁺ channel, I type, α1F	CHRNA5	15q24	cholinergic receptor, nicotinic, α5	ANKK4	10q24.3	ankyrin 4, cytoplasmic domain
CACNA1G	12p13.33	VG Ca ²⁺ channel, α2β1.4	CHRNA6	15q24	cholinergic receptor, nicotinic, α6	ANKK5	10q24.3	ankyrin 5, cytoplasmic domain
CACNA1H	10p12	VG Ca ²⁺ channel, β2	CHRNA7	15q24	cholinergic receptor, nicotinic, α7	ANKK6	10q24.3	ankyrin 6, cytoplasmic domain
ATP2A2	12q24.11	ER Ca ²⁺ -ATPase (SERCA)	CHRNA8	15q24	cholinergic receptor, nicotinic, α8	ANKK7	10q24.3	ankyrin 7, cytoplasmic domain
ATP2B2	3p21.3	plasma membrane Ca ²⁺ -ATPase (PMCA)	CHRNA9	15q24	cholinergic receptor, nicotinic, α9	ANKK8	10q24.3	ankyrin 8, cytoplasmic domain
ITPR3	6p21.31	IP3 receptor	CHRNA10	15q24	cholinergic receptor, nicotinic, α10	ANKK9	10q24.3	ankyrin 9, cytoplasmic domain
ITPRIP	10q25.1	IP3 receptor interacting protein	CHRNA11	15q24	cholinergic receptor, nicotinic, α11	ANKK10	10q24.3	ankyrin 10, cytoplasmic domain
ITPRIP2	12q24.11	IP3 receptor interacting protein 2	CHRNA12	15q24	cholinergic receptor, nicotinic, α12	ANKK11	10q24.3	ankyrin 11, cytoplasmic domain
ITPRIP3	12q24.11	IP3 receptor interacting protein 3	CHRNA13	15q24	cholinergic receptor, nicotinic, α13	ANKK12	10q24.3	ankyrin 12, cytoplasmic domain
ITPRIP4	12q24.11	IP3 receptor interacting protein 4	CHRNA14	15q24	cholinergic receptor, nicotinic, α14	ANKK13	10q24.3	ankyrin 13, cytoplasmic domain
ITPRIP5	12q24.11	IP3 receptor interacting protein 5	CHRNA15	15q24	cholinergic receptor, nicotinic, α15	ANKK14	10q24.3	ankyrin 14, cytoplasmic domain
ITPRIP6	12q24.11	IP3 receptor interacting protein 6	CHRNA16	15q24	cholinergic receptor, nicotinic, α16	ANKK15	10q24.3	ankyrin 15, cytoplasmic domain
ITPRIP7	12q24.11	IP3 receptor interacting protein 7	CHRNA17	15q24	cholinergic receptor, nicotinic, α17	ANKK16	10q24.3	ankyrin 16, cytoplasmic domain
ITPRIP8	12q24.11	IP3 receptor interacting protein 8	CHRNA18	15q24	cholinergic receptor, nicotinic, α18	ANKK17	10q24.3	ankyrin 17, cytoplasmic domain
ITPRIP9	12q24.11	IP3 receptor interacting protein 9	CHRNA19	15q24	cholinergic receptor, nicotinic, α19	ANKK18	10q24.3	ankyrin 18, cytoplasmic domain
ITPRIP10	12q24.11	IP3 receptor interacting protein 10	CHRNA20	15q24	cholinergic receptor, nicotinic, α20	ANKK19	10q24.3	ankyrin 19, cytoplasmic domain
ITPRIP11	12q24.11	IP3 receptor interacting protein 11	CHRNA21	15q24	cholinergic receptor, nicotinic, α21	ANKK20	10q24.3	ankyrin 20, cytoplasmic domain
ITPRIP12	12q24.11	IP3 receptor interacting protein 12	CHRNA22	15q24	cholinergic receptor, nicotinic, α22	ANKK21	10q24.3	ankyrin 21, cytoplasmic domain
ITPRIP13	12q24.11	IP3 receptor interacting protein 13	CHRNA23	15q24	cholinergic receptor, nicotinic, α23	ANKK22	10q24.3	ankyrin 22, cytoplasmic domain
