

# Pharmacogenetics of antipsychotics – from metabolic effects to symptom response

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# Antipsychotic drugs – pharmacology and pharmacogenetics

Why do *antipsychotic drugs* differ in their beneficial and adverse effects? - pharmacology

Why do *individuals* differ in their response to antipsychotic drug effects? – pharmacogenetics

- Understanding pharmacology can provide candidates for pharmacogenetic analysis;
- Findings of genetic association can indicate pharmacological mechanisms.

# Pharmacogenetics of antipsychotic drug treatment

## Pharmacogenetics

- Relationship between pharmacology and pharmacogenetics
- Pharmacogenetics applied to a current problem
  - Antipsychotic drug-induced weight gain
- Pharmacogenetics of symptom response
  - Negative and positive symptoms
- The future: pharmacogenetics and prescribing practice

# Weight gain following antipsychotic treatment in first episode schizophrenia

In 87 Spanish patients receiving mainly risperidone or olanzapine:

- At 3 months BMI increased by 10.1%.
  - 7.4% risperidone, 13.1% olanzapine
- At 9 months BMI increased by 17.1%.
  - 13.7% risperidone, 21.1% olanzapine
- Increase in BMI for **olanzapine**-treated patients after 9 months varied between 0% and 74% of body weight.

*(Templeman et al, 2005 Pharmacogenetics 15, 195-200 and unpublished data)*

# 5-HT<sub>2C</sub> receptors, genes and weight gain

Antipsychotics with greatest effects on weight gain have highest relative affinities for 5-HT<sub>2C</sub> receptors<sup>1</sup>

Incidence of obesity and type 2 diabetes associated with genetic variation in promoter region of 5-HT<sub>2C</sub> receptor<sup>3</sup>

Mice with a 5-HT<sub>2C</sub>-receptor 'knockout' exhibit obesity<sup>2</sup>

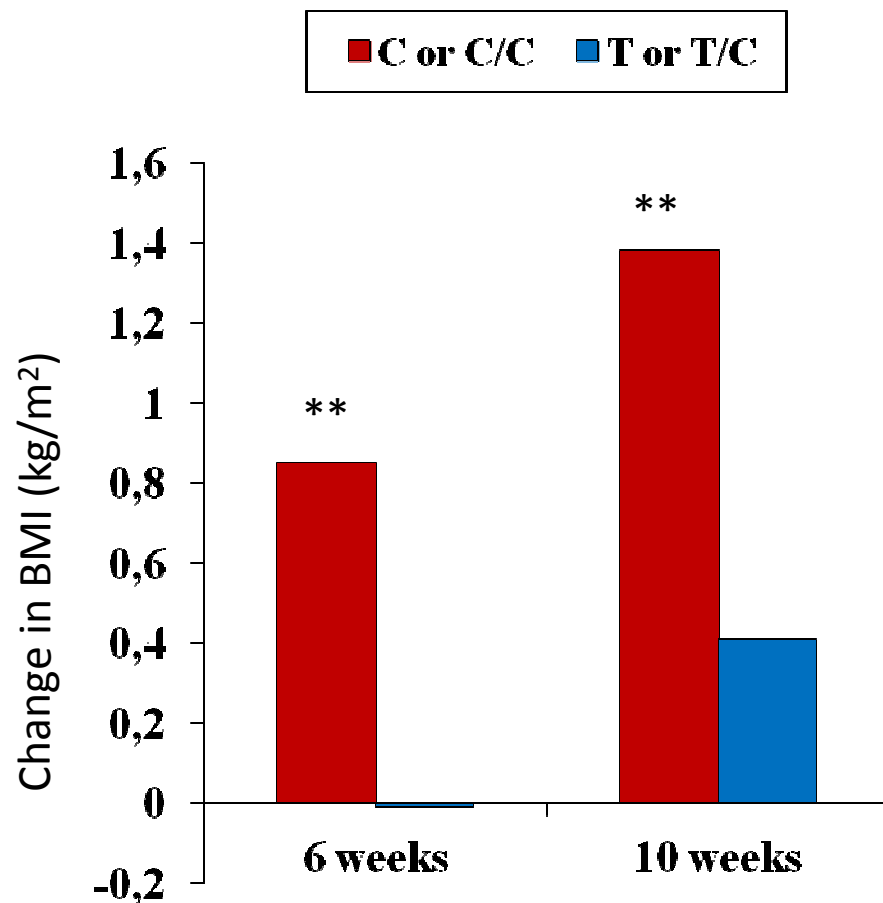
*Hypothesis: do 5-HT<sub>2C</sub> receptor polymorphisms predict antipsychotic-induced weight gain?*

