The Fourth Annual Pharmacogenetics in Psychiatry Meeting

April 14 and 15, 2005

The Fifth Annual Pharmacogenetics in Psychiatry Meeting

April 7 and 8, 2006

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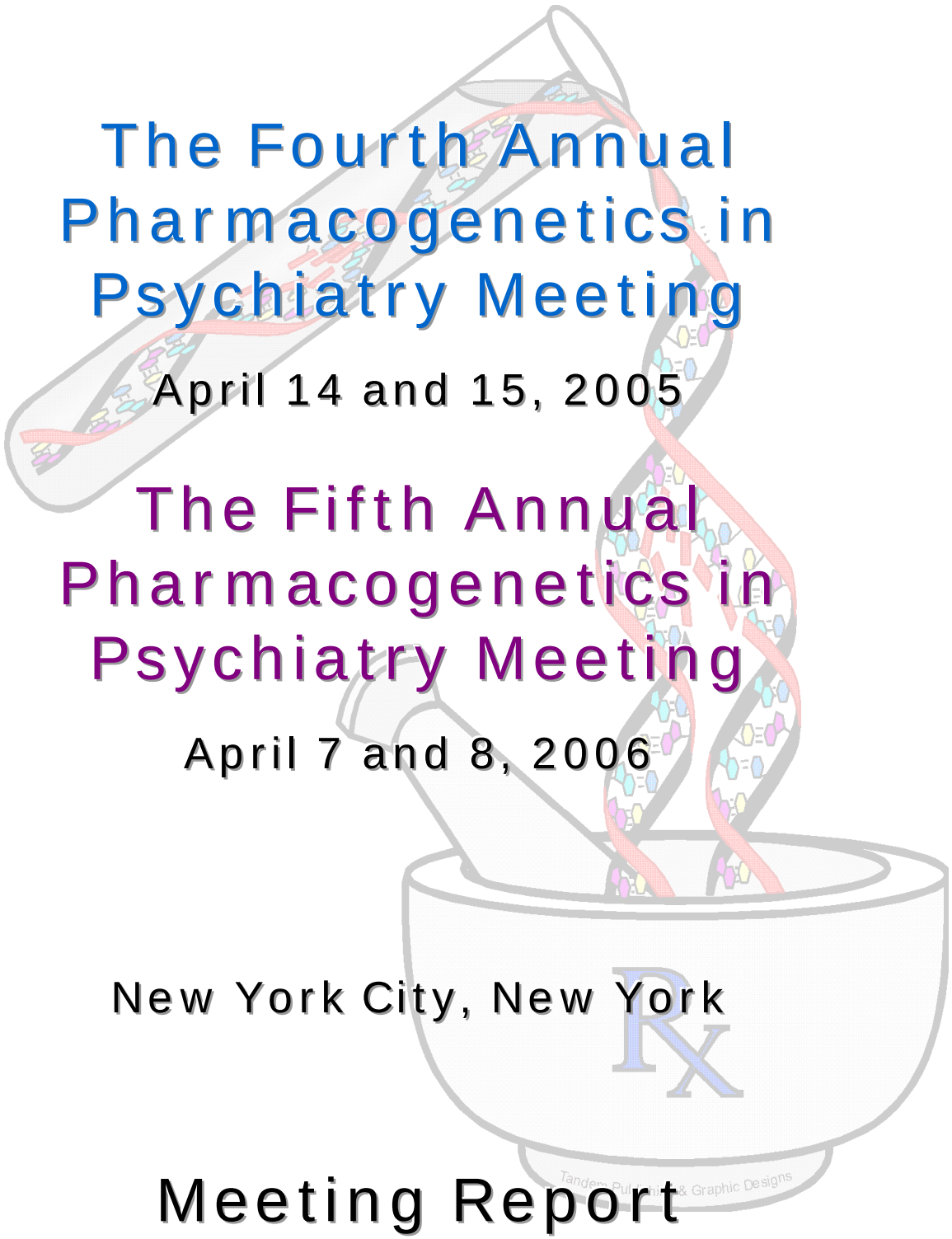
Meeting Report



North Shore LIJ The Zucker Hillside Hospital

North Shore-Long Island Jewish Health System

Pharmacogenetics in Psychiatry

The Fourth and Fifth Annual Pharmacogenetics in Psychiatry Meetings

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Conflicts of interest:
Dr. Aitchison has received AmpliChip CYP450 microarrays and associated support from Roche Diagnostics.
Dr. Kennedy is a consultant for Glaxo Smith Kline.
Dr. Malhotra is on the Roche Diagnostics advisory board and the Genaissance Pharmaceuticals scientific advisory board.