ITPRIP14	12q24.11	IP3 receptor interacting protein 14	CHRNA24	15q24	cholinergic receptor, nicotinic, α24	ANKK23	10q24.3	ankyrin 23, cytoplasmic domain
ITPRIP15	12q24.11	IP3 receptor interacting protein 15	CHRNA25	15q24	cholinergic receptor, nicotinic, α25	ANKK24	10q24.3	ankyrin 24, cytoplasmic domain
ITPRIP16	12q24.11	IP3 receptor interacting protein 16	CHRNA26	15q24	cholinergic receptor, nicotinic, α26	ANKK25	10q24.3	ankyrin 25, cytoplasmic domain
ITPRIP17	12q24.11	IP3 receptor interacting protein 17	CHRNA27	15q24	cholinergic receptor, nicotinic, α27	ANKK26	10q24.3	ankyrin 26, cytoplasmic domain
ITPRIP18	12q24.11	IP3 receptor interacting protein 18	CHRNA28	15q24	cholinergic receptor, nicotinic, α28	ANKK27	10q24.3	ankyrin 27, cytoplasmic domain
ITPRIP19	12q24.11	IP3 receptor interacting protein 19	CHRNA29	15q24	cholinergic receptor, nicotinic, α29	ANKK28	10q24.3	ankyrin 28, cytoplasmic domain
ITPRIP20	12q24.11	IP3 receptor interacting protein 20	CHRNA30	15q24	cholinergic receptor, nicotinic, α30	ANKK29	10q24.3	ankyrin 29, cytoplasmic domain
ITPRIP21	12q24.11	IP3 receptor interacting protein 21	CHRNA31	15q24	cholinergic receptor, nicotinic, α31	ANKK30	10q24.3	ankyrin 30, cytoplasmic domain
ITPRIP22	12q24.11	IP3 receptor interacting protein 22	CHRNA32	15q24	cholinergic receptor, nicotinic, α32	ANKK31	10q24.3	ankyrin 31, cytoplasmic domain
ITPRIP23	12q24.11	IP3 receptor interacting protein 23	CHRNA33	15q24	cholinergic receptor, nicotinic, α33	ANKK32	10q24.3	ankyrin 32, cytoplasmic domain
ITPRIP24	12q24.11	IP3 receptor interacting protein 24	CHRNA34	15q24	cholinergic receptor, nicotinic, α34	ANKK33	10q24.3	ankyrin 33, cytoplasmic domain
ITPRIP25	12q24.11	IP3 receptor interacting protein 25	CHRNA35	15q24	cholinergic receptor, nicotinic, α35	ANKK34	10q24.3	ankyrin 34, cytoplasmic domain
ITPRIP26	12q24.11	IP3 receptor interacting protein 26	CHRNA36	15q24	cholinergic receptor, nicotinic, α36	ANKK35	10q24.3	ankyrin 35, cytoplasmic domain
ITPRIP27	12q24.11	IP3 receptor interacting protein 27	CHRNA37	15q24	cholinergic receptor, nicotinic, α37	ANKK36	10q24.3	ankyrin 36, cytoplasmic domain
ITPRIP28	12q24.11	IP3 receptor interacting protein 28	CHRNA38	15q24	cholinergic receptor, nicotinic, α38	ANKK37	10q24.3	ankyrin 37, cytoplasmic domain
ITPRIP29	12q24.11	IP3 receptor interacting protein 29	CHRNA39	15q24	cholinergic receptor, nicotinic, α39	ANKK38	10q24.3	ankyrin 38, cytoplasmic domain
ITPRIP30	12q24.11	IP3 receptor interacting protein 30	CHRNA40	15q24	cholinergic receptor, nicotinic, α40	ANKK39	10q24.3	ankyrin 39, cytoplasmic domain
ITPRIP31	12q24.11	IP3 receptor interacting protein 31	CHRNA41	15q24	cholinergic receptor, nicotinic, α41	ANKK40	10q24.3	ankyrin 40, cytoplasmic domain
ITPRIP32	12q24.11	IP3 receptor interacting protein 32	CHRNA42	15q24	cholinergic receptor, nicotinic, α42	ANKK41	10q24.3	ankyrin 41, cytoplasmic domain