1. Reynolds and Kirk Pharmacol Ther 2010; 125, 169-179;

2. Tecott et al. Nature 1995;374:542-546;

3. Yuan et al. Diabetologia 2000;43:373-376

# Association of 5-HT<sub>2C</sub> receptor gene variation with antipsychotic-induced weight gain



- The functional -759C/T polymorphism was assessed in a sample of 117 drug-naïve newly-diagnosed Chinese patients, and change in BMI monitored over 10 weeks treatment.
- A strong association of genotype with change in BMI was found, with the T allele being protective against the initial increase in BMI (\*\* $p < 0.001$ ). (*Reynolds et al, 2002*)
- The effect transcends individual drug treatment, occurring in patients receiving only chlorpromazine, risperidone or clozapine (*Reynolds et al, 2003*).

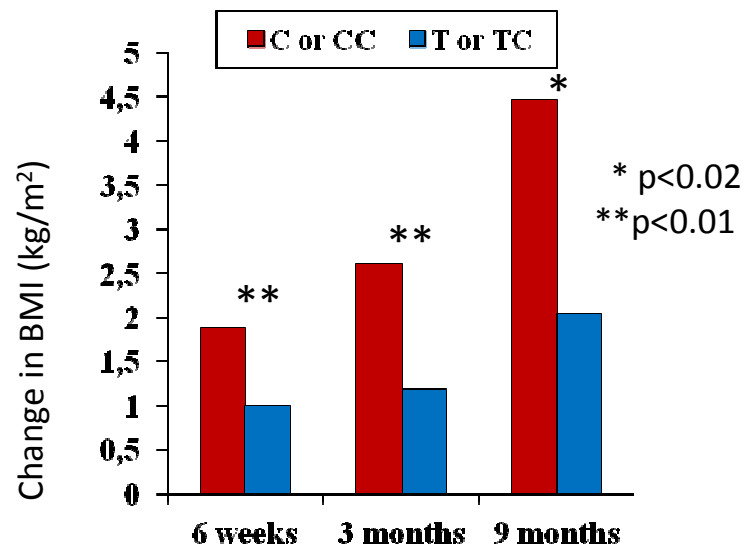
# Leptin promoter polymorphism and weight gain

- Mutations in the mouse and human leptin genes are associated with massive obesity (*Ohshiro et al, 2000*).
- A common promoter polymorphism (-2548A/G) influences gene expression and affects individual variation in tissue secretion of leptin (*Mammes et al, 1988; Hoffstedt et al, 2002*).

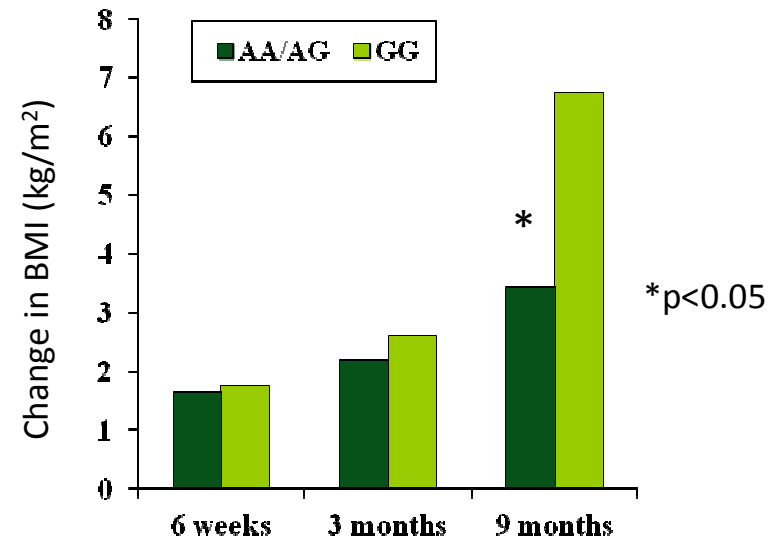
*Hypothesis: this polymorphism is associated with antipsychotic drug-induced weight gain in first-episode schizophrenia.*

# Association of 5-HT<sub>2C</sub> and leptin polymorphisms with drug-induced weight gain

First-episode Spanish patients with schizophrenia (initially n=72) were monitored for change in BMI after antipsychotic drug treatment.



