

Pharmacogenetics of response to Antidepressant Drugs

Developing New Medicines – An Introduction

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Basics of Pharmacogenetics

- The study of the influence of genetic factors on action of drugs (K.K. Jain 2009)



- The study of variability in drug response due to heredity (Pirmohamed 2001)
- Additional definitions (Roses 2004)
 - Safety pharmacogenetics: aimed at avoiding adverse drug reactions
 - Efficacy pharmacogenetics: meant to predict response to medication



Role of Pharmacogenetics in Pharmaceutical Industry

(K.K. Jain 2009)

- **Threefold role:**

- 1) Study of drug metabolism and pharmacological effects
- 2) Prediction of genetically determined adverse reactions
- 3) Drug discovery and development as an aid to planning clinical trials



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Genetic Factors Causes of Variations in Drug Metabolism

(K.K. Jain 2009)

- **Polymorphisms of:**
 - Drug metabolizing enzymes
 - Drug Transporters
 - Drug Receptors
 - Ion Channels
 - Signal Transduction Pathways



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Enzymes relevant to drug metabolism

(K.K. Jain 2009)

Phase I enzymes (predominantly oxidative)

- Alcohol dehydrogenase
- Cytochrome P-450 (CYP) with subtypes
- Dihydropyrimidine dehydrogenase
- Pseudocholinesterase
- Epoxide hydrolases

Phase II enzymes (conjugative)

- *N*-acetyl transferase 2
- Catechol *O*-methyltransferase
- Gluthathione-S transferase
- Sulfotransferases
- Thiopurine-S-methyltransferase



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Pharmacogenetics of Phase I Metabolism

(K.K. Jain 2009)

- P450 enzymes can alter, abolish or enhance drug metabolism
- There are more than 100 P450 genes that control these enzymes
- More than 50% of the clinically used drugs are cleared through the action of P450 enzymes
- Mutations in P450 genes could lead to poor metabolism of certain drugs
- Polymorphism in P450 genes may explain person-to-person variations seen in the intensity and duration of drug action as well as the occurrence of side effects



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Pharmacogenetics of Phase I Metabolism

(K.K. Jain 2009)

- **P450 CYP2D6 Inhibition by Selective Serotonin Reuptake Inhibitors (SSRIs)** can make changes in concentration of concomitant medication (drug-drug interactions)
 - Elevated desipramine concentrations noted when co-administered with paroxetine or increased phenytoin concentration reported when administered with sertraline
 - Significant interindividual differences in the magnitude of CYP2D6 inhibition noted due to pharmacokinetic variability of the inhibitor itself and variability in unbound drug concentration in plasma and hepatocytes
- **P450 polymorphism and response to Clopidrogel** was investigated as Clopidrogel requires transformation into an active metabolite by CYP450 for its antiplatelet effect
 - Carriers of reduced-function CYP2C19 allele had a relative reduction of 32.4% in plasma exposure to the active metabolite as compared with noncarriers
 - They also had diminished platelet inhibition and higher rate of major cardiovascular events including stent thrombosis (Simon 2009)
- **Glucose-6-Phosphate Dehydrogenase (G6PD)** deficiency and antimalarial drugs induced hemolysis was observed in the early 1950s
 - G6PD controls the flow of carbon through the pentose pathway, produces nicotinamide adenine dinucleotide phosphate (NADPH) and keep glutathione in reduced state
 - The absence of reduced glutathione due to G6PD deficiency allows oxidative drugs including primaquine, sulfonamides and chloramphenicol to oxidize sulfahydroxyl groups of hemoglobin leading to hemolysis
 - G6PD deficiency is sex-linked (chromosome X) recessive trait and widespread polymorphism affecting more than 400 million people worldwide
 - Prevalence of G6PD deficiency varies among ethnic groups (more frequent in males of African and Mediterranean descent)



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Pharmacogenetics of Phase II Metabolism

(K.K. Jain 2009)

