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Pharmacogenetics of antipsychotic-induced Parkinsonism and tardive dyskinesia

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2009

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Al Hadithy, A. F. Y. (2009). *Pharmacogenetics of antipsychotic-induced Parkinsonism and tardive dyskinesia: a focus on African-Caribbeans and Slavonic Caucasians*. s.n.

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CHAPTER 7

GENERAL DISCUSSION AND DIRECTIONS FOR FUTURE RESEARCH

General Discussion and Directions for Future Research

Antipsychotic-Induced Movement Disorders (AIMDs) can be classified into late onset (tardive), early onset (acute), and idiosyncratic events [Casey 2004; Gerlach 2002; Gerlach 1999; Trosch 2004; van Harten 1998]. Idiosyncratic events (e.g., neuroleptic malignant syndrome) are severe and life-threatening conditions, but they occur infrequently. Tardive and acute movement disorders occur more frequently and may cause considerable distress to the patient. Tardive dyskinesia (TD) and antipsychotic-induced parkinsonism (AIP) are two major subtypes of tardive and acute antipsychotic-induced movement disorders, respectively.

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). Table 1 provides an overview of the findings obtained.

Examination of Table 1 shows that the sub-symptoms of TD (TDof and TDlt) and AIP (rigidity, bradykinesia, and tremor at rest) may differ pharmacogenetically, since they exhibit differential associations with the polymorphisms studied. For example, whereas Ser9Gly (DRD3) polymorphism may be associated with TDlt in African-Caribbeans as well as in Slavonic Caucasians, it is unlikely to be associated with TDof. If genuine, our findings suggest a possible difference in the genetic liability of the sub-symptoms examined.

Another relevant finding is that ethnicity is an important determinant when studying TD and AIP pharmacogenetics. For example, in African-Caribbeans Cys23Ser polymorphism of HTR2C gene may be associated with TDof but not with TDlt, whereas the association is opposite in Slavonic Caucasians. The observed differential ethnic effects are possibly due to differences in the linkage disequilibrium (vide infra).

All of the studies mentioned in this thesis share a common merit: they dissect TD and AIP into their respective sub-symptoms (i.e., TD is dissected into TDof and TDlt; AIP is dissected into rigidity, bradykinesia, and tremor at rest). Although this approach is readily defensible, it has rarely been followed by the studies available on this topic: the majority of studies on AIMD pharmacogenetics examine TD and AIP as being one unitary entity.

As a matter of fact, AIP and TD should be dissected into their respective sub-symptoms, because the sub-symptoms are probably distinct clinical entities.

AIP sub-symptoms find their origin in distinct neurological circuits, have a separate pathophysiology, and/or genetic liability. For example, it has been shown that stimulation of certain brain regions in patients with Parkinson Disease (which has symptoms similar to those of AIP) may lead to differential effects on rigidity and tremor [Bejjani et al., 1997; Gross et al., 1999; Krack et al., 1998]. Furthermore, the symptomatic treatment of the Parkinson Disease is dependent on the symptoms exhibited [Koller 1992; Siemers 1992]: anticholinergics for instance are generally considered effective for rigidity but not for bradykinesia, which is better treated with Levodopa. In the current thesis we demonstrate pharmacogenetic differences between these different sub-symptoms of AIP.

Table 1: An overview of the findings of the studies included in the current thesis. AC and SC stand for African-Caribbeans and Slavonic Caucasians, respectively. TD and AIP stand for Tardive Dyskinesia and Antipsychotic-Induced Parkinsonism, respectively. Single Nucleotide Polymorphisms (SNPs) that are possibly associated (PA) are bold printed with the risk-allele (i.e., predisposing allele) reported between brackets. Non-significant findings (NS) are also reported for both ethnicities. On the day of assessment, the majority of the subjects utilized first-generation (typical) antipsychotics; 94% of the African-Caribbeans and 65% of the Slavonic Caucasians.