**5-HT<sub>2C</sub> receptor -759 C/CC** genotype was significantly associated with the treatment-induced increase in BMI, with the effect remaining in the long term.



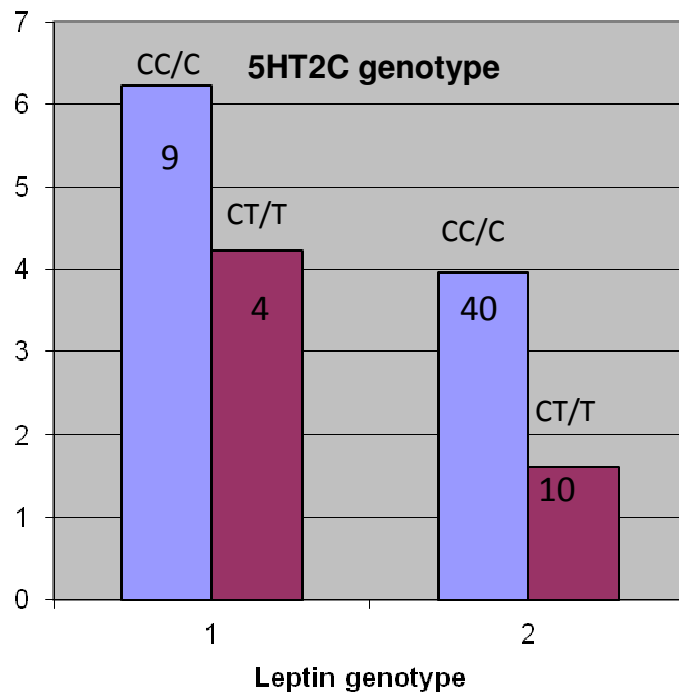
**Leptin -2548GG** genotype was significantly associated with increase in BMI in 9 months.

*(Templeman et al, 2005  
Pharmacogenetics 15, 195-200 )*



# Combined genotype effect on weight gain

## Increase in BMI following 9 months' antipsychotic drug treatment – effect of leptin and 5-HT2C receptor genotype



Genotypes account for 26% of variance at 3 months (with baseline weight as covariate), and 16% at 9 months.

Having leptin genotype 2 (AA or AG) and 5-HT2C receptor T allele provides relative protection from weight gain.

These data also identify a similar-sized “high risk” group at 9 months.

Both leptin and 5-HT2C receptor genotypes were associated with leptin concentrations pre-treatment.

