Supplementary methods

Interactome

The Menche et al.(1) interactome used in our main analyses includes the following sources of protein interaction databases: *i*) regulatory interactions derived from transcription factors binding to regulatory elements, *ii*) binary interactions from several yeast two-hybrid systematic high-throughput PPIs (2) and literature-curated data sets, *iii*) literature-curated interactions derived mostly from low-throughput experiments, manually curated using IntAct, MINT, BioGRID and HPRD, *iv*) metabolic enzyme-coupled interactions (from KEGG and BIGG databases), *v*) protein complexes from the CORUm database, *vi*) kinase-substrate pairs from the PhoshositePlus database, *vii*) Signaling interactions from Vinayagam et al.(3).

The STRING database, used for comparisons, consists of both physical and functional interactions through co-expression or participation in the same pathway, as well as predicted associations using computational techniques. Here, A combined score (0-1) is calculated from several different channels of evidence: conserved neighborhood, gene fusion, phylogenetic co-occurrence, co-expression, database imports, large-scale experiments, and literature co-occurrence, with scores of 0.4 – 0.7 considered as medium, and >0.7 as high confidence interactions(4). An experimental data score >0 can also be based on putative homologs found to interact in other species. We used combined scores of 0.7 in the main analyses.

Network Localization with degree preservation as control analyses

As node degree (number of edges of a node) in the interactome is biased towards well studied genes, we performed analyses using a method where node degree is preserved when selecting random gene sets(5). In this method, nodes are swapped randomly with nodes of the same degree, which preserves node degree and topology. As there are few high-degree nodes (hubs) a binning approach is used in this method (n≥100 nodes in each bin). We used 1000 random repetitions to generate a random distribution, $P(d_s)$, for comparison with d_s for the disease.

As shortest path length only captures one aspect of how interconnected a node set is, we also examined network neighborhood overlap (e.g. Jaccard similarity), based on the method described in Novarino et al.(6), which measures the fraction of shared neighbors between every pair of genes in the set. The network neighborhood overlap was computed for the disease gene set, and compared with 1000 random samples with node degree preserved.

Gene-set enrichment analyses using MAGENTA

MAGENTA takes as input the p-values of all SNPs from a GWAS of the trait of interest and a gene set of interest, in this case the latest GWAS of schizophrenia from PGC and a list of antipsychotic drug target genes. The procedures consist of four main steps to generate a gene set enrichment p-value; 1) Mapping the SNPs from the GWAS onto pre-defined genes, 2) determining the most significant SNP within each gene in the genome, 3) correcting gene p-value for gene property, such as gene size and LD structure, and 4) testing whether corrected gene p-value of the gene set is enriched for high ranks more than those from randomly sampled gene sets of identical set size from the genome.

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Identification of candidate drugs for repurposing

To identify drugs with other indications that target schizophrenia risk genes not targeted by antipsychotics, we searched the list of genes with >2 steps from an antipsychotic drug (n=53) against the validated drug targets of 9591 marketed and experimental drugs in the latest release of the Drugbank database, Version 5 release of July 2017(7) (https://www.drugbank.ca). Xml files for individual drug cards were analyzed and validated drug targets were extracted. The list of drugs with at least one of the genes from the list was extracted. Results are presented in Supplementary Table 5.

Assessment of over- or under-enrichment of risk gene sets

To estimate the statistical significance of the observation that none of the 77 schizophrenia risk genes that were not part of the Menche et al. interactome were directly targeted by an antipsychotic drug target gene, we calculate the p-value for under- or over-enrichment based on the cumulative distribution function (CDF) of the hypergeometric distribution, and a total number of 19,000 genes in the human genome(8), leaving 5,540 genes as not included in the Menche et al. interactome(1). Of these, eight genes were also a drug target. Thus, the numbers used for enrichment calculations were as follows: population n=5,540, population success=8, sample n=77, sample success=0.

We also used the hypergeometric test to test for over- or under-enrichment of schizophrenia risk genes (sample n=251) being at 0 (n=4), 1 (n=27), 2 (n=167) and >2 (n=53) steps from an antipsychotic drug target gene compared to all genes in the interactome (population n=13,460) at 0 (n=80), 1 (n=1,133), 2 (n=8,724) and >2 (n=3,523) steps from an antipsychotic drug target.

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Supplementary results

STRING database

We also examined the number of edges between each schizophrenia risk gene and its closest connected drug target gene using the STRING database (**Supplementary Table 4**). This indicated overall consistency between the networks, even though the Menche et al. (1) interactome was generally more conservative than the most stringent STRING confidence threshold (i.e. larger total number of edges). It was of particular importance to see if genes identified as being less connected to drugs in the Menche et al. interactome (>2 steps) had identified connections to antipsychotic drug targets in STRING. At the higher confidence threshold (>0.7), *PPP1R16B* was the only gene with >2 edges to a drug in the Menche et al. interactome. *PPP1R16B* was connected to the drug target *GSK3B*, based on co-mention in PubMed articles and putative homologs found to interact in other species only. Thus, consistency was high across the two databases.