Genes studied	SNP (common name)	dbSNP#	Movement Disorder studied	Samples studied	Findings TD			Findings AIP		
					Orofaciolingual	Limb/truncal	Rigidity	Bradykinesia	Tremor	
DRD2	-141CIns/Del	Rs1799732	AIP	AC	-	-	AC: PA (Del)	AC: NS	AC: NS	
	<i>TaqIA</i>	Rs1800497	AIP	AC	-	-	AC: NS	AC: NS	AC: NS	
	957C>T	Rs6277	AIP	AC	-	-	AC: NS	AC: NS	AC: NS	
DRD3	Ser9Gly	Rs6280	TD+AIP	AC+SC	AC: NS	AC: PA (9Ser)	AC: NS	AC: NS	AC: NS	
	102T>C	Rs6313	TD	AC	SC: NS	SC: PA (9Gly)	SC: -	SC: -	SC: -	
HTR2A	-1438G>A	Rs6311	TD+AIP	AC+SC	-	-	AC: NS	AC: NS	AC: NS	
	His452Tyr	Rs6314	AIP	AC	SC: NS	-	SC: -	SC: -	SC: -	
	-759C>T	Rs3813929	AIP	AC	-	-	AC: NS	AC: NS	AC: NS	
HTR2C	Cys23Ser	Rs6318	TD+AIP	AC+SC	AC: PA (23Cys)	-	AC: NS	AC: NS	AC: PA (23Ser)	
	+2971C>G	Rs4606	AIP	AC	SC: NS	SC: PA (23Cys)	SC: -	SC: -	SC: -	
RGS2	Ile105Val	Rs1695	TD	SC	SC: PA (105Val)	-	-	-	-	
SOD2	Ala9Val	Rs1799725	TD	SC	SC: PA (9Val)	-	-	-	-	
GPX1	Pro197Leu	Rs1050450	TD	SC	SC: NS	SC: NS	-	-	-	

Similarly, TDof differs phenomenologically from TDIt. Whereas the clinical presentation of TDof involves movements of mouth and face muscles, TDIt involves purposeless choreiform movements of trunk and/or limbs [van Harten 1998]. Also the age of onset may be different in TDof and TDIt: whereas TDof is more prevalent in older patients, TDIt occurs more often in younger patients [Campbell et al., 1983; Gualtieri et al., 1984; Tarsy et al., 1977]. Moreover, TDof and TDIt may respond differently to substances differing in pharmacological properties [Casey and Denney 1977; Lieberman et al., 1988b; Lieberman et al., 1988a]. Therefore, we agree with Paulsen et al. [1996] who have stated “one way to begin to clarify the potentially intricate pathophysiology of TD is to emphasize the clinical heterogeneity in TD to identify subtypes”.

The importance of the dissection of AIP and TD into their corresponding sub-symptoms into separate phenomena rather than composite entities has been corroborated by the pharmacogenetic differences observed in the studies of this thesis.

Our findings should however be interpreted carefully, since the studies outlined in the current thesis -like the majority of the studies on AIP and TD pharmacogenetics- exhibit numerous important limitations. Firstly, the patient numbers described in the present thesis are relatively small. Although this limitation is not uncommon among pharmacogenetic studies on AIMD, it may have led to false-positive or false-negative findings. This limitation is plausible since -to date- pharmacogenetic research has failed to establish common polymorphisms with marked effects on TD and AIP. Large samples may therefore be required to provide adequate power for the demonstration of statistically significant differences. To what extent the limited sample-size may have affected the findings of the current thesis is difficult to estimate. However, our study samples have been comprised of ethnically homogenous and relatively well-characterized inpatients of geographically confined areas. These merits may have compensated for the limited sample-sizes. Although, large samples of subjects well-phenotyped for TD and AIP sub-symptoms are difficult to collect, future research should preferably aim at larger samples.

Another limitation of the presented studies is the study design we used. The studies discussed in this thesis were retrospective investigations using pre-existing data that has been recorded for reasons other than pharmacogenetic research. Weakness and bias of studies with retrospective design are well documented [Hess 2004; Jorgensen and Williamson 2008]. Retrospective genetic-association studies are known for example to underestimate environmental factors (e.g., cumulative exposure to antipsychotic medications) in comparison to genetic factors [Jorgensen and Williamson 2008]. Therefore, prospective observational studies are required to confirm the associations found. However, such studies are costly and are barely justifiable if genotype-phenotype relationship has not been established previously [Ryan 2003]. These factors may explain why case-control and cohort studies have dominated the genetic literature [Jorgensen and Williamson 2008]. Future studies should address this issue more properly. The ongoing Dutch GROUP study on the genetics of psychosis and its treatment is one of the first large prospective studies in this field to address this issue.

Another, rather evident, limitation of the studies presented in this thesis relates to the choice of the genes and the Single Nucleotide Polymorphisms (SNPs). To date over 30,000 genes and 11 million SNPs have been catalogued [Court MH 2007; Jorgensen and Williamson 2008]. Which genes to include and which SNPs to genotype are therefore crucial questions in any candidate-gene study that require a systematic application of the available knowledge to maximize the a priori chance of detecting an association.

In the genes selected, we endeavored to base our choice whenever possible on the available knowledge (hypothesis driven approach). Nevertheless, TD and AIP are polygenic in nature and the omission of many other important genes can not be excluded. Furthermore, the SNPs to be chosen have to be either functional (i.e., affects directly protein function and/or density) or linked with the causative marker. A limitation of the studies presented here is that they were designed to examine single putatively functional SNPs. As opposed to haplotype analyses, this approach does not provide comprehensive coverage of the genetic variation in the genes studied. With high-throughput genotyping platforms being accessible at relatively low costs, future studies should focus more on covering as much as possible genetic variation. Alternatively, examining tagging SNPs and linkage disequilibrium patterns may shorten the list of the variants needed.

