

Supplementary Material

The *NDE1* Genomic Locus Affects Treatment of Psychiatric Illness through Gene Expression Changes Related to MicroRNA-484

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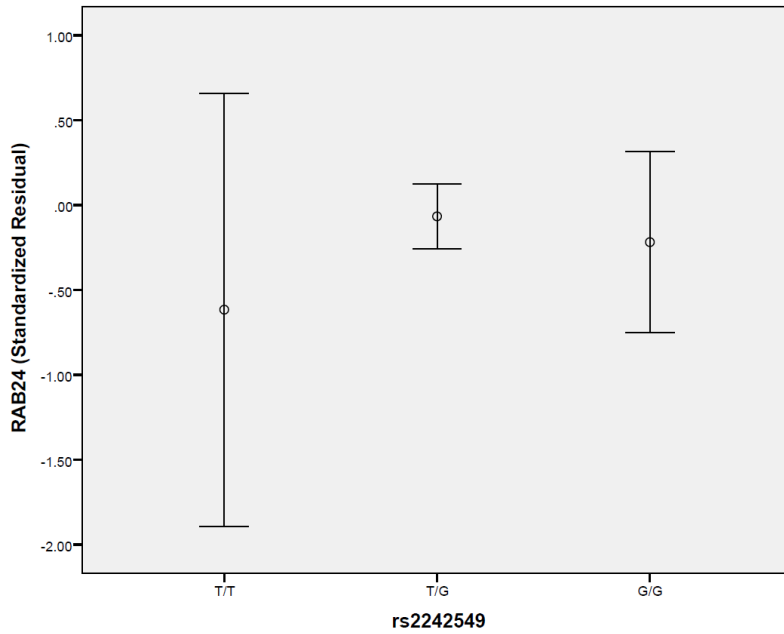
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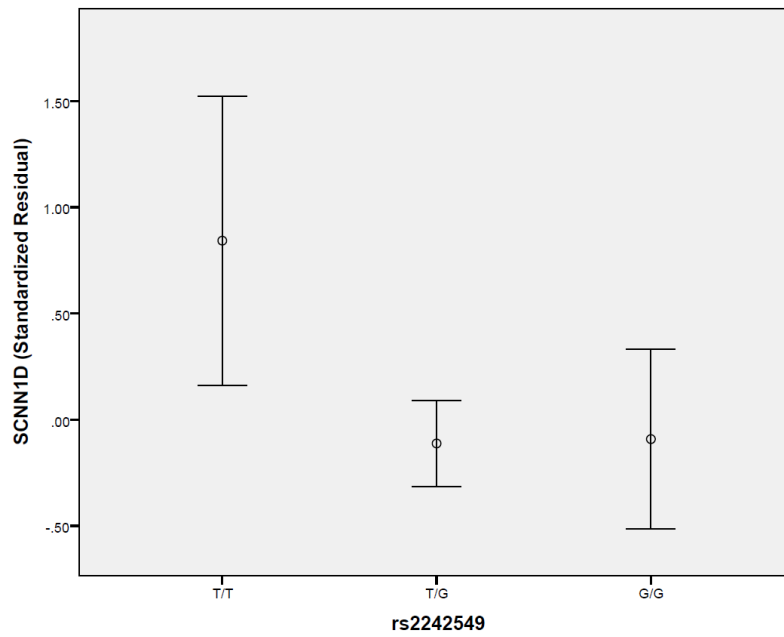
FIGURES

Figure S1: Graphical representation of the genetic effect of the *NDE1* rs2242549 SNP on the gene expression levels of a) the largest GTEx replicated positive effect *RAB24* (ILMN_2379718) b) the largest GTEx replicated negative effect *SCNN1D* (ILMN_1754757), c) the effect on *TRIOBP* (ILMN_1735788) which replicates from our previous study but not in the GTEx database, and d) the non-effect on *NDE1* (ILMN_1739805) which is highly significant in the GTEx database.

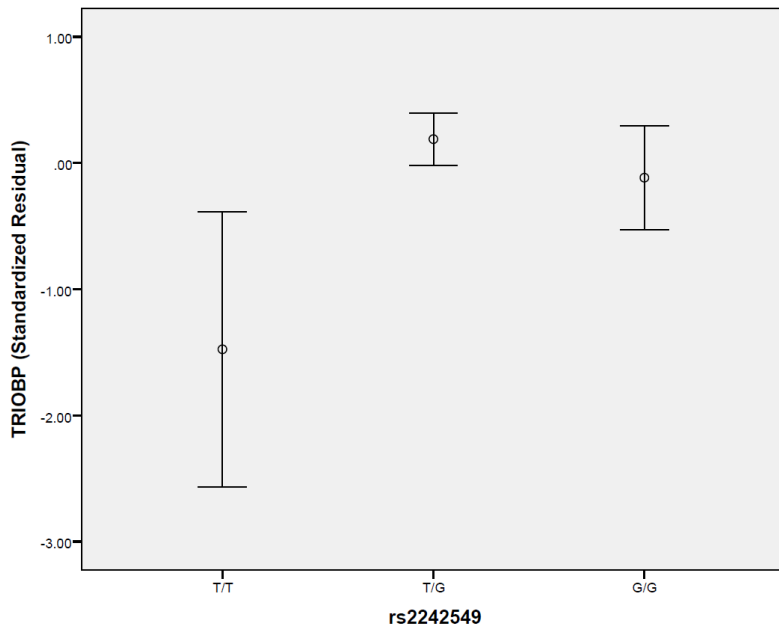
a)



b)



c)



d)