Schizophrenia gene networks were localized using degree preservation as control analyses
Control analyses using degree preservation and high-degree binning revealed similar results to the main analyses, i.e. significant localization of schizophrenia risk genes (Menche et al. interactome: mean $d_{schizophrenia}$=1.71, d_{random}=1.80, p=0.033. STRING database: mean $d_{schizophrenia}$=1.56, d_{random}=1.71, p=0.006).
Network neighborhood analyses showed a significantly higher fraction of shared neighbors between schizophrenia risk gene pairs compared with random gene sets (t=5.2, p=2.1 e-7).

Assessment of over- or under-enrichment of risk gene sets

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Test for under- or over- enrichment of schizophrenia risk genes based on number of steps from drug targets revealed a non-significant over-enrichment of risk genes 0-steps from an antipsychotic drug target (2.68 fold, p=0.06). No enrichment was seen for risk genes 1- and 2-steps from their closest antipsychotic drug target (1.28 folded over-enrichment, p=0.11, and 1.03 folded over-enrichment, p=0.31, respectively). Risk genes >2 steps from their closest antipsychotic drug target were significantly under-enriched (1.24 fold, p=0.04). These results support our findings of a drug-disease link through the interactome, and complement overrepresentation tests in Supplementary Table 4 where network topology was taken into account. Although underrepresented, risk genes >2 steps from a drug target may still have important functional role in the disease, and may be used to identify new targets for future drugs.

Relation between MHC genes and antipsychotic drugs

The MHC has been of special interest to the field because it has shown the strongest genetic association with schizophrenia. From the large number of genes in this region, we included *C4A* and *C4B*, because they were recently confirmed as schizophrenia risk genes (9). We found that both of these genes were located two steps from their closest connected drug target genes. Due to the high interest in these genes, we show their link to their closest antipsychotic drug targets in Supplementary Figure 2.

