**SUPPLEMENTARY INFORMATION**

**Supplementary information S2 | Genetic associations with psychiatric disorders with selected references**

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Locus symbol</th>
<th>Evidence*</th>
<th>Gene and variant function</th>
<th>Phenotypes implicated and evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong candidate genes</strong>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol dehydrogenase 2</td>
<td>ADH2</td>
<td>AMEL1-6</td>
<td>First step in alcohol degradation. Variants increase activity</td>
<td>Increased activity in ADH2 leads to unpleasant reaction and protection from alcoholism</td>
</tr>
<tr>
<td>Aldehyde Dehydrogenase 2</td>
<td>ALDH2</td>
<td>AMEL1,2,4,5,7</td>
<td>Enzyme breaks down acetaldehyde, an intermediate in alcohol metabolism. Null allele common in East-Asia</td>
<td>Individuals with little or no function experience “flushing” response when drinking alcohol and are thus protected from alcoholism</td>
</tr>
<tr>
<td>Catechol-O-methyl-transferase</td>
<td>COMT</td>
<td>AEFL9,12</td>
<td>Involved in degradation of neurotransmitters. Met allele 3 x less active than Val allele.</td>
<td>Maps to Velocardiofacial syndrome deletion. Association with cognitive processing replicated, also with pain threshold. Association with schizophrenia not confirmed</td>
</tr>
<tr>
<td>Dopamine receptor D4</td>
<td>DRD4</td>
<td>AEMF13-22</td>
<td>Receptor for dopamine. Length polymorphism (48 bp/16 aa) in C-terminus (intracellular loop).</td>
<td>7 repeat allele associated with attention deficit hyperactivity disorder (ADHD; meta analyses), contains many additional mutations in ADHD patients, and was selected for during evolution</td>
</tr>
<tr>
<td>γ aminobutyric acid (GABA) receptor alpha 2 subunit</td>
<td>GABRA2</td>
<td>AEML23,29</td>
<td>Subunit of receptor for inhibitory neurotransmitter GABA.</td>
<td>Under linkage peak for alcoholism and electrophysiological endophenotype. Haplotypes and SNPs associated with alcohol use disorders in several studies; some associations also with endophenotypes</td>
</tr>
<tr>
<td>Monoamine oxidase A</td>
<td>MAOA</td>
<td>AEFRZ10-42</td>
<td>Enzyme degrades serotonin. Rare null allele, and common functional promoter variants (2x, 3x, 4x 30 bp)</td>
<td>Family with null allele impulsive-aggressive. Mice replicate the aggression. Functional promoter variant associated with impulsive/antisocial behaviour in interaction with maltreatment.</td>
</tr>
<tr>
<td>Serotonin transporter</td>
<td>SLC6A4</td>
<td>AEFMZ43,52</td>
<td>Re-uptake of serotonin from synapse. S (short) promoter variant associated with decreased activity</td>
<td>s allele associated with increased neuroticism, depression symptoms in interaction with environmental factors (see Fig. 2), and amygdala processing in fMRI, and several other behavioural traits</td>
</tr>
<tr>
<td><strong>Possible candidate genes</strong>5</td>
<td></td>
<td></td>
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<tr>
<td>Brain-derived neurotrophic factor</td>
<td>BDNF</td>
<td>AEFZ33-63</td>
<td>Neuronal growth and survival. Met instead of Val in position 66 in precursor protein is dysfunctional.</td>
<td>Associated with eating disorders, and Met66Val mouse model shows increased anxiety. Associations with neuroticism and bipolar disorder were not confirmed</td>
</tr>
<tr>
<td>L- type Voltage dependent calcium Channel</td>
<td>CACNA1C</td>
<td>GR44-66</td>
<td>Channel mediates influx of Calcium.</td>
<td>Missense mutation (G406R) in Timothy syndrome (includes autism). Implicated as genome-wide significant in a combined analysis of three GWA datasets of bipolar disorder (BPD).</td>
</tr>
<tr>
<td>Contactin-associated like protein 2</td>
<td>CNTNAP2</td>
<td>AGLR67-70</td>
<td>Neurexin family. Clusters voltage-gated K channels at node of Ranvier.</td>
<td>SNPs in this gene in a linkage region associated with autism and mutations are found in rare autism cases</td>
</tr>
<tr>
<td>FK506-binding protein</td>
<td>FKBP5</td>
<td>AE71-78</td>
<td>Adaptive intracellular response to stress (hypothalamic-pituitary axis)</td>
<td>SNPs associated with anti-depressant response, major depressive syndrome (MDD), possibly BPD. Also post-traumatic stress disorder G x E interaction</td>
</tr>
<tr>
<td>Neuroligin 1, 3 and 4</td>
<td>NLG1, 3, 4</td>
<td>AFR70,79-84</td>
<td>Synaptic transmembrane proteins involved in cell adhesion; interact with neurexins.</td>
<td>Deletions in several cases linked to autism, several recent association studies</td>
</tr>
</tbody>
</table>