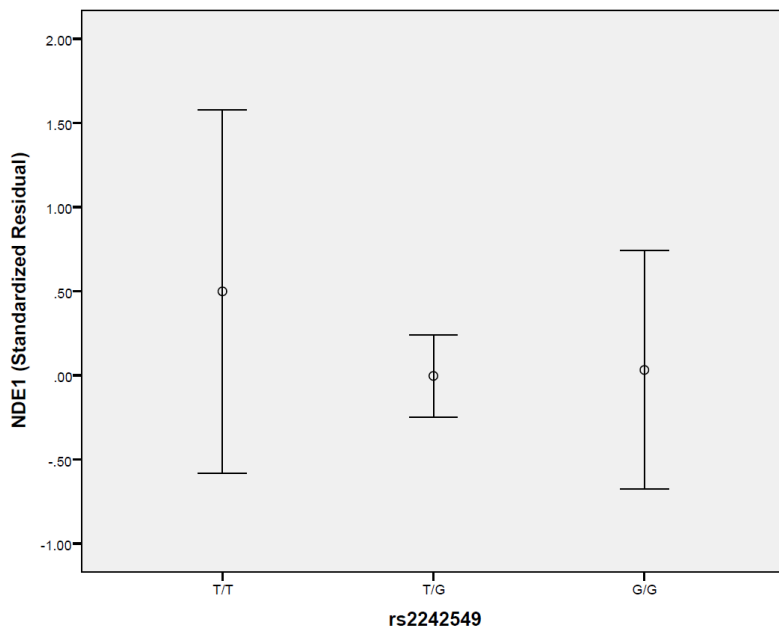
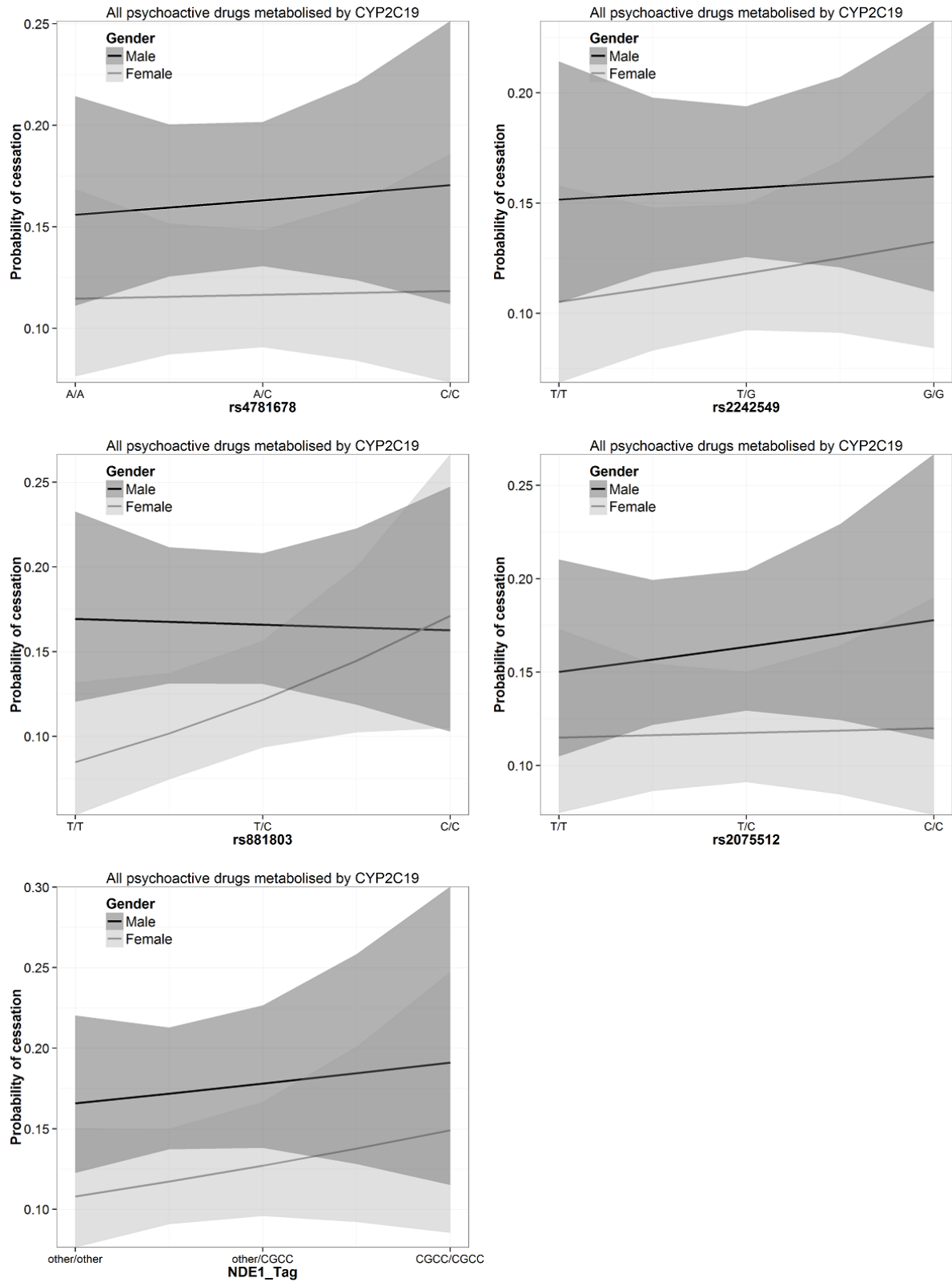