*(Templeman et al 2005 Pharmacogenetics 15, 195-200)*

# The FTO gene is associated with obesity

Scienceexpress

Report

## A Common Variant in the *FTO* Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity

Timothy M. Frayling,<sup>1,2†</sup> Nicholas J. Timpson,<sup>3,4†</sup> Michael N. Weedon,<sup>1,2†</sup> Eleftheria Zeggini,<sup>2,5†</sup> Rachel M. Freathy,<sup>1,2</sup> Cecilia M. Lindgren,<sup>3,5</sup> John R. B. Perry,<sup>1,2</sup> Katherine S. Elliott,<sup>3</sup> Hana Lango,<sup>1,2</sup> Nigel W. Rayner,<sup>2,5</sup> Beverley Shields,<sup>2</sup> Lorna W. Harries,<sup>2</sup> Jeffrey C. Barrett,<sup>2</sup> Sian Ellard,<sup>2,6</sup> Christopher J. Groves,<sup>5</sup> Bridget Knight,<sup>2</sup> Ann-Marie Patch,<sup>2,6</sup> Andrew R. Ness,<sup>7</sup> Shah Ebrahim,<sup>8</sup> Debbie A. Lawlor,<sup>9</sup> Susan M. Ring,<sup>9</sup> Yoav Ben-Shlomo,<sup>9</sup> Marjo-Riitta Jarvelin,<sup>10,11</sup> Ulk Sovio,<sup>10,11</sup> Amanda J. Bennett,<sup>5</sup> David Melzer,<sup>1,12</sup> Luigi Ferrucci,<sup>13</sup> Ruth J. F. Loos,<sup>14</sup> Inês Barroso,<sup>15</sup> Nicholas J. Wareham,<sup>14</sup> Fredrik Karpe,<sup>5</sup> Katharine R. Owen,<sup>5</sup> Lon R. Cardon,<sup>2</sup> Mark Walker,<sup>16</sup> Graham A. Hitman,<sup>17</sup> Colin N. A. Palmer,<sup>18</sup> Alex S. F. Doney,<sup>19</sup> Andrew D. Morris,<sup>19</sup> George Davey-Smith,<sup>4</sup> The Wellcome Trust Case Control Consortium,<sup>20</sup> Andrew T. Hattersley,<sup>1,2†</sup> Mark I. McCarthy<sup>2,5†</sup>

Frayling et al. Science 2007;316: 889-894

The first genome-wide association study of obesity identified a strong genetic contributor – a polymorphism in the FTO gene.

# Effect of FTO genotype on BMI in chronic schizophrenia

Rs9939609, one of several FTO polymorphisms associated with obesity, was associated with body weight in schizophrenia:

<i>Cohort</i>	<i>Mean age</i>	<b>BMI (kg/m<sup>2</sup>) by FTO genotype</b>			
		<i>AA</i>	<i>AT</i>	<i>TT</i>	
<b>Control subjects<sup>1</sup></b> (Oxford biobank; n=765)	40.6 y	26.43	25.36	25.48	
<b>Chronic schizophrenia<sup>2</sup></b> (Belfast study; n=122)	41.4 y	32.64	29.74	27.53	<i>p=0.013</i>

Each A allele of rs9939609 is associated with an average BMI increase of:

- 0.36 kg/m<sup>2</sup> in control subjects<sup>1</sup>
- 2.24 kg/m<sup>2</sup> in subjects with chronic schizophrenia

<sup>1</sup> From: Frayling et al. Science 2007;316: 889-894

<sup>2</sup> Reynolds et al. Int J Neuropsychopharmacol 2013;14: 1-5

# The FTO gene and antipsychotic drug-induced weight gain

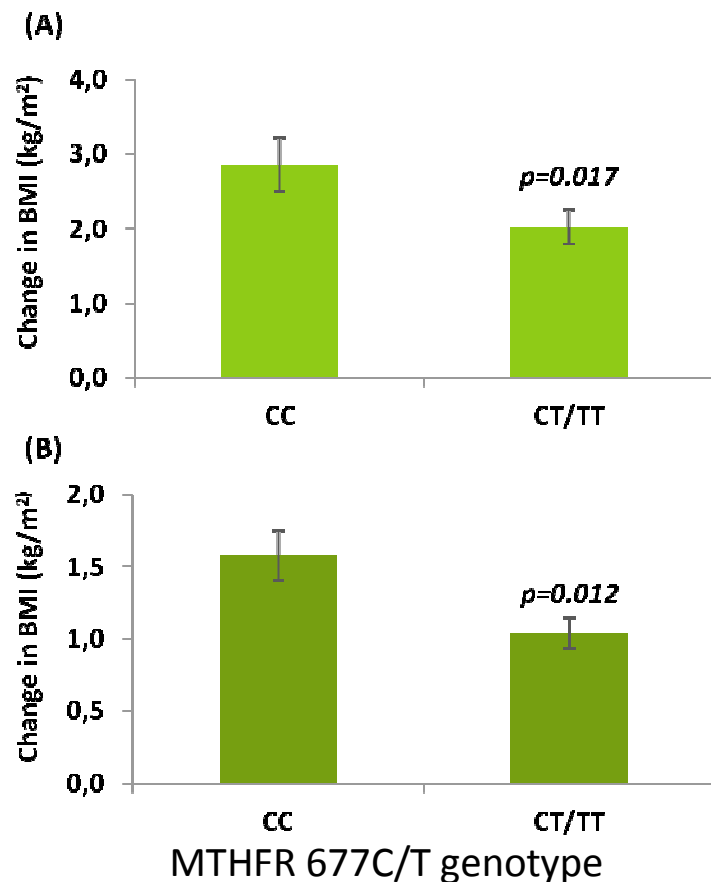
- Association of the “obesity risk” FTO polymorphism (rs9939609 A/T)...
- with body weight in chronic schizophrenia:
  - FTO genotype has a profound effect on body weight (13kg difference between AA and TT genotypes) and is associated with metabolic syndrome.
- but not with weight gain in first-episode schizophrenia:
  - Alone, FTO has no significant effect on initial weight gain
  - But it does have a small influence on baseline weight
- Therefore, chronic drug treatment of schizophrenia greatly enhances the influence of this obesity risk factor.