Introduction

The field of pharmacogenetics in psychiatry has expanded over the last few years to necessitate a dedicated meeting on the issue along with symposia in larger, more general psychiatric conferences. The first Annual Pharmacogenetics in Psychiatry meeting was held in New York in 2001, and the fact that there has evolved a well-attended yearly meeting is testament to both the importance of dedicated research in the field and the great interest and enthusiasm that both researchers and clinicians have in the topic. This article reviews the progression in the field as illustrated by the Annual Meetings from 2005-2007 (New York).Academics in the field and local clinicians with an interest in the area have bee well represented at all meetings. Presenters have highlighted achievements and future directions of this exciting area.

Keynote presentations: The Future of Pharmacogenetics in Psychiatry?

Both the 2005 and 2006 meetings included keynote presentations form leading researchers in the field. Speakers in 2005 were David Goldstein (UCL, UK), David Goldman (NIAAA, USA), and Terry Goldberg (NIMH, USA), whilst Goldstein also presented the plenary lecture at the 2006 meeting. In the first 2005 keynote lecture, Goldstein encouraged researchers to think about the biological mechanisms behind drug administration; specifically metabolism in the liver (performed by CYP450 enzymes), and the mechanism of entering the brain via the blood-brain barrier (in part facilitated by multidrug resistence protein 1, coded for by the gene *ABCB1*) when embarking on pharmacogenetic studies. Using pharmacogenetic treatment of epilepsy as an example, he reported how one variant of the metabolic *CYP2C9* gene (*CYP2C9*3)* was found to be associated with a low average phenytoin dose required to control epilepsy, whilst in an investigation of haplotype-tagging Single Nucleotide Polymorphisms (tSNPs) of *SCN1A* (Neuronal Sodium Channel Alpha Subunit), one tSNP (tSNP7) was found to be associated with carbamazepine dose. Carbamazapine binds to the SCN1A protein, and this gene had previously been associated with epilepsy (eg. Ohmori et al. 2002). The associated tSNP is an intronic polymorphism, lying in the consensus splicing sequence between neonatal (5N) and adult (5A) forms of exon 5 in *SCN1A*, and functional investigations indicated that it affects the ratio of 5N:5A in mRNA (Tate et al. 2005). In a study of resection samples from patients with temporal lobe epilepsy (TLE), genotypes of tSNP7 associated with increased 5N were increased in non-seizure focus temporal lobe samples in comparison to non-epileptic brain samples or the seizure focus (hippocampus). The up-regulation of 5N in the temporal lobe of TLE patients is consistent with studies of seizures in animal models, and highlights the importance of both developmental and functional effects of variation in maintaining appropriate gene expression. In a further study, Dr. Goldstein reported allele-specific expression of the *ABCB1* C3435T polymorphism, which showed an over-expression of the C allele in heterozygotes, in refractory epilepsy. Dr. Goldstein and colleagues plan to conduct further

expression studies of the polymorphism in brain samples in an attempt to identify anti-epileptic medication that might be effective through this mechanism.

In his 2006 plenary lecture, Goldstein had moved on to controversially state that “metabolism [in terms of pharmacogenetic variation] is not that important.” Evidence behind this statement came from his work in candidate gene studies of the pharmacogenetics of response to phenytoin that he had introduced in the previous year, since the drug target (*SCN1A*) had a greater effect on maintenance dose than did the *CYP2C9* gene. He suggested that pharmacodynamic determinants might be more useful in psychiatry than pharmacokinetic targets.