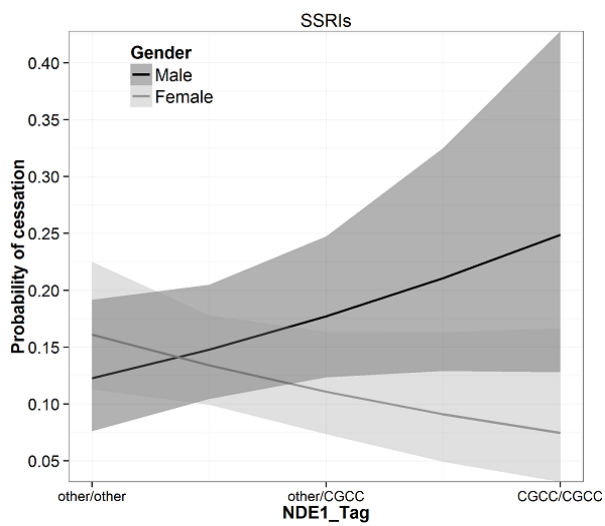
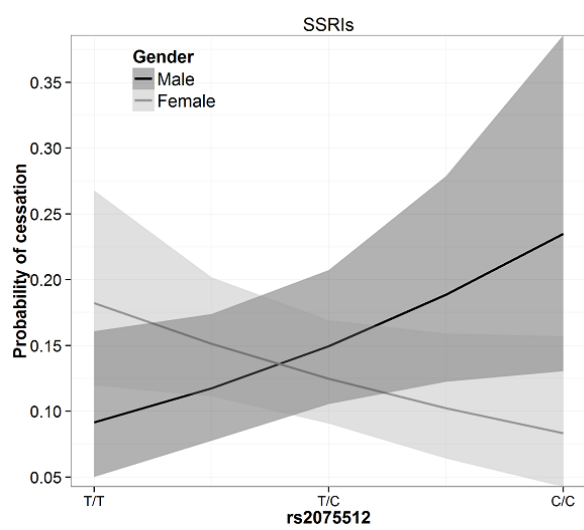
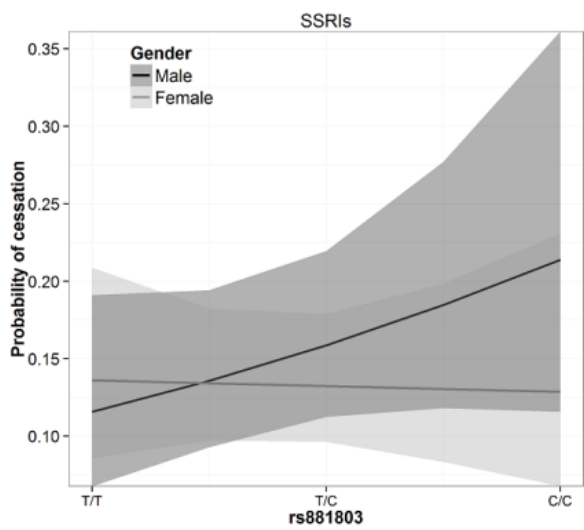
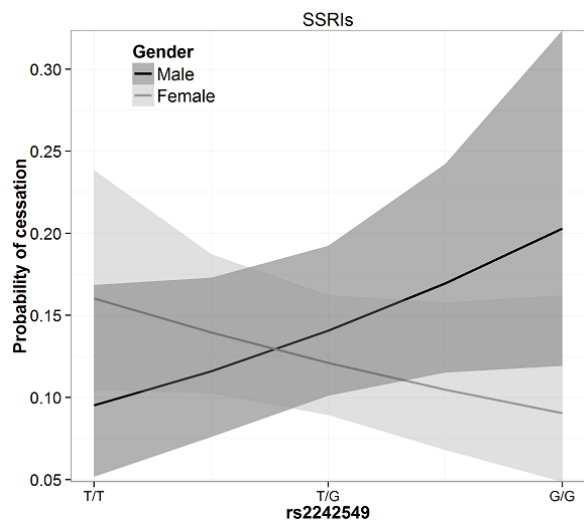
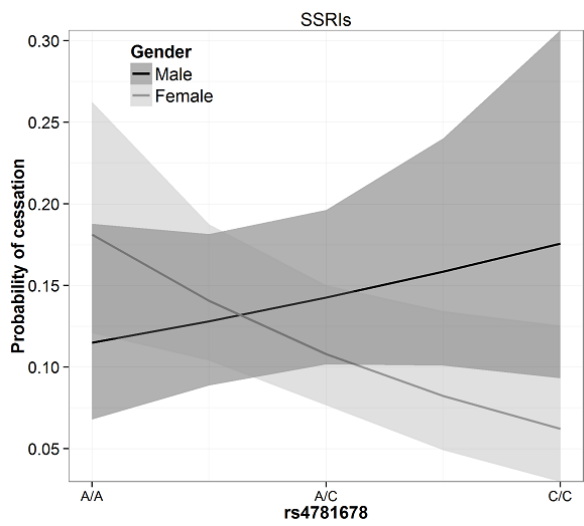
Figure S2:

Graphical representation of the gender by genetic interaction effect on medication groupings.