- **N-Acetyltransferase** variation in NAT gene can lead to slow acetylator phenotype and cause toxicity when exposed to drugs such as isoniazid, procainamide and hydralazine, whereas the fast acetylator phenotype may not respond to isoniazid and hydralazine in the management of tuberculosis and hypertension respectively
- **Uridine Diphosphate-Glucuronosyltransferase**
 - Uridine diphosphate-glucuronosyltransferase 1A1 has a frequency of 10% among whites
 - It is involved in metabolism of bilirubin and polymorphism in UDG1A1 gene is associated with Gilbert's syndrome (hyperbilirubinemia)
 - Patients with low UGT1A1 activity might be at increased risk for antitumor agent irinotecan toxicity due to increased concentration of its active metabolite not being glucuronidated by UGT1A1



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Genetic Polymorphism (variation) of Drug Transporters and Drug Targets (receptors)

(K.K. Jain 2009)

- Transporters have important role in regulation of absorption, distribution and excretion of many medication
- Membrane transporters are encoded by numerous genes
- Example of ABC transporter superfamily consisting of eight families
- One of these is P-glycoprotein also called multidrug resistance protein (MDR-1) which serves as transporter that extrudes numerous drugs out of cells (one variant with low MDR-1 expression results in enhanced digoxin plasma levels and altered drug distribution)
- Genetic variation in drug targets(e.g. receptors) can have profound effect on drug efficacy and failure and alter process of signal transduction
 - serotonin transporter/antidepressants/antidepressant response
 - dopamine receptors/antipsychotics/antipsychotic response/frequency of extrapyramidal symptoms
 - ACE/ACE inhibitors/renoprotective effects/blood pressure reduction



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Pharmacogenetics in Drug Safety

(K.K. Jain 2009)

- Susceptibility to Adverse Drug Reactions (ADR) varies with genetic makeup
- Polymorphisms in the genes that code drug-metabolizing enzymes, drug transporters and ion channels can affect an individual's risk of having an ADR
- Examples of Malignant Hyperthermia when exposed to anesthetics due to inherited mutation in the gene for the ryanodine receptor (RYR1) that resides in the membrane of sarcoplasmic reticulum
- Clozapine-induced Agranulocytosis due to human leukocyte antigen (HLA) complex gene variability
- Carbamazepine induced Steven-Johnson syndrome and toxic epidermolysis
- Lower doses or oral anticoagulant warfarin should be used in patients with CYP2C9 gene variants (currently complications of warfarin therapy account for 10.5% of hospital admissions due to ADRs)
- Statin-induced myopathy in patients with single nucleotide polymorphism on SLCO1B1 gene on chromosome 12



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Burden of Major Depressive Disorder (MDD)

- Lifetime prevalence 12.8% (Alonso et al. 2004)
- 15% of MDD individuals die by suicide (Guze and Robins 1970)
- Morbidity, mortality and financial costs comparable to hypertension and diabetes (WHO 2007)
- Depressive disorders account for up to 80% of all psychiatric hospitalizations (Shapiro et al. 1984)



Current treatment facts for MDD

- Even though different classes of antidepressant drugs (ADD) have been used to treat depressive symptoms the treatment efficacy is often incomplete
- 60-70% do not experience remission (Moncrieff and Kirsch, 2005)
- 30-40% do not show significant response (Moncrieff and Kirsch, 2005)
- Antidepressant response is usually associated with 2-4 weeks lag before improvement which exposes patients to an ineffective therapy period, higher risk of worsening of clinical conditions, higher risk of premature discontinuations and install feeling of hopelessness possibly leading to high suicidal risk (Serretti A et al 2008)
- Side effects are common (40-90%) (Cramer and Rosenheck 1998)
- Clinical choice of the specific drug is partially determined by the probability of occurrence of unwanted effects



Pharmacogenetics of Antidepressant Response

- Possible source of the variation antidepressant treatment outcome are genetic differences
- Response to ADD is an inheritable trait:
 - Angst (1964) reported that 28 out of 41 first-degree relative pairs on imipramine treatment were concordant regarding antidepressant response
 - Pare and colleagues (1962) consistently reported that relatives of depressed patients treated with same ADD had equivalent responses with an overall response rate of 42%
 - Four out of eight members of the same family suffering from depressive disorders who were resistant to tricyclic antidepressants all responded to monoamine oxidase inhibitor treatment (O'Reilly 1994)
 - There was 67% concordance rate for response in 45 first-degree relative pairs who were treated with fluvoxamine for six weeks (Franchini 1998)