ITPRIP33	12q24.11	IP3 receptor interacting protein 33	CHRNA43	15q24	cholinergic receptor, nicotinic, α43	ANKK42	10q24.3	ankyrin 42, cytoplasmic domain
ITPRIP34	12q24.11	IP3 receptor interacting protein 34	CHRNA44	15q24	cholinergic receptor, nicotinic, α44	ANKK43	10q24.3	ankyrin 43, cytoplasmic domain
ITPRIP35	12q24.11	IP3 receptor interacting protein 35	CHRNA45	15q24	cholinergic receptor, nicotinic, α45	ANKK44	10q24.3	ankyrin 44, cytoplasmic domain
ITPRIP36	12q24.11	IP3 receptor interacting protein 36	CHRNA46	15q24	cholinergic receptor, nicotinic, α46	ANKK45	10q24.3	ankyrin 45, cytoplasmic domain
ITPRIP37	12q24.11	IP3 receptor interacting protein 37	CHRNA47	15q24	cholinergic receptor, nicotinic, α47	ANKK46	10q24.3	ankyrin 46, cytoplasmic domain
ITPRIP38	12q24.11	IP3 receptor interacting protein 38	CHRNA48	15q24	cholinergic receptor, nicotinic, α48	ANKK47	10q24.3	ankyrin 47, cytoplasmic domain
ITPRIP39	12q24.11	IP3 receptor interacting protein 39	CHRNA49	15q24	cholinergic receptor, nicotinic, α49	ANKK48	10q24.3	ankyrin 48, cytoplasmic domain
ITPRIP40	12q24.11	IP3 receptor interacting protein 40	CHRNA50	15q24	cholinergic receptor, nicotinic, α50	ANKK49	10q24.3	ankyrin 49, cytoplasmic domain
ITPRIP41	12q24.11	IP3 receptor interacting protein 41	CHRNA51	15q24	cholinergic receptor, nicotinic, α51	ANKK50	10q24.3	ankyrin 50, cytoplasmic domain
ITPRIP42	12q24.11	IP3 receptor interacting protein 42	CHRNA52	15q24	cholinergic receptor, nicotinic, α52	ANKK51	10q24.3	ankyrin 51, cytoplasmic domain
ITPRIP43	12q24.11	IP3 receptor interacting protein 43	CHRNA53	15q24	cholinergic receptor, nicotinic, α53	ANKK52	10q24.3	ankyrin 52, cytoplasmic domain
ITPRIP44	12q24.11	IP3 receptor interacting protein 44	CHRNA54	15q24	cholinergic receptor, nicotinic, α54	ANKK53	10q24.3	ankyrin 53, cytoplasmic domain
ITPRIP45	12q24.11	IP3 receptor interacting protein 45	CHRNA55	15q24	cholinergic receptor, nicotinic, α55	ANKK54	10q24.3	ankyrin 54, cytoplasmic domain
ITPRIP46	12q24.11	IP3 receptor interacting protein 46	CHRNA56	15q24	cholinergic receptor, nicotinic, α56	ANKK55	10q24.3	ankyrin 55, cytoplasmic domain
ITPRIP47	12q24.11	IP3 receptor interacting protein 47	CHRNA57	15q24	cholinergic receptor, nicotinic, α57	ANKK56	10q24.3	ankyrin 56, cytoplasmic domain
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ITPRIP49	12q24.11	IP3 receptor interacting protein 49	CHRNA59	15q24	cholinergic receptor, nicotinic, α59	ANKK58	10q24.3	ankyrin 58, cytoplasmic domain
ITPRIP50	12q24.11	IP3 receptor interacting protein 50	CHRNA60	15q24	cholinergic receptor, nicotinic, α60	ANKK59	10q24.3	ankyrin 59, cytoplasmic domain
ITPRIP51	12q24.11	IP3 receptor interacting protein 51	CHRNA61	15q24	cholinergic receptor, nicotinic, α61	ANKK60	10q24.3	ankyrin 60, cytoplasmic domain