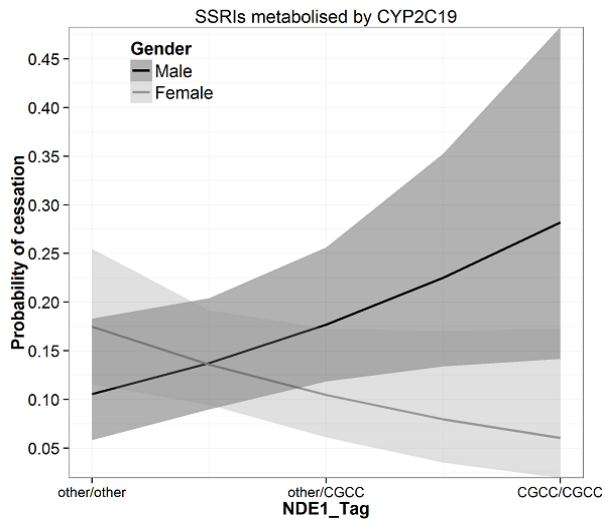
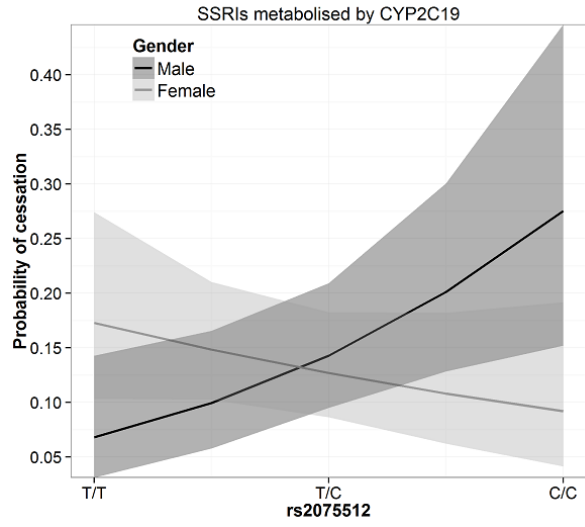
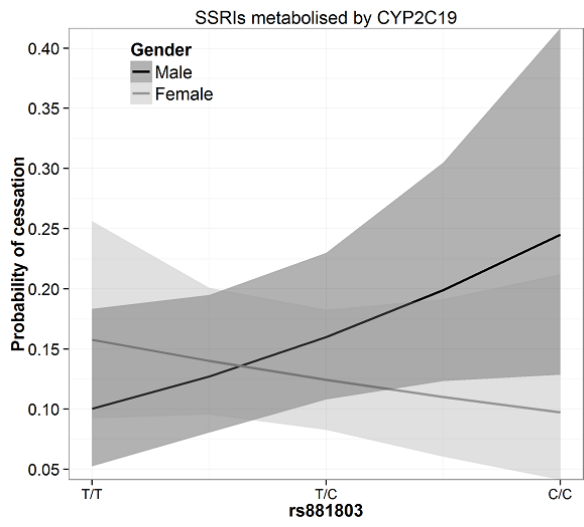
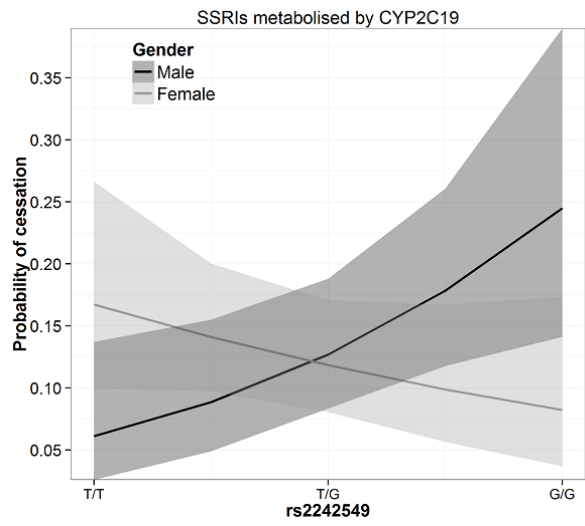
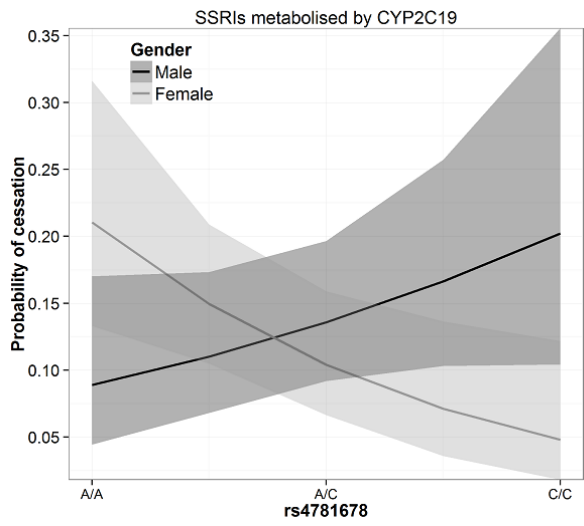
All psychoactive drugs metabolised by CYP2C19 (Amitriptyline, Citalopram, Diazepam, Escitalopram, Fluoxetine, Mianserin, Sertaline)