Pharmacogenetics of Antidepressant Response

- **Pharmacokinetics**

- The way in which the drug is distributed in or clear from the body and involves absorption of an antidepressant, distribution through hydrophilic and hydrophobic spaces, metabolism and excretion (Serretti et al. 2008)

- **Pharmacodynamics**

- Antidepressant interaction with its receptors and transporters and with downstream processes such as second-messenger systems (Perlis 2007)



Pharmacokinetics of Antidepressant Response

(Serretti et al. 2008)

■ Cytochrome P450

- Class of heme-containing proteins that represents major enzymes responsible for oxidation and reduction of numerous endogenous substrates and drugs
- Over 50 isoenzymes
- Responsible for the catabolism of at least 30 different classes of drugs
- **CYP2D6** most investigated regarding metabolism of ADD
- Found in 22q13.1 position and spans 4,382 bases
- 75 different alleles
- Those gene variants associated with different drug metabolism rates
- Individuals classified as poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM) metabolizers
- % of PM varies across different ethnic groups (5-10% in Caucasians, much rarer in Black Americans and Orientals and in 0.22% of Koreans)



Pharmacokinetics of Antidepressant Response

(Serretti et al. 2008)

■ **Cytochrome P450 CYP2D6**

- UM have been shown to have multiple copies of the CYP2D6 with a direct influence on plasma drug concentration: standard doses of antidepressant nortriptyline will show inadequate therapeutic antidepressant response (Dalen 1998)
- Side effects are more frequent in PM subjects
- Tricyclic antidepressants (TCAs) have small therapeutic windows because of their side-effect profile: a dose adjustment for patients with CYP2D6 variants has been proposed (de Leon 2007)
- PMs of CYP2D6 ought to receive about 50% of the recommended dose of amitriptyline (Kirchheiner 2001)
- A clomipramine elimination via CYP2D6 has been hypothesized to be saturable therefore PMs may require 60% of the recommended dose and EMs 120% (Thuerlauf and Lunkenheimer 2006)
- CYP2D6 variants influence plasma levels of paroxetine and venlafaxine (Ozdemir 1999, Shams 2006) and fluoxetine and norfluoxetine (Scordo 2005)



Pharmacokinetics of Antidepressant Response

(Serretti et al. 2008)

■ **Cytochrome P450 CYP2D6**

- Selective Serotonin Reuptake Inhibitors (SSRIs) display distinct profile of CYP inhibition
 - Fluvoxamine therapeutic effects are associated with CYP2D6 polymorphism in Japanese subjects (Suzuki et al. 2006)
 - Fluoxetine and norfluoxetine are potent CYP inhibitors and their effects can persist for several weeks after discontinuation because of their long half-life (Hemeryck and Belpaire 2002)
 - Sertraline is a moderate CYP2D6 inhibitor
 - Citalopram appears to have little effect on the major CYP isoforms (Rao 2007)
- This must be taken into consideration when polytherapy treatment is started
 - The impact of CYP2D6 variants might be greater for combined SSRI + TCA treatments
 - Co-administration of paroxetine and desipramine in EM who had at least two functional copies of the CYP2D6 gene was found to result in 5-fold decrease in desipramine clearance (Brosen 1993)



Pharmacokinetics of Antidepressant Response

(Serretti et al. 2008)

■ P-glycoprotein

- ATP-dependent drug efflux pump (transporter protein) and the product of ABCB1 gene, which limits uptake and accumulation of some lipophilic drugs into key organs (Serretti et al. 2008)
- It is a plasma membrane transporter that exports certain drugs against the concentration gradient in intestines, kidneys and testes (Serretti et al. 2008)
- It constitutes important part of blood-brain barrier by exporting substrates out of the brain back to the circulation (Serretti et al. 2008)
- Relevant for following antidepressants (amitriptyline, nortriptyline, citalopram, venlafaxine and sertraline) (Serretti et al. 2013)
- Gene encoding P-glycoprotein is localized on chromosome 7 in position 7q21.1 (Fojo 1987)
- Genetic variation 3,435C>T was associated with higher fluvoxamine levels in the CT genotype group than in CC genotype group (Fukui 2007)
- The same variation was found to be associated with a higher risk of nortriptyline-induced postural hypotension in patients treated for major depression (Roberts 2002)
- Association between number of SSRI-related side effects and ABCB1 polymorphisms (de Klerk 2012)