Supplementary references

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Supplementary Figures

Supplementary Figure 1. All schizophrenia risk genes with >2 steps/edges to an antipsychotic target (n=53), with their 1 step interactome neighbors (n=122). Edges of risk genes are shown as thick dark lines; edges between two interacting genes are shown as thin light lines. SCZ=schizophrenia.
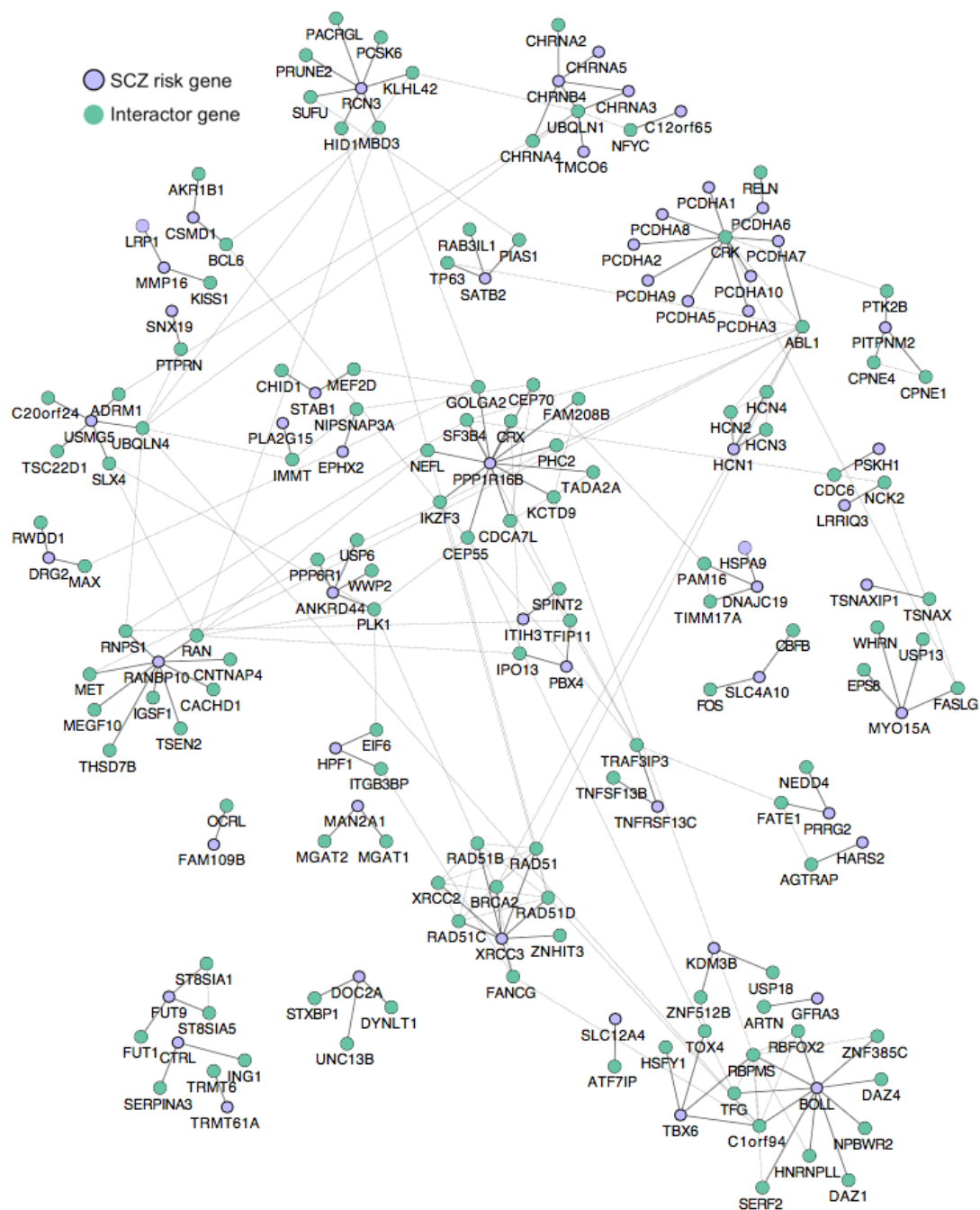
Supplementary Figure 2. Connection between *C4A* and *C4B*, representing association signals from the Major histocompatibility complex (MHC) region, and their closest antipsychotic drug targets. Both genes are 2 steps from their closest connected antipsychotic drug target, which is not an extreme event based on the hypergeometric distribution (p=0.44, population n=251, population success=167, sample n=2, sample success=2). SCZ=schizophrenia.
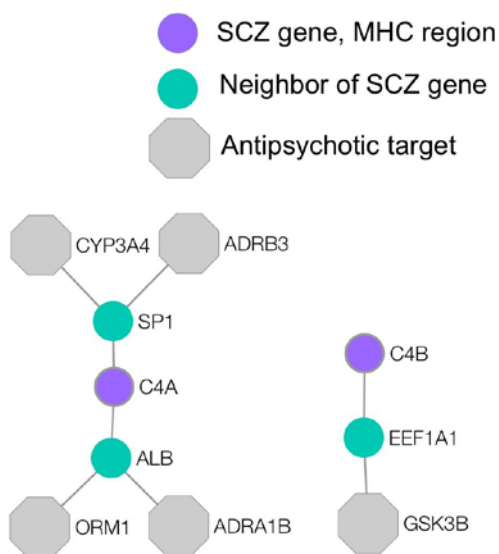
Supplementary Tables

Supplementary Table 1. Gene ontology enrichment results from ToppGene for: **a)** All schizophrenia risk genes (n=328), **b)** Interconnected risk genes; schizophrenia genes that are connected with at least one other LD independent schizophrenia risk gene (i.e. not from the same loci in the GWAS, n=79), **c)** schizophrenia risk genes belonging to the largest connected component (n=32).

Supplementary Table 2. a) All schizophrenia risk genes, together with their shortest

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number of steps to an antipsychotic drug target (0, 1, 2, or >2) in the Menche et al. interactome. Gene ontology enrichment results from ToppGene for schizophrenia risk genes **b)** =<1 step, **c)** 2 steps, and **d)** >2 steps from a drug target.

Supplementary Table 3. Number of edges between risk genes and antipsychotic drug targets in Menche et al. interactome and the STRING database, using combined score thresholds of 0.4 and 0.7.

Supplementary Table 4. Number of schizophrenia risk genes interconnected to other risk genes and within the largest connected component (i.e. a subsection of interconnected risk genes) by number of steps to antipsychotic drug target genes. Overrepresentation of risk genes close to drug targets was seen among both interconnected risk genes ($\chi^2(2)$ =32.455, p=9.0e-8) (a) and genes within the largest connected component (fishers exact test, p=0.00036) (b).

	Steps to drug target gene		
(a)	**≤1**	**2**	**>2**
Interconnected risk genes (n=79)	19 (61 %)	58 (35 %)	2 (4 %)
Risk genes not interconnected (n=172)	12 (39%)	109 (65%)	51 (96%)
All genes	31	167	53
(b)			
Largest connected component (n=32)	10 (32 %)	21 (13 %)	1 (2%)
Risk genes not within the largest connected component (n=219)	21 (68 %)	146 (87%)	52 (98%)
All genes	**31**	**167**	**53**

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Supplementary Table 5. Drugs from the DrugBank that directly target schizophrenia risk genes that are positioned >2 steps from an antipsychotic drug target in the Menche et al. interactome.