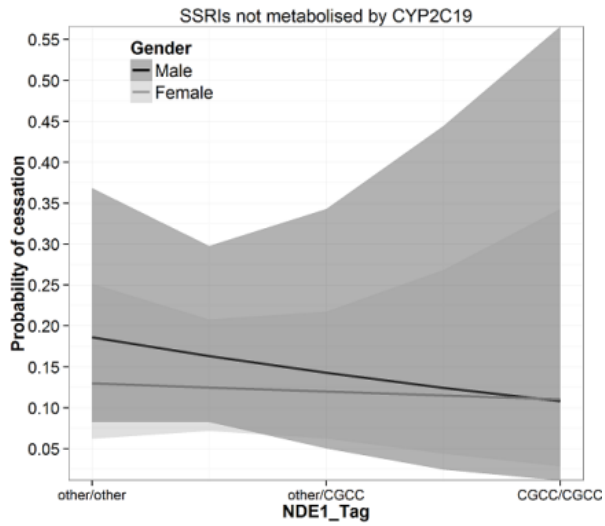
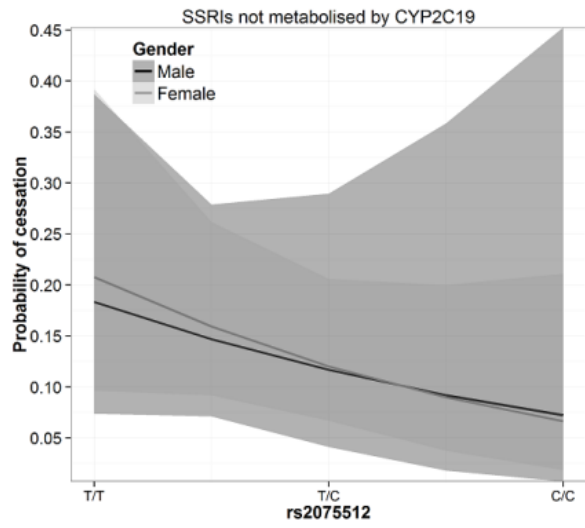
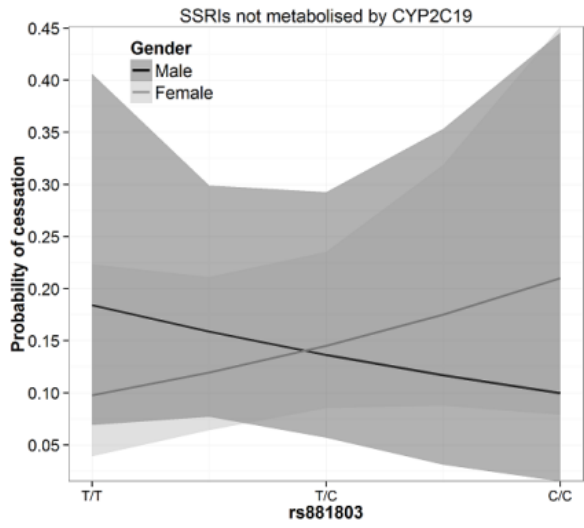
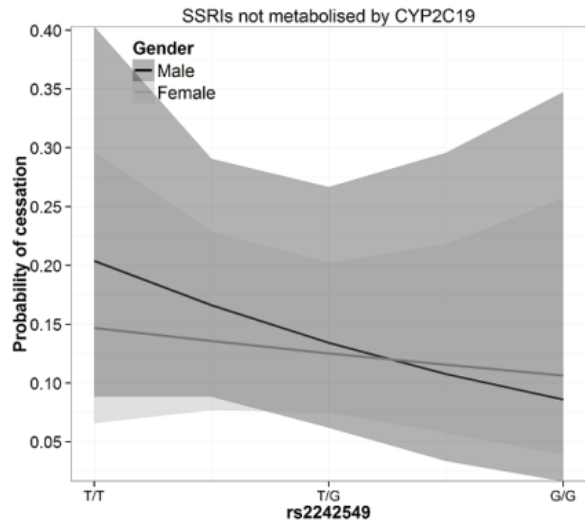
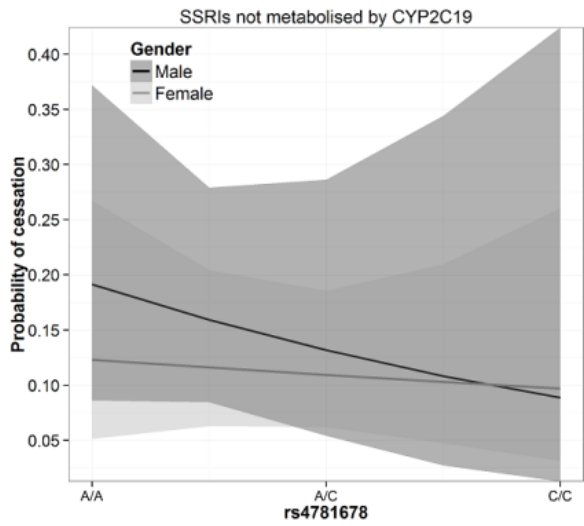
SSRIs (Citalopram, Escitalopram, Fluvoxamine, Fluoxetine, Paroxetine, Sertaline)