Pharmacodynamics of Antidepressant Response

(Serretti et al. 2008 and 2013)

- Monoamine Metabolic Enzymes
- Monoamine Transporters
- Monoamine Receptors
- Intracellular Signal Transduction Pathways
- HPA Axis and Stress Hormone System
- ACE-Substance P System
- Interleukin 1- Beta
- Endogenous CLOCK System
- Glutamatergic system
- Neurotrophic factors



Monoamine Metabolic Enzymes

(Serretti et al. 2008)

■ Tryptophan Hydroxylase (TPH)

- Catalyzes the rate-limiting step in serotonin (5-HT) biosynthesis
- Long-term treatment of rats with SSRI has been shown to upregulate mRNA and protein levels of TPH (Kim 2002)
- According to monoaminergic theory of depression the presence of TPH1*_a allele was found to be associated with suicidal behavior and poor response to antidepressant treatment (Rujescu 2003)
- TPH2 seems to be more selectively expressed in brain areas compared to TPH1 (Zill 2007)
- The TPH2 gene is in position 12q21.1 and its variation have been associated with major depression (Zill 2004) and suicidal behavior
- Zhang (2004) found that 5HT levels from cells expressing arginine at position 447 in TPH were reduced by 55% compared to cells expressing proline at position 447 due to functional (C1473G) single-nucleotide polymorphism (SNP)
- Zhang (2005) also identified a 1,463-A transition in the TPH2 gene
- This functional SNP in TPH2 replaces Arg441 with His which resulted in approximately 80% loss of function in serotonin production



Monoamine Metabolic Enzymes

(Serretti et al. 2008)

■ Catechol-O-Methyltransferase (COMT)

- Is involved in the catabolic pathways of noradrenaline (NE) and dopamine (DA)
- It indirectly affects brain serotonin tone, given the reciprocal interaction between DA and 5HT
- There is evidence of interactions between serotonergic and dopaminergic systems and it seems that increase of dopamine concentration in the whole brain could be limiting factor for antidepressant-like effect of antidepressants (Arias 2006)
- COMT gene has been mapped to chromosome 22
- Functional polymorphism (SNP) consisting of transition of guanine to adenine leading to Val-Met substitution in MB-COMT was reported by Lachman (1996)
- The presence of the Met allele has been reported to be associated with lower enzymatic activity (Mannisto and Kaakkola 2005)
- This polymorphism has been associated with higher risk of suicidal behavior and personality traits (Craddock 2006) and worse response to mirtazapine (Szegedi 2005) and citalopram (Arias 2006)



Monoamine Metabolic Enzymes

(Serretti et al. 2008)

■ Monoamine Oxidase A

- Is a major degrading enzyme in the metabolic pathways of monoamine neurotransmitters (NE,DA, 5-HT)
- The gene encoding MAO-A is located in position Xp11.23 (Sabol 1998)
- Its absence in human beings has been found to be life compatible (Sims 1989) and associated with psychiatric-like syndrome characterized by borderline mental retardation and abnormal behavior such as impulsive aggression, attempted rape and exhibitionism
- This syndrome was found to be associated with punctual non-sense mutation in MAO-A gene (Brunner 1993)
- MAO-A genetic variations are supposed to influence the mechanism of action of SSRIs through an interaction with serotonin transporter (SERT) (Maes and Meltzer 1995)
- Bipolar disorder as well as suicidal tendency, personality features, aggressive behavior, alcoholism and response to ADD in females has been associated with polymorphism located 1.2 kb upstream of the MAO-A coding sequences
- This polymorphism affects the transcription of the MAO-A promoter: alleles with 3.5 or 4 copies of repeat sequences are transcribed 2-10 times more efficiently than those with 3 or 5 copies of the repeat (Sabol 1998)