# MTHFR and antipsychotic drug-induced weight gain

- Methylene tetrahydrofolate reductase (MTHFR) is an important enzyme in one-carbon metabolism
  - It mediates the production of the methyl donor S-adenosylmethionine, a process dependent on folate availability
- The MTHFR gene has two functional missense coding region polymorphisms
  - 677C/T and 1298A/C are both reported to influence enzyme activity
- These polymorphisms are associated with clinical effects
  - One or other is reportedly associated with many disorders including depression and schizophrenia, with response to treatment in these diseases and with metabolic pathology in schizophrenia.

# MTHFR genotype effect on weight gain

## Change in BMI in first-episode, drug naïve psychosis – effect of methylenetetrahydrofolate reductase genotype



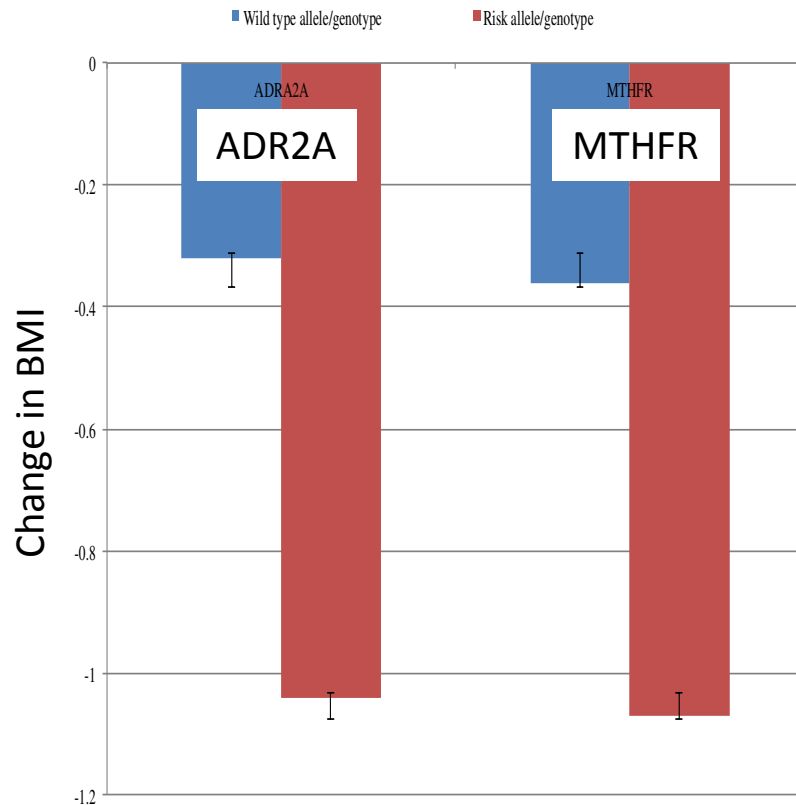
Two cohorts of initially drug-naïve subjects receiving antipsychotics for 13 weeks (n=72 Spanish; Fig A) or 8-10 weeks (n=182 Chinese; Fig B) were genotyped for the MTHFR 677C/T.

Both samples showed a significant association with MTHFR genotype.

In each case there was an additive effect with the 5-HT<sub>2C</sub> receptor gene SNP.