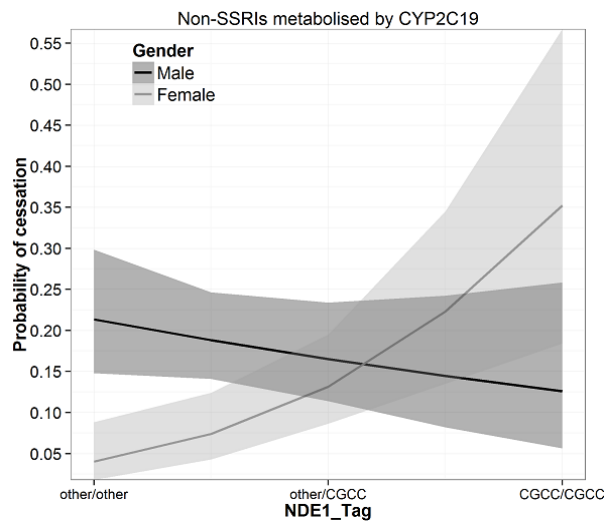
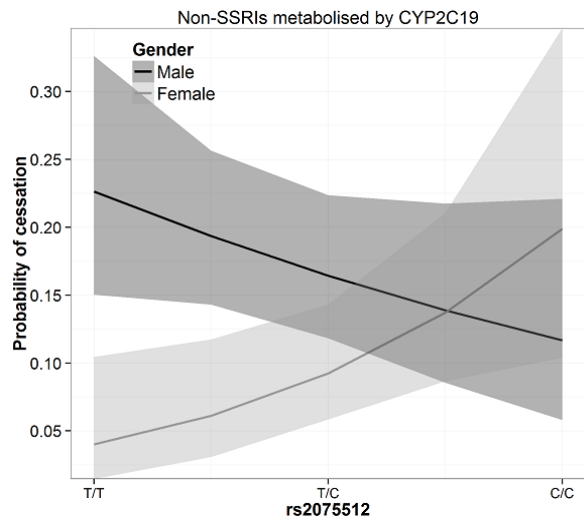
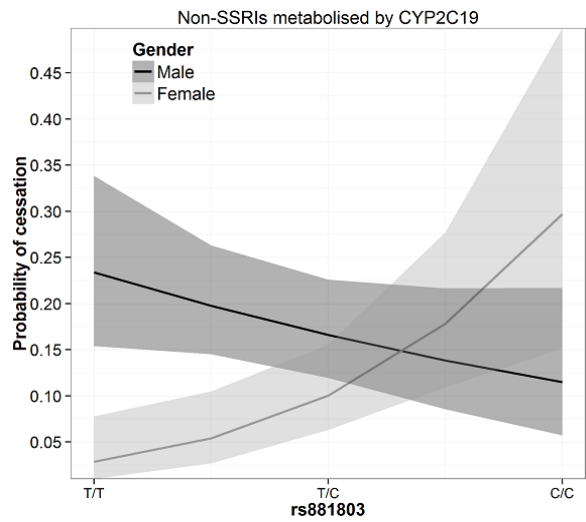
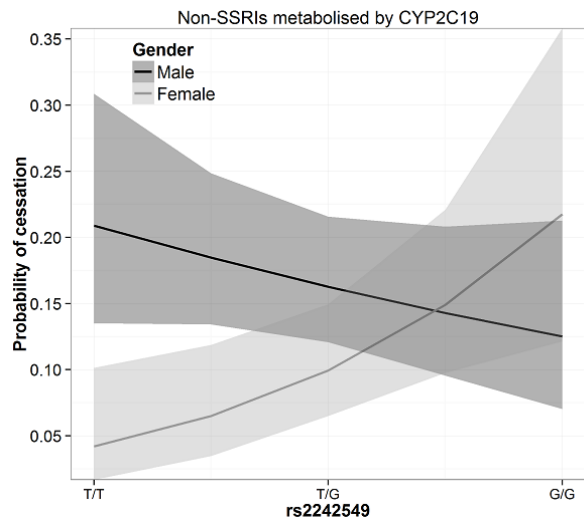
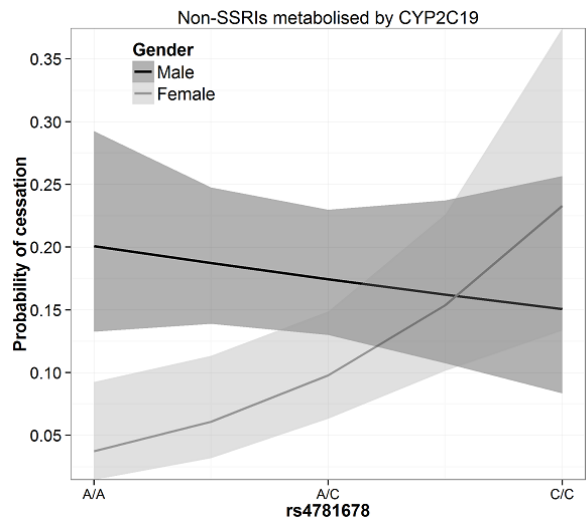
SSRIs metabolised by CYP2C19 (Citalopram, Escitalopram, Fluoxetine)



SSRIs not metabolised by CYP2C19 (*Fluvoxamine, Paroxetine, Sertaline*)



Non-SSRIs metabolised by CYP2C19 (Amitriptyline, Diazepam, Mianserin)



TABLES

Table S1: Results of the genome wide gene expression analysis and replication. Sheet 1 (Table S1 a) p-value <0.05) lists all probes that were significantly altered for each of the five DISC1 network variants tested at the p-value threshold of p<0.05. Table includes effect size (β), standard error, t value and p-value for the three cohorts tested. In addition it lists those genes replicated from our previous study, and the q-value for the study in the family cohort. Sheet 2 (Table S1 b) q-value <0.05) list all the same properties as in Sheet 1, but restricted to those probes that survived false discovery correction.

Separate Excel File: Table S1.xlsx

Table S2: Results of the association analysis between individual psychoactive medications and the variants studied. a) p-values for the additive model controlling for gender, b) p-values for the additive model in interaction with gender, c) Odds ratios (and 95% CI) for the interaction terms that were significant at the uncorrected p-value ≤ 0.05 level. P-values, and their respective ORs, below 0.0021 are below the Bonferroni correction threshold for the 24 medications tested.

a)