Monoamine Transporters

(Serretti et al. 2008 and 2013)

■ Serotonin Transporter (SERT)

- SERT SCL6A4 is target of primary interest in ADD pharmacogenetics
- It is a principal site of action of many ADD (SSRI, TCA)
- SERT knockout mice show increased anxiety and inhibited exploratory locomotion, together with a reduction in aggressive behavior and home cage activity
- Human SERT is encoded by a single gene SLC6A4 on chromosome 17
- 171 polymorphisms are known so far
- Most promising variations seem to be those in the promoter zone especially 5-HTTLPR
- The presence of different alleles could affect SERT expression
- The long (L) allele has twice SERT expression than the short (S) form
- Serretti (2007) showed that 5-HTTLPR S/S patients have selective and slower improvement of depressive "core" and somatic anxiety symptoms
- L allele or LL genotype is associated with better antidepressant outcome but on the other hand there are also negative reports (Serretti 2013)
- The S/L genotype and S/S genotype showed differences in the frequency of adverse events during SSRIs treatment (dermatologic reactions, weight change and fatigue)(Smits 2007). Available studies suggested S allele as a risk factor (Perlis 2003)
- Ogilvie (1996) identified another polymorphism influencing SERT expression STin2 that can play a role as a risk factor for depressive disorder and suicide behavior and was also found to affect antidepressant response in large Korean sample (Kim 2000)
- SNP located upstream of the 5-HTTLPR revealed a significant influence on antidepressant response
- In an interesting clinical efficacy oriented study it has been demonstrated that a genetic assessment on HTTLPR before initiating antidepressant treatment and thus identifying subjects with the risk of non-response, is associated with better clinical outcome (Smits 2007)



Monoamine Transporters

(Serretti et al. 2008)

■ Norepinephrine Transporter (NET)

- SLC6A2 gene encodes norepinephrine (noradrenaline) transporter which is responsible for reuptake of norepinephrine into presynaptic nerve terminal (Kim 2006)
- The gene is localized at position 16q12.2 (Bruss 1993) and spans 45,934 bp
- 267 genetic variations are known so far
- The reuptake of noradrenaline occurs via specific Na(+) and Cl(-) dependent transport system which is a target for TCAs such as desipramine and imipramine
- Genetic variations have been proven to be influencing its functions
- A369 P variant is associated with lack of transport activity
- N292T was found to impede expression of NET
- F528C demonstrated increased functionality
- Noradrenaline Reuptake Inhibitor (NRI) antidepressant response was associated with G1287A polymorphism: GG genotype was associated with better response

■ Dopamine Transporter (DAT)

- The gene for dopamine transporter (DAT1) is chromosome 5p15.3 (Giros 1992)
- 502 variations are known so far
- 40-bp variable number tandem repeat (VNTR) polymorphism in exon 15 of DAT1 is associated with faster onset of AD response when the allelic variant with enhanced expression (10 repeat variant) is present (Kirchheiner 2006)
- This is consistent with the hypothesis that an enhanced dopaminergic tone impairs at least in part antidepressant efficacy



Monoamine Receptors

(Serretti et al. 2008)

■ Serotonin receptor 5-HT1A

- 5-HT1A receptors are present pre- and post-synaptically in different brain areas
- Gene is located in position 5q11.2-q13 (Kobilka 1987)
- Spans 1269 bp and has 45 genetic variations
- 5-HT1A G(-1019) allele fails to bind Deaf-1 and Hes5 repressors and this lead to upregulation of receptor expression (Lemonde 2003)
- This mechanism might mediate the association of the G(-1019) allele with depression and suicide (Lemonde 2003)
- This allele may also contrast effect of antidepressant drugs by increasing inhibitory 5-HT1A autoreceptors

■ Serotonin receptor 5-HT2A

- In amygdala 5-HT2A receptor activation is a component of antidepressant response
- Located in position 13q14-q21 (Chen 1992)
- Spans over 20kb
- Both imaging and clinical studies have reported that drugs with HTR2A agonist properties may have euphoriant effects (Newton 2006)
- Paroxetine may exert its effects by downregulation of 5 HT2A receptors (Meyer 2001) and nefazodone exerts its antidepressant effects partially through HTR2A receptor antagonism (Heimrick-Luecke 1994)
- Three types of polymorphism have been implicated in AD response: T(102)C, G(-1438)A and C(1420)T