Name	ID	Target genes	Phase	Indications
Dextromethorphan		CHRNA2 CHRNA3 CHRNA4 CHRNA7 CHRNB2 CHRNB4 GRIN3A OPRD1 OPRK1 OPRM1 PGRMC1 SIGMAR1 SLC6A2 SLC6A4	approved	For treatment and relief of dry cough.
Galantamine	DB00674	ACHE BCHE CHRNA1 CHRNA10 CHRNA2 CHRNA3 CHRNA4 CHRNA5 CHRNA6 CHRNA7 CHRNA9 CHRNB1 CHRNB2 CHRNB3 CHRNB4 CHRND CHRNE CHRNG	approved	For the treatment of mild to moderate dementia of the Alzheimer's type. Has also been investigated in patients with mild cognitive impairment who did not meet the diagnostic criteria for Alzheimer's disease.
Levamisole	DB00848	ALPPL2 CHRNA3 lev-1 unc-29 unc-38 unc-63	vet_approved; withdrawn	For adjuvant treatment in combination with fluorouracil after surgical resection in patients with Dukes' stage C colon cancer. Also used to treat malignant melanoma and head/neck cancer.
Pentolinium	DB01090	CHRNA10	approved	Used to produce

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		CHRNA3 CHRNB4		controlled hypotension during surgical procedures and in hypertensive crises.
Bupropion	DB01156	CHRNA3 SLC6A2 SLC6A3	approved	For the treatment of depression and as aid to smoking cessation.
Levomethadyl Acetate	DB01227	CHRNA3 CHRNB4 OPRM1	approved	For the treatment and management of opiate dependence. It is sometimes used to treat severe pain in terminal patients.
Varenicline	DB01273	CHRNA3 CHRNA4 CHRNA6 CHRNA7	approved; investigational	For use as an aid in smoking cessation.
Cytisine	DB09028	CHRNA3 CHRNA4 CHRNA6 CHRNA7	approved; investigational	Indicated for use in smoking cessation.
Swainsonine	DB02034	MAN2A1	experimental	
2-Deoxy-2-Fluoro-Alpha-D-Mannosyl Fluoride	DB02318	MAN2A1	experimental	
Ghavamiol	DB02492	MAN2A1	experimental	
Kifunensine	DB02742	MAN1B1 MAN2A1 MSDC	experimental	
5-Fluoro-Beta-L-Gulosyl Fluoride	DB03008	MAN2A1	experimental	
5-Thio-a/B-D-Mannopyranosylamine	DB03414	MAN2A1	experimental	
1-deoxymannojirimycin	DB03955	MAN2A1	experimental	
(1R,2R,3R,4S,5R)-4-(BENZYLAMINO)-5-(METHYLTHIO)CYCLOPENTANE-1,2,3-TRIOL	DB06984	MAN2A1	experimental	
(1S,2S,3R,6R)-4-(hydroxymethyl)-6-(octylamino)cyclohex-4-ene-1,2,3-triol	DB08321	MAN2A1	experimental	

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Marimastat	DB00786	MMP1 MMP10 MMP11 MMP12 MMP13 MMP14 MMP15 MMP16 MMP17 MMP19 MMP2 MMP20 MMP21 MMP23A MMP24 MMP25 MMP26 MMP27 MMP28 MMP3 MMP7 MMP8 MMP9	approved; investigational	For the treatment of various cancers
Batimastat	DB03880	ADAM28 ADAMTS5 MMP12 MMP16 MMP8	experimental	
Potassium Chloride	DB00761	SLC12A1 SLC12A2 SLC12A4 SLC12A5 SLC12A6 SLC12A7	approved; withdrawn	For use as an electrolyte replenisher and in the treatment of hypokalemia.
Bumetanide	DB00887	CFTR SLC12A1 SLC12A2 SLC12A4 SLC12A5	approved	For the treatment of edema associated with congestive heart failure, hepatic and renal disease including the nephrotic syndrome.
N-Cyclohexyl-N'-(4-Iodophenyl)Urea	DB02029	EPHX2	experimental	
N-Cyclohexyl-N'-Decylurea	DB03677	EPHX2	experimental	
N-Cyclohexyl-N'-(Propyl)Phenyl Urea	DB04213	EPHX2	experimental	

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N-[(CYCLOHEXYLAMINO)CARBONYL]GLYCINE	DB08256	EPHX2	experimental
4-{[(CYCLOHEXYLAMINO)CARBONYL]AMINO}BUTANOIC ACID	DB08257	EPHX2	experimental
6-{[(CYCLOHEXYLAMINO)CARBONYL]AMINO}HEXANOIC ACID	DB08258	EPHX2	experimental
7-{[(CYCLOHEXYLAMINO)CARBONYL]AMINO}HEPTANOIC ACID	DB08259	EPHX2	experimental

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