| | <i>DISC1</i> rs821616 | <i>NDE1</i> rs4781678 | <i>NDE1</i> rs2242549 | <i>NDE1</i> rs881803 | <i>NDE1</i> rs2075512 | <i>NDE1</i> Tag Haplotype | <i>PDE4B</i> rs7412571 |
|-----------------|--------------------------|--------------------------|--------------------------|-------------------------|--------------------------|------------------------------|---------------------------|
| Tramadol | 0.96 | 0.93 | 0.43 | 0.36 | 0.42 | 0.57 | 0.041 |
| Paracetamol | 0.64 | 0.53 | 0.79 | 0.45 | 0.82 | 0.35 | 0.081 |
| Biperiden | 0.77 | 0.37 | 0.54 | 0.24 | 0.62 | 0.20 | 0.78 |
| Chlorpromazine | 0.50 | 0.79 | 0.095 | 0.35 | 0.15 | 0.67 | 0.054 |
| Levomepromazine | 0.98 | 0.0009 | 0.056 | 0.019 | 0.0022 | 0.018 | 0.17 |
| Perphenazine | 0.78 | 0.54 | 0.33 | 0.52 | 0.71 | 0.48 | 0.19 |
| Thioridazine | 0.048 | 0.12 | 0.10 | 0.16 | 0.83 | 0.31 | 0.94 |
| Haloperidol | 0.82 | 0.69 | 0.66 | 0.68 | 0.64 | 0.98 | 0.061 |
| Chlorprothixene | 0.74 | 0.35 | 0.60 | 0.20 | 0.32 | 0.34 | 0.65 |
| Zuclopenthixol | 0.60 | 0.31 | 0.15 | 0.85 | 0.29 | 0.80 | 0.24 |
| Clozapine | 0.50 | 0.79 | 0.91 | 0.93 | 0.66 | 0.64 | 0.80 |
| Olanzapine | 0.78 | 0.38 | 0.10 | 0.27 | 0.23 | 0.64 | 0.32 |
| Quetiapine | 0.02 | 0.30 | 0.58 | 0.76 | 0.89 | 0.92 | 0.74 |
| Risperidone | 0.23 | 0.068 | 0.49 | 0.63 | 0.081 | 0.061 | 0.70 |
| Diazepam | 0.14 | 0.20 | 0.63 | 0.64 | 0.68 | 0.28 | 0.0083 |
| Oxazepam | 0.67 | 0.57 | 0.71 | 0.90 | 0.10 | 0.19 | 0.45 |
| Temazepam | 0.38 | 0.17 | 0.017 | 0.15 | 0.77 | 1.00 | 0.041 |
| Zopiclone | 0.43 | 0.66 | 0.57 | 0.83 | 0.98 | 0.67 | 0.85 |
| Amitriptyline | 0.68 | 0.057 | 0.29 | 0.27 | 0.52 | 0.034 | 0.75 |
| Fluoxetine | 0.56 | 0.18 | 0.88 | 0.89 | 0.67 | 0.66 | 0.35 |
| Citalopram | 0.79 | 0.86 | 0.48 | 0.55 | 0.44 | 0.81 | 0.94 |
| Sertraline | 0.98 | 0.72 | 0.35 | 0.43 | 0.32 | 0.92 | 0.77 |
| Mianserin | 0.90 | 0.16 | 0.42 | 0.36 | 0.16 | 0.34 | 0.68 |
| Mirtazapine | 0.64 | 0.20 | 0.35 | 0.69 | 0.29 | 0.65 | 0.81 |

p-values that are below the Bonferroni threshold are in bold.

b)

| | <i>DISC1</i> rs821616 | <i>NDE1</i> rs4781678 | <i>NDE1</i> rs2242549 | <i>NDE1</i> rs881803 | <i>NDE1</i> rs2075512 | <i>NDE1</i> Tag Haplotype |
|-----------------|--------------------------|--------------------------|--------------------------|-------------------------|--------------------------|------------------------------|
| Tramadol | 0.092 | 0.91 | 0.67 | 0.43 | 0.56 | 0.95 |
| Paracetamol | 0.14 | 0.48 | 0.66 | 0.33 | 0.74 | 0.43 |
| Biperiden | 0.53 | 0.21 | 0.35 | 0.41 | 0.53 | 0.43 |
| Chlorpromazine | 0.24 | 0.39 | 0.71 | 0.80 | 0.77 | 0.90 |
| Levomepromazine | 0.35 | 0.35 | 0.18 | 0.28 | 0.23 | 0.091 |
| Perphenazine | 0.18 | 0.67 | 0.41 | 0.37 | 0.83 | 0.44 |
| Thioridazine | 0.87 | 0.67 | 0.56 | 0.21 | 0.25 | 0.37 |
| Haloperidol | 0.096 | 0.55 | 0.73 | 0.61 | 0.86 | 0.60 |
| Chlorprothixene | 0.40 | 0.14 | 0.029 | 0.036 | 0.29 | 0.35 |
| Zuclopendixol | 0.11 | 0.91 | 0.92 | 0.14 | 1.00 | na |
| Clozapine | 0.83 | 0.051 | 0.67 | 0.93 | 0.048 | 0.75 |
| Olanzapine | 0.81 | 0.76 | 0.92 | 0.85 | 0.71 | 0.73 |
| Quetiapine | 0.87 | 0.87 | 0.63 | 0.23 | 0.75 | 0.75 |
| Risperidone | 0.29 | 0.067 | 0.022 | 0.27 | 0.17 | 0.64 |
| Diazepam | 0.02 | 0.009 | 0.007 | 0.0015 | 0.0078 | 0.0016 |
| Oxazepam | 0.04 | 0.49 | 0.16 | 0.66 | 0.26 | 0.65 |
| Temazepam | 0.12 | 0.50 | 0.91 | 0.51 | 0.86 | 0.69 |
| Zopiclone | 0.60 | 0.099 | 0.031 | 0.005 | 0.46 | 0.11 |
| Amitriptyline | 0.47 | 0.96 | 0.71 | 0.31 | 0.076 | 0.82 |
| Fluoxetine | 0.27 | 0.21 | 0.49 | 0.51 | 0.23 | 0.031 |
| Citalopram | 0.36 | 0.0042 | 0.0013 | 0.055 | 0.0023 | 0.026 |
| Sertraline | 0.92 | 0.94 | 0.47 | 0.19 | 0.37 | 0.80 |
| Mianserin | 0.56 | 0.055 | 0.019 | 0.0023 | 0.0058 | 0.0023 |
| Mirtazapine | 0.64 | 0.46 | 0.46 | 0.82 | 0.34 | 0.55 |

p-values that are below the Bonferroni threshold are in bold.

na = instances where, despite the frequency cut-offs enforced, not enough data points were available for statistical analysis.