■ Serotonin receptor 5-HT6

- Located in position 1p36.13 (Kohen 1996)
- G-protein coupled receptor which stimulates adenylyl cyclase via G protein coupling
- Animal studies reported its role in some behavioral (novelty seeking) and instrumental learning (Ballaz 2007, Mitchell 2007)
- AD response was found to be influenced by polymorphism T(267)C in the first exon with C/T genotype carriers found to display greater efficacy of the AD treatment (Kohen 1996)



Monoamine Receptors

(Serretti et al. 2008)

■ Norepinephrine receptors

- Norepinephrine has a primary role in the regulation of energy and alertness (Nutt 2007)
- Beta1 adrenergic receptor gene (ADRB1 gene) has been the most investigated candidate gene
- Located in 10q24-q26 position (Yang-Feng 1990)
- ADRB1 is an important regulator of mood, memory, neuroendocrine activity and it is involved in the mediation of antidepressant effect (Crismann 2001)
- ADRB1 Gene is highly polymorphic and the functional SNP (G1165C) was associated with enhanced coupling to the stimulatory G protein and increased adenylyl cyclase activation
- Consistently CC homozygote may show faster and better response to various antidepressant drugs (Zill 2003)

■ Dopamine receptors

- Dopamine system is highly involved in depressive spectrum symptomatology (Geracitano 2006)
- It has been suggested that the pathophysiologic process in melancholic depression involves a decreased dopaminergic neurotransmission owing to hypersensitive inhibitory 5-HT₂ hetero receptors located on dopaminergic neurons
- Treatment with most antidepressant drugs downregulate these receptors which allow increased dopaminergic firing and an antidepressant effect
- An interaction between the serotonergic and dopaminergic systems in the nucleus accumbens has been established as motivation and hedonia have been associated with DA release in the nucleus accumbens (Zangen 2001)
- D₂, D₃ and D₄ are G-protein coupled receptors
- Role of DRD₂, DRD₃ and DRD₄ genes was investigated in relation to antidepressant response with conflicting results



Intracellular signal transduction pathways (Serretti et al. 2008)

■ **G-protein Beta-3 subunit**

- Coded by GNB3 gene
- The G proteins are heterotrimers consisting of alpha, beta and gamma subunits that dissociate after receptor activation
- These proteins convey signals in cells initiated by the activation of many receptors which are then translated into various intracellular systems (Wess 1998)
- It has been estimated that about 80% of all known hormones, neurotransmitters and neuromodulators elicit cellular responses through G proteins (Chen 1999)
- The high degree of complexity generated by interactions of G-protein-coupled receptors may be one mechanism by which neurons acquire flexibility for generating the wide range of responses observed in the nervous system (Chen 1999)
- The gene for subunit beta 3 is located at 12pter-p12.3 (Levine 1990)
- A polymorphism C825T was identified in exon 10 of GNB3
- GNB3(825)T variant was found to predict better ADD response in several studies (Zill 2000, Serretti 2003)



HPA Axis and Stress-Hormone System

(Serretti et al. 2008)

- Dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis is one of the most robust findings in many patients with major depression (up to 70%) (Holsboer 2000)
- It was reported that the alterations of corticotropin releasing hormone (CRH) function contribute to the pathogenesis of depression: concentration of CRH in the cerebrospinal fluid (CSF) are elevated (Liu 2002)
- There are two primary receptor subtypes for CRH in the CNS: corticotropin-releasing hormone receptor 1 and 2 (CRHR1 and CRHR2)
- CRHR1 is considered to play key role in mediating the CRH-elicited effects in depression and anxiety (Van Pett 2000)



HPA Axis and Stress-Hormone System

(Serretti et al. 2008)