In the second keynote presentation in 2005, Goldberg reviewed studies of performed at the Clinical Brain Disorders Branch (CBDB), NIH, as part of the “neurocognition as endophenotype for pharmacogentic studies” section of the meeting. He presented results of investigations of genotypic modulation by *COMT* (Catechol-O-Methyltransferase) and *G72* (a gene linked to schizophrenia) of cognitive responses to psychotropic medication. In healthy controls, those with the *COMT* 158 Val/Val genotype performed worse than those with the Met/Met on measures of working memory; *COMT* was therefore hypothesized to be involved in cognitive updating. In attentional and intradimensional set-shifting tasks, individuals with schizophrenia and the Val/Val genotype performed worse than those Val/Met or Met/Met, whilst the opposite pattern of genotype effect was seen in the siblings and healthy controls (i.e. Val/Val > Val/Met > Met/Met in performance). Factor analysis with several prefrontal cortex related cognitive measures revealed that the effect of *COMT* genotype was observed to be particularly strong in cognitive tasks related to target detection. Furthermore, in studies of treatment with olanzapine, Met/Met individuals showed greatest improvement in performance (Bertolino et al., 2004) and a genotype effect was also observed on a cognitive endophenotype in a typical/atypical antipsychotic crossover trial. Goldberg expanded on these findings in his lecture in 2006 (see “neurocognition as an endophenotype for pharmacogenetic studies”). In regard to *G72*, a differential effect of one SNP (SNP10) was seen on working memory in individuals with schizophrenia as compared to siblings and controls; in atypical and typical antipsychotic-treated subjects, individuals with the A/A genotype of SNP10 showed the greatest memory improvement. Given that both *COMT* and *G72* are associated with working memory, the interaction between the two was investigated. In both individuals with schizophrenia and healthy controls, a *COMT* by *G72* interaction was observed. In individuals with schizophrenia, those with *COMT* Val/Val and *G72* SNP10 T/T showed greatest impairment in response on the continuous performance task (CPT), verbal paired associate learning test, and 1-back (memory task), with the variance accounted for by the interaction term approaching 5%, 4%, and 2% respectively. In healthy controls, the interaction term accounted for between 5 and 10% on different cognitive measures. These data show a clear effect of genotype on memory-related

endophenotypes in schizophrenia, and hold some promise for development of management strategies for adverse side-effects

Moving on to the topic of pharmacogenetic studies in the field of addiction biology, Goldman presented the third keynote lecture in 2005 on the "pharmacogenetics of antidepressant drug response" section of the meeting. A review of the heritability of various substance misuse disorders Goldman *et al*. (2005) had shown that the heritability varied between 40% (for hallucinogens) to 70% (for opioids). He then outlined the difference between polygenicity (multiple genetic variants leading to affected status in a given individual) and heterogeneity (multiple genetic variants leading to affected status, with different variants leading to the affected status in different individuals), and how a combination of polygenicity and heterogeneity would be consistent with some apparently conflicting findings in genetic association studies. Using *COMT* as an example, Goldman reviewed associations between the same SNP Goldberg had discussed earlier (Val158Met) and harm avoidance (Enoch et al, 2003), and postulated that the Met/Met genotype was associated with increased anxiety and stress reactivity. In contrast, the Val/Val genotype was seen in a higher frequency in individuals with substance abuse or dependence in a study of Finnish alcoholics (Vandenbergh et al, 1997). Goldman postulated that both the Val158 (via behavioral dyscontrol) and the Met158 (via increased anxiety) could lead to addictive behaviors; this hypothesis would be consistent with the association of the Val158 with addiction in most studies but with the Met158 with addiction in a Chinese study. Moving on to studies of OCD (Obsessive Compulsive Disorder), the role of variation in the serotonin transporter (*5-HTT*) was discussed. The 5-HTTLPR (serotonin transporter length polymorphic region) is a functional polymorphism in the promoter that has two common forms, long (*l*) and short (*s*), the s form being associated with reduced transcription and transporter density. This polymorphism has enjoyed much attention in all areas of psychiatric genetics, although findings have often been inconsistent. Recently, an A>G SNP in the 5-HTTLPR sixth repeat element was described which creates a binding site for the transcription factor AP-2, and in studies of lymphoblastoid cell lines, the presence of a G allele reduced levels of basal 5-HTT mRNA. Tentative suggestions have been made that this SNP might account for some of the non-replications with this gene; however, Goldman acknowledged that there was still significant variability of expression level with the L_A/L_A genotypic group (ie. *ll* homozygotes with wild-type 'A' alleles of the SNP), but a haplotype using a marker from the 3' region predicted some of this variation. The L_A allele was twice as common in OCD cases versus controls, and was two-fold overtransmitted (compared with S/L_G) in a transmission disequilibrium test (TDT) analysis of OCD trios. This is interesting in view of the previous report by Ozaki et al. (2003) of an association between the Ile425Val variant of the serotonin transporter gene (*5-HTT*) and treatment-resistant OCD, and indicates that combinations of functional variants throughout the gene might pre-dispose individuals to the disorder.