# Genotype effect on weight loss

## Change in BMI after switch to aripiprazole or ziprasidone – effect of alpha adrenergic receptor 2A and MTHFR genotype



Malaysian patients receiving antipsychotics (n=115) and showing symptoms of metabolic syndrome were switched randomly to ziprasidone or aripiprazole.

Subjects were genotyped for a series of SNPs in candidate genes.

Significant associations with weight loss after 6 months (LOCR analysis) were found for SNPs in genes for alpha adrenergic receptor 2A and MTHFR.

*Roffei et al, 2014*

# Genetic association with antipsychotic-induced weight gain

- Genetic variations associated with metabolic consequences of antipsychotic drug treatment include:
  - **5-HT<sub>2C</sub> receptor** gene polymorphisms with weight gain
  - **leptin** gene polymorphism with weight gain and metabolic syndrome
  - **MTHFR** gene polymorphism with weight gain
  - **FTO** gene polymorphism with obesity in chronic schizophrenia
- Other genetic factors are involved; previous studies identified associations of antipsychotic-induced obesity or weight gain with polymorphisms in genes including:
  - $\alpha$ 2A adrenoceptor, G-protein beta3 subunit, promelanin concentrating hormone and melanocortin receptor 4.



# Genetic testing for antipsychotic-induced weight gain?

- Genetic factors may account for much of the variance in body weight gain in patients receiving antipsychotics.
- Other factors inevitably contribute, including exercise and diet.
- Nevertheless, the huge concern over metabolic consequences of antipsychotic drug treatment indicates the potential value of genetic testing as an aid for practitioner and patient in choice of treatment and lifestyle advice.

# Consequences of antipsychotic drug treatment

In blocking dopamine D2 receptors, antipsychotic drugs are often effective in treating the positive symptoms of schizophrenia and manic symptoms of bipolar disorder.

Major problems remain:

- Lack of response of 10-20% of patients to any antipsychotic treatment
- Poor response to treatment of negative, cognitive and depressive symptoms

# Pharmacogenetic studies of treatment response in schizophrenia

- Pharmacogenetic studies in schizophrenia have addressed the genetic determinants of *antipsychotic drug response*.
- Candidate genes most studied include 5-HT<sub>2A</sub> and dopamine D<sub>2</sub> receptors – antipsychotic drug targets.
- Large GWAS studies have rarely provided consistent results with functionally-relevant genes.
- Limitations of such drug response studies include:
  - Lack of first-episode drug-naïve patients
  - Differential effects of drugs on positive, negative and cognitive features of schizophrenia

# Negative and depressive symptoms are important targets for antipsychotic drugs

- Negative symptoms and depression are important symptoms of schizophrenia.
- Antidepressant action is thought to involve effects regulating the activity of **serotonin** neurotransmission. Potential antidepressant drug targets additional to the serotonin reuptake site include:
  - 5-HT<sub>2A</sub>, 2C and 1A receptors
- The serotonin system has also been implicated in negative symptoms and their response to antipsychotic drugs.
  - SSRIs as adjunctive treatment relieve negative symptoms of schizophrenia in some patients (*Silver et al, 2004*).