■ **CRH Receptor I**

- CRF is a 41-amino acid peptide synthesized in the hypothalamus and capable of stimulating the production of adrenocorticotrophic hormone (ACTH)
- CRHR1 gene contains 14 exons spanning 20kb of genomic DNA
- CRHR1 antagonist have consistently demonstrated antidepressant properties in experimental animal and human studies (Seymour 2003, Kehne 2007)
- Some evidence points to a relevance of CRHR1 variants and antidepressant response in particular association of CRHR1 rs242941 G/G genotype and fluoxetine therapeutic response (Licinio 2004)

■ **Glucocorticoid Receptor (GR)**

- Glucocorticoid hormones like other classes of steroid hormones exert their cellular action by complexing with a specific cytoplasmatic receptor which in turn translocates to the nucleus and binds to specific sites on chromatin where plays crucial role in gene expression
- The gene is located on 5q31-q32
- Functional polymorphism of GR gene (ER22/23EK) showed significantly faster clinical response to antidepressant therapy as well as better cognitive functioning during depression (van Rossum 2006)



Other relevant genes (Serretti et al. 2008)

▪ **Angiotensin Converting Enzyme – Substance P System**

- Angiotensin converting enzyme (ACE) is associated with series of actions influencing blood pressure through renin-angiotensin cascade interfering with the secretion of hormones (ACTH,CRH) (Jezova 1998)
- It is also expressed in the CNS where its primary function comprises degradation of neuropeptides including substance P (SP)
- Influence of SP on pathophysiology of depression has been hypothesized consistent with the finding that administration of SP agonists have antidepressant effects and SP concentration was found to be diminished after antidepressant treatment (MAO-I) (Kramer 1998, Nutt 1998)
- The presence of a deletion variant (D/) in the ACE gene was found to be associated with higher ACE plasma levels and higher SP levels (Rigat 1990, Arinami 1996) and a faster response to antidepressants (Baghai 2001)
- Also another component of ACE-SP system angiotensin II receptor gene was included among outcome predictors in major depression (Bondy 2005)

▪ **Interleukin 1- Beta**

- One potential pathway by which depression may impact health is through modulation of immune function
- Depressed individuals have been shown to display reductions in measures of cellular immune competence as well as elevated markers of systematic inflammation
- There is evidence suggesting strong influences in both directions between cytokines and neurotransmitters
- Gene located on the chromosome 2q13-q21 position
- IL-1 beta activates brain noradrenergic, serotonergic systems
- It also reduces acetylcholine release in hippocampus and potentiates GABA effects
- Homozygosity for the -511T allele of the IL-1beta gene was found to be more associated with a trend to lower severity of depressive symptoms and more favorable fluoxetine response (Yu 2003)



Other relevant genes

- **Endogenous CLOCK System** (Serretti et al. 2008)
 - Circadian rhythms are ruled by a tiny brain region of the hypothalamic suprachiasmatic nucleus (SCN) which expresses several CLOCK genes
 - Located in position 4q12 contains 20 exons (Steeves 1999)
 - One polymorphism a T-to-C substitution (CLOCK 3111T/C) is known to affect mRNA stability and half life (Mignone 2002)
 - In healthy subjects this C allele was associated with significantly higher “eveningness”, delay in preferred timing for activity or sleep (Katzenberg 1998)
 - In mood disorders the same C variant was coupled with higher recurrence rates in bipolar patients (Benedetti 2003), increased lifetime sleep disturbances (Serretti 2003) and persistence of insomnia during antidepressant treatment (Serretti 2005)
- **Glutamatergic System** (Serretti et al. 2013)
 - Despite monoamines are considered pivotal in MDD, the glutamatergic theory of depression recently gained growing interest
 - The glutamatergic theory posits that glutamate may shape the risk of depression influencing neuronal fate (neurotoxicity) or the unfolding of new neuronal nets (neuroplasticity)
 - GRIK4 (glutamate receptor, ionotropic kainate 4) has been repeatedly investigated as it has been suggested by the reduced anxiety and depression (antidepressant-like) phenotype of GRIK4 (-/-) mice
 - GRM7 gene (glutamate receptor metabotropic 7) seems also a promising gene as it has been associated with the risk of MDD (Shyn 2011) and the available evidence suggest it may play a role in mood regulation (Zhou 2009)