Pharmacogenetics of Drug Response*.*

As to be expected, both meetings included sessions focusing on the genetic factors involved in drug response and both antipsychotics and antidepressants were covered. In 2005, the first session focused on antipsychotics, with predictors of response to olanzapine as hot topics. Initially, D. Rujescu (University of Munich, Germany) reported data from a genetic association study on response to haloperidol which showed an association between the Taq1A polymorphism 3' of the *DRD2* (dopamine D_2 receptor) gene and response in both positive and negative symptoms of schizophrenia.

Continuing on this theme, T. Lencz (Recognition and Prevention program, USA) reported an association between sustained response to either risperidone or olanzapine in a first episode treatment trial and two SNPs in the *DRD2* promoter (-141C Ins/Del and the –241A>G); 'A' and del carriers showed the longest time to respond to medication. These studies, in keeping with earlier work (see Malhotra *et al.*, 2004), suggest that *DRD2* is involved in at least some aspects of antipsychotic response. .

In a study of negative symptoms (rated on the Scale for Assessment of Negative Symptoms, SANS) in response to olazapine, J. Bishop (University of Iowa, USA) reported an association with *GRM3* (encoding the metabotropic glutamate-3 receptor) genotypes,. He also outlined a possible interactive effect with the –1438A SNP of the Serotonin Receptor 2A (*5-HT2A)* gene*.* These two markers were suggested to be useful predictors of clinical response to olanzapine in schizophrenia.

Using a slightly different, pre-clinical approach, S.H. Fatemi (University of Minnesota, USA) reported preliminary data from a microarray study of the frontal cortex of chronic olanzapine-treated rats in an attempt to identify novel genes involved in drug response. The validity of this approach was confirmed with identification of 24 down- and 28 up-regulated genes.

The pharmacogenetics of antidepressant response was addressed in all years, with presentations including prediction of citalopram and lithium response on the program. J. Kelsoe (University of California, USA) highlighted the current challenges of treatment of bipolar disorder (BPD), in that there is currently no effective method to predict response, since individual variation is large. In an attempt to address this, Kelsoe and colleagues looked at a number of different genes that have been implicated in lithium response in clinical subtypes of BPD. Their results indicated that *NTRK2* (Neurotrophic Tyrosine Kinase, Receptor, Type 2) and *GRK3* (Beta-Adrenergic Receptor Kinase 2) are associated with euphoric and dysphoric mania respectively, suggesting that different genes and pathways might operate in different manic subtypes. In an attempt to unravel the complex mechanisms behind antidepressant response in

BPD, Kelsoe undertook a neural network analysis, and whilst he tentatively suggested that the genes involved in response might also be involved in susceptibility, preliminary results suggested that this approach could hold some promise in uncovering predictors of specific response pathways.

Both G. Laje (NIMH, USA) and E.J. Peters (University of California) described results from the Sequenced Treatment Alternatives for Depression (STAR*D) study, a study of almost 2000 patients with major depressive disorder (MDD) who were treated with the antidepressant citalopram. The goal was to improve the outcome in patients with treatment-resistant depression by determining what might be the best course of action for such individuals, along with predicting efficacy and side effects. Laje described an association with a SNP in the 2nd intron of the *5-HT2A* gene (rs7997012), where the 'A' allele predicted a better outcome after 6 week's treatment. Interestingly, this allele is 6 times more common in Caucasian than black subjects, suggesting this could contribute to population-specific differences in response within this sample. to complement this, Peters *et al.* resequenced the coding region of serotonergic genes previously associated with antidepressant response, namely Tryptophan Hydroxylase 1 and 2 (*TPH1* and *TPH2*) and *5-HT2A,* with the aim to undertake gene-gene interaction analysis of suitable candidates.