Genotype cut-off minor homozygote frequency ≥ 0.05 ; Drug usage frequency cut-off = a medication has been used for 3 months or less ≥ 15 times.

c)

| | <i>DISC1</i> rs821616 | <i>NDE1</i> rs4781678 | <i>NDE1</i> rs2242549 | <i>NDE1</i> rs881803 | <i>NDE1</i> rs2075512 | <i>NDE1</i> Tag Haplotype |
|-----------------|--------------------------|--------------------------|-----------------------------------|------------------------------------|--------------------------|------------------------------------|
| Chlorprothixene | - | - | 9.21 (1.26-67.33) | 4.94 (1.11-22.05) | - | - |
| Clozapine | - | - | - | - | 3.35 (1.01-11.09) | - |
| Risperidone | - | - | 0.35 (0.14 - 0.86) | - | - | - |
| Diazepam | 3.67 (1.23-10.97) | 4.28 (1.44-12.74) | 4.28 (1.49-12.31) | 6.20 (2.02-19.09) | 5.14 (1.54-17.17) | 6.13 (1.99-18.85) |
| Oxazepam | 0.26 (0.07-0.94) | - | - | - | - | - |
| Zopiclone | - | - | 4.42 (1.15-17.03) | 6.07 (1.72-21.42) | - | - |
| Fluoxetine | - | - | - | - | - | 0.13 (0.02-0.84) |
| Citalopram | - | 0.22 (0.08-0.62) | 0.21 (0.08-0.54) | - | 0.21 (0.07-0.57) | 0.33 (0.12-0.88) |
| Mianserin | - | - | 7.22 (1.38-37.00) | 37.32 (3.62-384.18) | 21.78 (2.45-194.05) | 115.91 (5.42-2476.98) |

Odds ratios that are below the Bonferroni threshold are in bold.

Table S3: Drug names used in this article, their corresponding ATC code and classification, and their main metabolising enzyme(s)

| | ATC Code | Use | Class | Metabolising Enzyme(s)¹ |
|---------------------------------|-----------------|-----------------------------------|--|---|
| Tramadol | N02AX02 | Opioids | Other | CYP2D6, CYP3A4 |
| Paracetamol | N02BE01 | Other analgesics and antipyretics | Anilides | CYP2E1, CYP2A6, CYP3A4, CYP1A2 |
| Biperiden | N04AA02 | Anticholinergic agents | Tertiary amines | |
| Chlorpromazine | N05AA01 | Antipsychotics | Phenothiazines with aliphatic side-chain | CYP2D6 |
| Levomepromazine | N05AA02 | Antipsychotics | Phenothiazines with aliphatic side-chain | CYP2D6 |
| Perphenazine | N05AB03 | Antipsychotics | Phenothiazines with piperazine structure | CYP2D6 |
| Thioridazine | N05AC02 | Antipsychotics | Phenothiazines with piperidine structure | CYP2D6 |
| Haloperidol | N05AD01 | Antipsychotics | Butyrophenone derivatives | CYP2D6, CYP3A4, CYP3A5, CYP3A7, CYP1A2 |
| Chlorprothixene | N05AF03 | Antipsychotics | Thioxanthene Derivative | |
| Zuclopenthixol | N05AF05 | Antipsychotics | Thioxanthene Derivative | CYP2D6 |
| Clozapine | N05AH02 | Antipsychotics | Diazepines, oxazepines, thiazepines and oxepines | CYP1A2, CYP3A4 |
| Olanzapine | N05AH03 | Antipsychotics | Diazepines, oxazepines, thiazepines and oxepines | CYP1A2, CYP2D6 |
| Quetiapine | N05AH04 | Antipsychotics | Diazepines, oxazepines, thiazepines and oxepines | CYP3A4, CYP3A5, CYP3A7 |
| Risperidone | N05AX08 | Antipsychotics | Other | CYP2D6, CYP3A4 |
| Diazepam | N05BA01 | Anxiolytics | Benzodiazepine derivatives | CYP2C19 , CYP3A4 |
| Oxazepam | N05BA04 | Anxiolytics | Benzodiazepine derivatives | |
| Temazepam | N05CD07 | Hypnotics and Sedatives | Benzodiazepine derivatives | CYP3A4 |
| Zopiclone | N05CF01 | Hypnotics and Sedatives | Benzodiazepine related drugs | CYP3A4, CYP2C8 |
| Amitriptyline | N06AA09 | Antidepressants | Non-selective monoamine reuptake inhibitors | CYP2C19 , CYP2D6, CYP1A2, CYP3A4 |
| Fluoxetine | N06AB03 | Antidepressants | Selective serotonin reuptake inhibitors | CYP2C9, CYP2D6, CYP3A4, CYP2C19 |
| Citalopram | N06AB04 | Antidepressants | Selective serotonin reuptake inhibitors | CYP2C19 , CYP3A4, CYP2D6 |
| Paroxetine² | N06AB05 | Antidepressants | Selective serotonin reuptake inhibitors | CYP2D6 |
| Sertraline | N06AB06 | Antidepressants | Selective serotonin reuptake inhibitors | CYP2B6, CYP2C19³ , CYP2C9, CYP3A4 |
| Fluvoxamine² | N06AB08 | Antidepressants | Selective serotonin reuptake inhibitors | CYP2D6, CYP1A2 |
| Escitalopram² | N06AB10 | Antidepressants | Selective serotonin reuptake inhibitors | CYP2C19 , CYP3A4, CYP2D6 |
| Mianserin | N06AX03 | Antidepressants | Other | CYP3A4, CYP1A2, CYP2C19 , CYP2D6 |
| Mirtazapine | N06AX11 | Antidepressants | Other | CYP1A2, CYP2D6, CYP3A4 |

1 From KEGG Drug database (49), DrugBank (50), PharmaGKB (51), and CPIC Guidelines for SSRIs (52)

2 Medication was not used frequently enough during the 10 years collected here for inclusion in analysis of singular drugs. Drug usage frequency cut-off = a medication has been used for 3 months or less ≥ 15 times.

3 Expressly stated in the DrugBank database (50) that CYP2C19 only plays a minor role in the metabolism of sertraline. Therefore it has not been grouped with the others that are metabolised by CYP2C19.