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### SUPPLEMENTARY INFORMATION

<table>
<thead>
<tr>
<th>Controversial candidate genes</th>
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<tr>
<td><strong>D-amino acid oxidase activator (G72).</strong></td>
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<tr>
<td>Neurexin</td>
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<tr>
<td>Purinergic receptor P2X, ligand-gated ion channel 7</td>
</tr>
<tr>
<td>Regulator of G-protein signalling 4</td>
</tr>
<tr>
<td>Tryptophan hydroxylase2</td>
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<tr>
<td>Wolfram syndrome gene</td>
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</tbody>
</table>

| Neurexin | NRXN1 | **AR**<sup>76,79,82,85-87</sup> | Neuronal cell-cell interaction; implicated in synapse formation. | Patients with balanced translocation break. One association. |
| Purinergic receptor P2X, ligand-gated ion channel 7 | P2RX7 | **ALF**<sup>57,76,88-97</sup> | CNS expressed ligand-gated metabotropic 7 transmembrane calcium channel | In linked 12q24 region. Different alleles associated with risk for BPD, MDD, anxiety; some of these studies are large. |
| Regulator of G-protein signalling 4 | RGS4 | **AL**<sup>98-110</sup> | Accelerates GTPase activities of certain G protein alpha-subunits. | Decreased expression in schizophrenia (SZ) post-mortem brains. In SZ-linkage region; SNP associated with SZ. |
| Tryptophan hydroxylase2 | TPH2 | **AL**<sup>111-121</sup> | Brain form of rate-limiting enzyme for serotonin synthesis | Reported association with impulsivity and suicidality, ADHD, MDD and BP. |
| Wolfram syndrome gene | WFS1 | **AFR**<sup>122-137</sup> | Transmembrane channel in endoplasmic reticulum; role in calcium homeostasis | Recessive null alleles associated with Wolfram syndrome with psychiatric illness. Heterozygotes are at increased risk of mental illness. H611R allele may be associated with suicidality. |

### Strong evidence is indicated when at least one of the phenotypes was confirmed by meta-analysis. Possible evidence is indicated when there is congruent evidence but not confirmed in larger or meta-analyses, or not enough time has passed for confirmation attempts. Controversial results are those with different alleles in different studies, in different populations, or contradictory results from meta-analyses. There are many more controversial results, but only those genes much discussed in the current literature are shown.
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*A: Association studies with psychiatric disorder in one or more studies; G: Association in comprehensive study or genome wide association study; E: Association with endophenotype; M: Meta-analysis confirms association; L: in linkage region; R: Mutation in this gene in Mendelian and/or rare disorder with related phenotype; F: Functional evidence for associated variant; Z: evidence from animal model.

References:
61. Sen, S. et al. A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. *Neuropsychopharmacology* 28, 397-401
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(2003).
92. Curtis, D. et al. Genome scan of pedigrees multiply affected with bipolar disorder provides further support for the presence of a susceptibility locus on chromosome 12q23-q24, and suggests the presence of additional loci on 1p and 1q. *Psychiatr Genet* 13, 77-84 (2003).
Li, D. & He, L. Association study between the dystrobrevin binding protein 1 gene (DTNBP1) and schizophrenia: a meta-analysis. *Schizophr Res* **96**, 112-8 (2007).


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