ITPRIP52	12q24.11	IP3 receptor interacting protein 52	CHRNA62	15q24	cholinergic receptor, nicotinic, α62	ANKK61	10q24.3	ankyrin 61, cytoplasmic domain
ITPRIP53	12q24.11	IP3 receptor interacting protein 53	CHRNA63	15q24	cholinergic receptor, nicotinic, α63	ANKK62	10q24.3	ankyrin 62, cytoplasmic domain
ITPRIP54	12q24.11	IP3 receptor interacting protein 54	CHRNA64	15q24	cholinergic receptor, nicotinic, α64	ANKK63	10q24.3	ankyrin 63, cytoplasmic domain
ITPRIP55	12q24.11	IP3 receptor interacting protein 55	CHRNA65	15q24	cholinergic receptor, nicotinic, α65	ANKK64	10q24.3	ankyrin 64, cytoplasmic domain
ITPRIP56	12q24.11	IP3 receptor interacting protein 56	CHRNA66	15q24	cholinergic receptor, nicotinic, α66	ANKK65	10q24.3	ankyrin 65, cytoplasmic domain
ITPRIP57	12q24.11	IP3 receptor interacting protein 57	CHRNA67	15q24	cholinergic receptor, nicotinic, α67	ANKK66	10q24.3	ankyrin 66, cytoplasmic domain
ITPRIP58	12q24.11	IP3 receptor interacting protein 58	CHRNA68	15q24	cholinergic receptor, nicotinic, α68	ANKK67	10q24.3	ankyrin 67, cytoplasmic domain
ITPRIP59	12q24.11	IP3 receptor interacting protein 59	CHRNA69	15q24	cholinergic receptor, nicotinic, α69	ANKK68	10q24.3	ankyrin 68, cytoplasmic domain
ITPRIP60	12q24.11	IP3 receptor interacting protein 60	CHRNA70	15q24	cholinergic receptor, nicotinic, α70	ANKK69	10q24.3	ankyrin 69, cytoplasmic domain
ITPRIP61	12q24.11	IP3 receptor interacting protein 61	CHRNA71	15q24	cholinergic receptor, nicotinic, α71	ANKK70	10q24.3	ankyrin 70, cytoplasmic domain
ITPRIP62	12q24.11	IP3 receptor interacting protein 62	CHRNA72	15q24	cholinergic receptor, nicotinic, α72	ANKK71	10q24.3	ankyrin 71, cytoplasmic domain
ITPRIP63	12q24.11	IP3 receptor interacting protein 63	CHRNA73	15q24	cholinergic receptor, nicotinic, α73	ANKK72	10q24.3	ankyrin 72, cytoplasmic domain
ITPRIP64	12q24.11	IP3 receptor interacting protein 64	CHRNA74	15q24	cholinergic receptor, nicotinic, α74	ANKK73	10q24.3	ankyrin 73, cytoplasmic domain
ITPRIP65	12q24.11	IP3 receptor interacting protein 65	CHRNA75	15q24	cholinergic receptor, nicotinic, α75	ANKK74	10q24.3	ankyrin 74, cytoplasmic domain
ITPRIP66	12q24.11	IP3 receptor interacting protein 66	CHRNA76	15q24	cholinergic receptor, nicotinic, α76	ANKK75	10q24.3	ankyrin 75, cytoplasmic domain
ITPRIP67	12q24.11	IP3 receptor interacting protein 67	CHRNA77	15q24	cholinergic receptor, nicotinic, α77	ANKK76	10q24.3	ankyrin 76, cytoplasmic domain
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ITPRIP71	12q24.11	IP3 receptor interacting protein 71	CHRNA81	15q24	cholinergic receptor, nicotinic, α81	ANKK80	10q24.3	ankyrin 80, cytoplasmic domain
ITPRIP72	12q24.11	IP3 receptor interacting protein 72	CHRNA82	15q24	cholinergic receptor, nicotinic, α82	ANKK81	10q24.3	ankyrin 81, cytoplasmic domain
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