In all three years, A. Serretti (Vita-Salute University, Italy) presented increasingly comprehensive overviews of the pharmacogenetics of antidepressant efficiency. He described the findings that had already been made and replicated in terms of antidepressant response (eg. *5-HTT, 5-HT2A*), and candidates that still require replication (eg. Circadian Locomoter Output Cycles Kaput gene, *CLOCK*). However, he made the point that despite this evidence, these data can not be employed clinically as of yet, since even the strongest findings combined account for only 5% of the variance in antidepressant response. In the same session in 2006, Serretti reported expanded analysis of antidepressant response, including the SNP within the 5-HTTLPR that Goldman had introduced in the earlier meeting. His group showed that this SNP was associated with differential response to antidepressants, and is a promising candidate for future pharmacogenetic studies. In addition, Serretti reported genetic association studies of three variants of the human PERIOD3 (*hPER3*) gene, which is involved in circadian timing. Each of the polymorphisms was associated with different aspects of depressive symptomology. Serretti and colleagues hypothesized that a rare haplotype was associated with atypical depressive features (late onset, worse mood in evenings, etc.). This association, if replicated, might have therapeutic implications for the treatment of atypical depression.

Replicating the work of Seretti and colleagues, H. Sakul (Pfizer Inc. USA) reported results from placebo-controlled SSRI trials conducted by Pfizer in which the contribution of the 5-HTTLPR to response had been investigated. In four out of six trials conducted, a positive association

between *l/l* genotype and response to sertraline on the CGI-I (Clinical Global Impression–Improvement scale). It was hypothesized that one possible reason for the lack of association in two studies was differences in severity of depression in the inclusion criteria.

Finally, in an investigation of metabolism genes Goldberg had introduced earlier, K. Aitchison (Institute of Psychiatry, UK) reported results of a pilot study of response to treatment with tricyclic antidepressants (TCAs), in which an association between change in depression scores and *CYP2C19* gene dosage was found, whilst *CYP2D6* genotypic category was strongly predictive of dose corrected combined TCA level (consistent with Kirchheiner et al., 2004), and the effect of CYP2D6 inhibitors on TCA level was particularly marked for genotypes containing an intermediate metabolizer (IM) allele (Tandon et al, [this should be submitted by the time you submit this, or reference as 2005, which is an abstract]). These data suggest that, with antidepressants at least, metabolic genes do have a role in gene dosage and response.

Pharmacogenetics of Drug-Induced Adverse Effects

Another regular session of this meeting is drug-induce adverse reactions (ADRs), especially those induced by antipsychotics. This is a very important area of research, since side effects of drugs severely affect the probability of compliance. In both the 2005 and 2006 sessions, antipsychotic-induced weight gain was the main topic, with six presentations reviewing new advances in uncovering genetic predictors. D. Müller (University of Toronto, Canada). presented new findings on genetic variation in the neurotransmitter and appetite/energy/fat regulating system in antipsychotic-induced weight gain with an average treatment of more than 8 weeks. Significant associations were observed for Leptin (*LEP)*, Cholecystokinin (*CCK* ligand), Brain Derived Neurotrophic Factor (*BDNF*), and 25 kDa Synaptosome-associated Protein (*SNAP-25*), while a trend was also observed for a SNP in exon 7 of the *DRD2* gene. In 2006, Muller went on to describe a finer-scale analysis of *DRD2* in the same sample, and demonstrated an association with two SNPs in exon 7 (rs6275 and rs6277) and weight gain in response to clozapine; evidence supplied at these meeting suggests that *DRD2* is indeed an important risk factor for antipsychotic response and/or adverse effects.

The finding in *LEP* is of particular interest because it is in accordance with findings on antipsychotic-induced weight gain in the literature, and was also addressed by V. Ellingrod (University of Iowa College of Pharmacy, USA) at the 2006 meeting. Ellingrod described the effect of olanzipine treatment in patients with scizophrenia, and found that there was also an association with the both *LEP* and leptin receptor *(LEPR*) gene polymorphisms and weight gain, but only in individuals with high plasma concentrations of olanzapine. This gene-plasma level association has possible implications for screening of individuals prior to treatment with olanzapine to minimise weight-related side effects.