The list of limitations can be extended to also include the type of the statistical analyses applied. Since researchers and clinicians heavily base their findings and conclusions on a predefined cut-off value for α (level of significance), the type of the statistical analyses applied is a key factor in the evaluation of the effects of gene variation and is at least as important as the choice of type of the study design and the genotype to be assessed. That the type of the statistical analyses applied is crucially important has been illustrated in chapters 3 and 4. In these chapters we have applied multiple statistical methods (two-part model analysis, logistic and lognormal regression) primarily as an attempt to reduce the chance of false positive and negative findings. Currently, little—if any— effort has been done to define a gold standard for the type of the statistical analyses that need to be applied in pharmacogenetics generally and in pharmacogenetics of antipsychotics particularly.

Finally, an important question arises regarding the clinical value of the polymorphisms studied: can the findings of the present thesis be utilized in daily clinical practice for tailor-made pharmacotherapy? For the time being the answer is probably and regretfully ‘no’.

Firstly, although SNPs may theoretically impact the function of underlying genes, their biological effects—particularly in the case of the polymorphisms studied—are considered to be weak and dependent on the co-presence of genetic, environmental, and epigenetic factors. This fact leaves the clinician incapable of accurately predicting the outcome of the therapy by the use of several SNPs.

Secondly, the pathophysiology of TD and AIP is complex, poorly-understood, and likely to be polygenic. Given the interplay between the genes involved in TD and AIP (e.g., the interplay between DRD2 and HTR2A receptors), the possible effects of genetic variations maybe offset by differences in the activity of other proteins

involved. This interplay makes the study of the pharmacogenetics of pharmacodynamic/pathophysiology genes extremely difficult, in contrast to the pharmacogenetics of pharmacokinetics genes (e.g., cytochrome P450 2D6) where a clear-cut relationship may be present between the blood-levels of the substrate and the presence of a genetic variation.

Thirdly, differences in linkage disequilibrium (LD) patterns may be present, even between subjects of similar race (e.g., 2 Negroid subjects may exhibit difference LD patterns). This variation significantly reduces the clinical utility of the SNPs studied. For example, in African-Caribbeans the 9Ser allele of the Ser9Gly (DRD3) polymorphism predisposes to higher TDIt values, whereas in Slavonic Caucasians it confers protection against TDIt. How the effects of this polymorphism should be interpreted in ethnically-mixed subjects is currently unclear, particularly since current methods of ethnotyping are of limited accuracy (e.g., ‘eyeball-ethnotyping’ or ‘surname ethnotyping’). Haplotype-based instead of genotype-based approach may perhaps increase the applicability of pharmacogenetic-based risk prediction. However, the development of genotype-haplotype inference is currently ongoing and in-vitro haplotyping is currently not feasible.

Fourthly, in the era of evidence-based medicine, the practical value of the polymorphisms studied remains limited, even for those polymorphisms exhibiting a relatively strong association (-141CIns/Del and rigidity), since all of the studies to date on this topic are retrospective and cross-sectional in nature. Large, prospective, and genotype-randomized clinical trials are required to establish the value of genotyping in homogenous samples. However, as stated by Ryan [Ryan 2003], such studies are costly and can be justified only if there is a reproducible genotype-phenotype association. Since non-replication is a general problem among pharmacogenetic and genetic-association studies (e.g., among 55 genetic meta-analyses only 16% of associations were subsequently replicated [Jorgensen and Williamson 2008]), the clinical applicability of pharmacogenetic testing in pharmacodynamics has a long way to go.

CONCLUSIONS

Despite the limitations, the studies presented in this thesis have merits not shared by the majority of the pharmacogenetic studies on AIMD. Furthermore, the studies discussed in this thesis enhance our understanding of TD and AIP and suggest directions for future research. We have shown that in pharmacogenetic studies on AIMD and especially in relation to pharmacodynamics genes, basic pharmacological principles (e.g., studying well characterized responses and considering the pharmacological affinities of the drugs examined) are of utmost importance but are rarely acknowledged. We have also shown that the sub-symptoms of TD (TDof and TDIt) and AIP (rigidity, bradykinesia, and tremor at rest) may differ pharmacogenetically. This finding corroborates previous non-genetic findings that these sub-symptoms are clinically distinct entities. We therefore believe that

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the present thesis significantly broadens and extends our scarce knowledge on AIP and TD pharmacogenetics.

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