Other relevant genes

- **Neurotrophic factors** (Serretti et al. 2013)
 - Neurotrophin hypothesis of MD was formulated after the observation that hippocampus atrophy following stress was reversed by ADD in parallel to an increase in the expression of neurotrophic factors especially brain-derived neurotrophic factor (BDNF)
 - An increase in BDNF expression was recently confirmed in peripheral cells of depressed patients during treatment (Cattaneo 2013)
 - The most investigated variant within the BDNG gene is 196G/A or Val66Met since it has been reported to affect intracellular trafficking and activity-dependent secretion of BDNF
 - In humans the Met allele is associated with poorer episodic memory, abnormal hippocampal activation and metabolism (Egan 2003)
 - In mice Met/Met genotype did not show any increase in hippocampus BDNF levels during fluoxetine treatment and had impaired survival of newly born cells in gyrus dentatus (Bath 2012)
 - Vascular Endothelial Growth Factor (VEGF) has also been implicated in neurotrophin and neurogenesis (Sun 2003)
 - Animal studies demonstrated the VEGF levels are increased by several ADD including SSRIs and that VEGF signaling is required for antidepressant-induced behavioral response (Warner-Schmidt and Duman 2007)
 - In MDD patients higher expression of VEGF mRNA in peripheral leukocytes was associated with depressive state and recovery of these levels occurred in parallel with clinical improvement (Iga 2007)
 - Promising candidate gene is also Dystrobrevin binding protein 1 (DTNBP1 gene) which may play role in actin cytoskeleton organization, neurite outgrowth, synaptic signaling, regulation of glutamatergic neurotransmission and neuroplasticity



SWOT Analysis of the pharmacogenetic studies applied to antidepressant therapy

(Lanni et al. 2013)

Strengths

- To help the promotion of patients not responding sufficiently or suffering adverse effects during treatment
- To use genetic markers for prediction of treatment outcome

Opportunities

- Discovery of clinically useful predictors
- Shedding light on mechanism of drug action
- Identification of new targets not directly involved in mechanism of action

Weaknesses

- Inadequate sample size
- Lack of replication
- Differences in diagnosis (linked to different versions of the HAM-D used)
- Use of different classes of antidepressants and/or different agents of same class
- Differences in dosages

Threats

- Phenotype definition
- Diagnostic uncertainty



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Clinical Applications and Final Conclusions (Serretti 2013)

- Clinical applications of pharmacogenetics have already produced relevant effects in other field of medicine especially oncology (e.g. for treatment of breast cancer) (Paik et al. 2006)
- Antidepressant response is notably influenced by genetic variants (Tansey 2013)
- The best candidate identified so far appears SLC6A4 and its role is supported by strong biological plausibility
- Study aimed to evaluate cost-effectiveness of functional polymorphism 5-HTTLPR (44bp insertion/deletion) genotyping prior to antidepressant treatment has been recently carried out
- The analysis suggested an increase in both antidepressant response and tolerability when genetic test is used
- As MDD does not appear as uniform disease but includes heterogenous clinical conditions such as melancholic or anxious depression this might also predict differential response to ADD therefore future pharmacogenetic studies should consider separate analysis of these subgroups i.e. clinically homogenous patients in order to reduce great variability within the same diagnosis
- Pharmacogenetics provides also a unique tool to increase knowledge about antidepressant mechanism of action
- The idea that unsatisfying antidepressant response are partially due to lack of antidepressants with alternative mechanism of action is well supported (Nutt 2006)
- Thus the engineering of molecules with truly innovative mechanism of action should be a priority along with identification of response predictors



Questions



WORLDWIDE CLINICAL TRIALS
SCIENTIFICALLY MINDED • MEDICALLY DRIVEN

Hvala Takk skal du ha **σας ευχαρισ**

kob kun man **Grazie** terima kasi

d'akujem **Merci** teşekkür ederim

dziękuję Tuken takk **shukran**

paldies **Thank You!** **Děkuji**

Спасибо **Gracias** teşekkür

Kei Xei **Danke** **ありがとう** obrigado

Grazzi Terima kasih **salamat**