Staying with olanzapine, Y. Chagnon (Universite Laval Robert-Gifford, Canada) tested for an association between body mass index (BMI) as a side effect of antipsychotics and the Pro-Melanin Concentrating Hormone (*PMCH*) gene. This gene, known to be involved in the control of food intake and energy expenditure in rats, had been selected because a previous genome scan over multigenerational pedigrees using a chronic phenotype of obesity under antipsychotics revealed a linkage peak on chromosome 12 close to the position of *PMCH* (Chagnon et al., 2004). Two SNPs located each end of *PMCH* were genotyped in schizophrenic patients and controls, and a possible association between antipsychotic-induced change in BMI with both SNPs of *PMCH* was noted in patients treated with olanzapine but not with risperidone. In 2006, Chagnon decsribed a two- stage linkage scan that complemented this work, and they identified a number of genes possibly associated with weight gain, including Disrupted In Schizophrenia 1 (*DISC1*), *DTNBP1* and *5-HT2A*. Chagnon noted the interesting point that in the first scan, the effect of *DTNBP1* was only observed when BMI was taken into consideration, suggesting that this could be a general obesity factor and that BMI should be included as a co-factor in these types of analyses.

Finally, in a move away from weight-gain as a side-effect, Clozapine-induced agranulocytosis (CIA) was discussed in both 2005 (M. Athanasiou; Genaissance, USA) and 2006 (A. Malhotra, the Zucker Hillside Hospital, USA). CIA is a potentially fatal, acute condition resulting in reduction in white blood cell count (neutrophil count <500/mm^3), and the risk is such that users of clozapine must have cell counts monitored regularly as a preventative measure. As a result, there is large impetus to identify those individuals who might possess genetic vulnerability to the condition before treatment with clozapine. Athanasiou reported on novel genes found to be associated with CIA,.noting that if a test could be developed that predicts CIA in 80% of patients (with a false rate of 20%), such a test would lead to a reduction of CIA in 75% of cases. 74 candidate genes were sequenced based on their involvement in clozapine metabolism, promyelocytic differentiation and previous discoveries with CIA. Two genes in the HLA complex (*HLA-DQB1* and *HLA-C*) and three novel genes were found to be significantly associated with CIA (adjusted $p<.05$). The combination of one marker of the *HLA-DQB1* gene with one novel gene marker revealed a sensitivity of 79% and a specificity of 80% with an adjusted odds ratio of 20.9. Malhotra expanded on these findings in 2006, to demonstrate that the combination of *HLA-DQB1* and R-Beta Granulocyte-Macrophage Colony Stimulating Factor (*CSF2RB*) gave sensitivity of 80% and a specificity of almost 100%. Although he stressed that replication of these findings is very important, the possibility of these reults translating into a clinical test for CIA is very high.

Neurocognition as an Endophenotype for Pharmacogenetic Studies.

Following on from the discussion of genetic predictors of adverse side-effects, all three meetings included a session focusing on the effect of drug treatment on cognition, and the

various technological approaches to testing it. In 2005, K. Burdick (The Zucker Hillside Hospital, USA) reviewed neurocognitive genetic association studies relevant to schizophrenia, and described the role of a risk haplotype in *DTNBP1* on general cognitive ability ('g') and negative symptoms (as measured by SCID-IV) in schizophrenic patients and controls. Consistent with previous work, carriers of the risk haplotype performed worse in every measure of cognitive performance, and had more negative symptamology than non-carriers. These results suggested that *DTNBP1* might be a target for treatment of decreases in cognitive performance in schizophrenia. However, their preliminary work suggests that this gene is not implicated in response to atypical antipsychotics, although trials specifically targeting cognitive enhancement with antipsychotics (pramipexole and D-serine transport inhibitor) and genotype effect are currently underway.

A. Papassotiropoulos (University of Zurich, Switzerland) reported genetic association studies of variation in verbal episodic memory in Swiss university students and non-university employees. A significant association between a SNP in the *5-HT2A* gene (His452Tyr) polymorphism and 5 minute delayed recall had been found (de Quervain et al, 2003), with individuals with the His/His genotype group performing better than those with the His/Tyr. In a further study of subjects aged between 18-90, this association held up only in individuals under 45 years of age, which was interpreted as being caused by the phenomenon of reduced $5HT_{2A}$-receptor density with increasing age (Sheline et al, 2002). Subsequent fMRI studies of the this SNP revealed His/Tyr subjects had increased activation in a memory retrieval paradigm, further evidence that this polymorphism might be involved in memory. In addition, Papassotiropoulos described work his group had been conducting into the role of the prion protein gene (*PRNP*), since prion-like conformational changes might be related to synaptic changes involved in long-term memory in Aplysia (Si et al, 2003). In verbal memory studies of the M129V polymorphism of the *PRNP,* 129M/M or M/V subjects performed better than 129V/V in 24-hour delayed recall. Papassotiropoulos and de Quervain had also replicated the association reported by Malhotra *et al* (2002) between the *COMT* Val158Met polymorphism and working memory, finding Val carriers to perform worse than Met carriers in immediate recall.