# 5-HT1A receptors and antipsychotic drug response

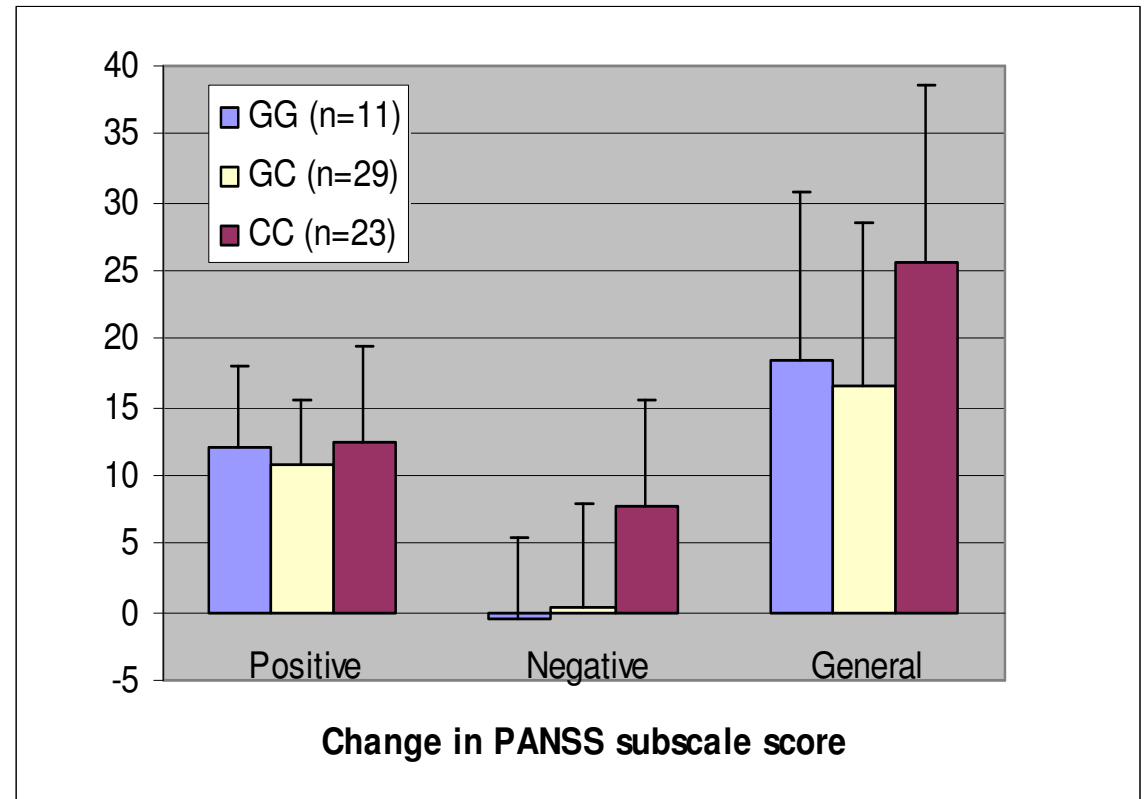
- 5-HT1A receptors control 5-HT neuronal activity and are involved in:
  - antidepressant drug action
  - cognitive and other functions of 5-HTand may contribute to the action of some second generation antipsychotics
- Genetic variation in the 5-HT1A receptor gene is associated with depression and suicide (*Lemondé et al, 2003*).

Does this genetic factor influence antipsychotic drug response?

# Association of 5-HT1A receptor promoter polymorphism and symptom outcome

Association of the -1019G/C SNP with response to 3 months' antipsychotic treatment was assessed in 63 drug naïve patients with first-episode psychosis.

- Genotype was associated with change in total PANSS ( $p=0.007$ ).
- This reflected a significant association of genotype with changes in negative PANSS and in general PANSS.
- Genotype and baseline score accounted for >40% of variance in negative symptom change.



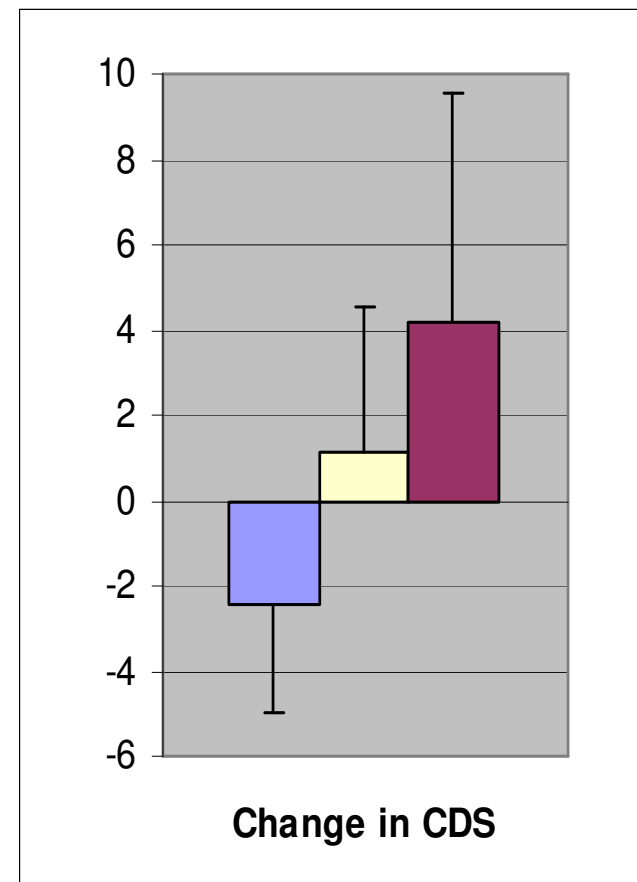
Reynolds et al. (2006) *Am J Psych* 163, 1826-1829.

