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Pharmacogenetics of antipsychotic-induced Parkinsonism and tardive dyskinesia

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**SUMMARY
IN ENGLISH**

The human nuclear genome consists of 23 pairs of chromosomes with each chromosome containing a single deoxyribonucleic acid (DNA) molecule. Chemically, DNA is a long polymer (double helix) of small building units (nucleotides). There are four types of DNA building units: adenine (A), guanine (G), cytosine (C) and thymine (T).

The basic functional unit of the genome is the gene. A gene is a portion of the genetic information that codes for one or more proteins. Proteins are important molecules for the function of all human cells.

The genetic information dictated by genes is represented by the sequence in which nucleotides occur (i.e., DNA sequence). DNA sequence determines which and how much proteins must be synthesized at a given point of time. Genes may thus carry essential information for development and proper function of cells and tissues.

The DNA sequences of the same genes of different individuals exhibit variability. The majority of the observed sequence variations between people appears to result from single nucleotide polymorphisms (SNPs), which are single base pair substitution (e.g., GAT in stead of CAT). Due to these and other mutations, DNA is an important source of the variability in response to drugs in animal and human beings.

The study of how DNA variations relate to variability in drug response is called pharmacogenetics.

Antipsychotics comprise a group of drugs used for the symptomatic treatment of a range of psychotic disorders including schizophrenia. Movement disorders (also known as extrapyramidal syndromes, EPS) occur frequently with the use of antipsychotics and may cause considerable distress to the patient.

Tardive dyskinesia (TD) and antipsychotic-induced parkinsonism (AIP) are two major subtypes of antipsychotic-induced movement disorders.

In the present thesis several pharmacogenetic aspects of TD (part I) and AIP (part II) have been examined in two different ethnic groups; African-Caribbean psychiatric inpatients from Curaçao (Netherlands Antilles) and Slavonic Caucasians from Tomsk (Siberia, Russia).

In **chapter 1** we provide a general introduction on pharmacogenetics, antipsychotics and antipsychotic-induced movement disorders.

In **chapters 2 and 3 (part I)**, we describe the pharmacogenetic associations between polymorphisms of the dopamine D3 (DRD3), serotonin 2A (HTR2A), and 2C (HTR2C) receptor genes and two TD subsyndromes, orofaciolingual (TDof) and limb-truncal (TDlt) dyskinesias, in African-Caribbeans and in Slavonic Caucasians, respectively.

These genes are important targets of antipsychotics in human brains. Both of the studies identify significant and differential associations between Ser9Gly (DRD3), -1438G>A (HTR2A), and Cys23Ser (HTR2C) polymorphisms and the subsyndromes TDof and TDlt (see Table 1 in Chapter 7 for an overview).

Summary in English

In **chapter 4 (part I)**, we describe in Slavonic Caucasians the pharmacogenetic associations between TDof and TDIt and polymorphisms of glutathione S-transferase P1 (GSTP1), superoxide dismutase-2 (SOD2), and glutathione peroxidase-1 genes (GPX1). These genes are involved in protection mechanisms against neuronal degeneration due to oxidative stress. Oxidative stress has been proposed as a mechanism for tardive dyskinesia (TD) pathogenesis. The findings of our study on these genes do not suggest an association with Pro197Leu (a polymorphism of GPX1 gene), but do suggest an association with Ile105Val and Ala9Val (polymorphisms of GSTP1 and SOD2 gene, respectively) and dyskinesias (TDof and TDIt).

In **chapter 5 (part II)**, we investigate in African-Caribbeans the association between several polymorphisms in dopamine D2 (DRD2), DRD3, HTR2A, and HTR2C receptor genes and AIP and three of its subsymptoms (rigidity, bradykinesia, and rest-tremor). In that study we report an association between -141CIns/Del (a polymorphism of DRD2 gene) and rigidity and between the Cys23Ser (a polymorphism of HTR2C gene) and AIP as well as bradykinesia. However, the study does not provide evidence for a genetic association between rest-tremor and any of the polymorphisms studied.

In **chapter 6 (part II)**, we endeavored to reproduce in our African-American sample findings from the literature that suggest a clinically and statistically significant association between AIP, rigidity, bradykinesia, and rest-tremor and a polymorphism (rs4606 SNP) in the gene encoding for Regulators of G-protein Signaling-2 (RGS2) protein, which is involved in the intracellular signaling of a number of G-protein coupled receptors (such as HTR2A). In contrast to literature findings, we find no evidence for a genetic association between rs4606 and AIP or any of its subsymptoms in our African-Caribbean sample and we hypothesize that the observed lack of association is due probably to differences in serotonin 2A-receptor affinities of the antipsychotics utilized.

In **chapter 7**, we discuss the findings and their limitations and provide recommendations for future research.