# Association of 5-HT1A receptor promoter polymorphism and depressive symptom outcome

**Association of the -1019G/C SNP with response to 3 months' antipsychotic treatment was assessed in 63 drug naïve patients with first-episode psychosis.**

- Genotype was associated with change in Calgary Depression Score ( $p=0.001$ ).
- **Genotype and baseline score accounted for ~75% of variance in the change in depressive symptoms.**
- Subjects with a GG genotype showed a significant deterioration in depressive symptoms ( $p<0.01$ ).
- The G allele significantly predicted poorer response to negative and depressive symptoms response in patients receiving risperidone or olanzapine alone – the associations generalized to different drugs.

*Reynolds et al. (2006) Am J Psych 163, 1826-1829.*



# Pharmacogenetic factors in positive and negative symptom response to antipsychotic drugs

Gene investigated:	Polymorphism:	Association with symptom subgroup:	Reference
Dopamine D2 receptor ( <i>DRD2</i> )	Ser311cys	<i>Positive</i>	(Lane et al. 2004)
	Taq1A	<i>Positive</i>	(Suzuki et al. 2000)
Dopamine D3 receptor ( <i>DRD3</i> )	Ser9gly	<i>Negative</i>	(Lane et al. 2005)
	Ser9gly	<i>Positive</i>	(Reynolds et al. 2005)
	-205A/G, Ser9gly	<i>Positive</i>	(Staddon et al. 2002)
	Ser9gly and others	<i>Positive</i>	(Adams et al. 2008)
NA transporter ( <i>SLC6A2</i> )	1287G/A, -182T/C	<i>Positive</i>	(Meary et al. 2008)
5-HT <sub>2A</sub> receptor ( <i>HTR2A</i> )	102T/C	<i>Negative</i>	(Lane et al. 2002)
	-1438A/G	<i>Negative</i>	(Hamdani et al. 2005)
	-1438A/G	<i>Negative</i>	(Ellingrod et al. 2003)
5-HT <sub>2C</sub> receptor ( <i>HTR2C</i> )	-759C/T	<i>Negative</i>	(Reynolds et al. 2005)
5-HT <sub>1A</sub> receptor ( <i>HTR1A</i> )	-1019C/G	<i>Negative</i>	(Reynolds et al. 2006)
	-1019C/G	<i>Negative</i>	(Mossner et al. 2009)
	-1019C/G	<i>Negative</i>	(Wang et al. 2008)
Serotonin transporter ( <i>SLC6A4</i> )	HTTLPR ins/del	<i>Negative</i>	(Vazquez-Bourgon et al. 2010)



# Pharmacogenetics of antipsychotic drug response

- There are other candidate genes associated with negative symptom response; these include some implicated as genetic risk factors for schizophrenia including:
  - Glutamate metabotropic receptor3 (GRM3)
  - Dysbindin
  - RGS-4
  - Catechol O-methyltransferase (COMT)
- These associations may relate to genetic effects on the pathology of schizophrenia. Thus pathological subtypes may show different symptom responses to antipsychotic drug treatment.

# Treating schizophrenia – towards personalized medicine

## Present problems with antipsychotic drug treatment

- Severe side effects, including
  - weight gain and related metabolic consequences
  - consequences of raised prolactin
- Poor response of negative and cognitive symptoms

## Future prospects in treating schizophrenia include

- Genetic testing for individual assessment of:
  - Severity of side effects
  - likelihood of good symptom response to treatment
- Future studies need to determine:
  - Sensitivity and specificity of such genetic tests
  - Value and utility of predictive testing in the clinic