In 2006, Papassotiropoulos expanded on this work to report on results of a genome-wide association scan of episodic memory using 500K SNP micraorrays. They uncovered 45 SNPs associated with episodic memory, all of which were expressed in brain. One of these genes is *KIBRA* (kidney and brain expressed protein), which has high expression in the hippocampus consistent with a role in memory. Further genotyping studies in other cohorts have replicated this association with episodic memory, making *KIBRA* a useful target for studies of both human cognition and drug response. C. Opgen-Rhein (Charite-University Medicine Berlin, Germany) described the role of *BDNF* and Ionotropic N-Methyl-D-Aspartate Glutamate Receptor 3A (*GRIN3A)* in attention in schizophrenic individuals. Using schizophrenic patients and controls,

Opgen-Rhein and colleagues demonstrated that polymorphisms in both these genes influenced conflict effect, a domain of attention. These results suggest both the validity of attention as an endophenotype of schizophrenia, and that variation if *BDNF* and *GRIN3A* might be targets for treating cognitive deficits in schizophrenia.

In 2005, the potential for neuroimaging as a tool to uncover pharmacogenetic phenotypes was introduced, with presentations by P. Szeszko (Zucker Hillside Hospital, USA) and T. Goldberg. Szeszko had already described the previous year an association between *BDNF* Val66Met polymorphism and hippocampal volume in first episode schizophrenia, the Val/Val genotype being associated with greater volume. It was hypothesized that the Val/Met polymorphism affects hippocampal development in both healthy controls and individuals with schizophrenia, with perhaps a subset of individuals with schizophrenia showing a more marked effect of this polymorphism.

In 2006, Szesko described the effect of *DISC1* Leu607Phe polymorphisms on prefrontal grey matter volume. A risk haplotype within this gene had previously been associated with decreased grey matter volume (Cannon et al., 2005), and Szeszko demonstrated that this was also the case in his sample of schizophrenics. In addition, it was also shown that this polymorphism was associated with greater severity of hallucinations, and provided a potential mechanism for which *DISC1* might confer risk for schizophrenia/ schizoaffective disorder. Furthermore, since atypical antipsychotics increase expression of *DISC1* (Chiba et al., 2006), as well as increasing prefrontal cortex thickness, Szeszko postulated that genetic variation in *DISC1* could be associated with treatment response via prefrontal cortex circuitry. Goldberg presented results from a study of 42 individuals under the hypothesis that *COMT* Val158Met variation would predict variation in prefrontal cortex efficiency as measured by BOLD (blood oxygen level depletion) tests after treatment with tolcapone, a *COMT* inhibitor. He demonstrated that COMT genotype did predict differences in response; Val/Val individuals showed an overall improvement, whilst Met/Met individuals worsened. He hypothesised optimal dopamine function is on an inverted 'U' curve, and that response is genotype-driven, so that under baseline conditions Met/Met individuals have optimal function, whilst Val/Val and Val/Met are sub-optimal. At baseline, Met/Met individuals perform better in cognitive tasks than Val/Val, but under conditions of high load (eg. increased dopamine, treatment with tolcapone), the distribution shifts, so that Val/Val individuals are at the peak of functioning, and the functioning of other genotypes is decreased.

Emerging Methods in Pharmacogenetics in Psychiatry

Several presentations throughout the course of the three meetings had demonstrated that newer methodologies of assessing the role of genetic variation could be successfully applied to the field pharmacogenetics in psychiatry (eg. microarrays, functional imaging, and novel

statistical methodologies). Such presentations highlighted the advances being made which were relevant to this specific field and also indicated the potential of using novel approaches to existing problems.

S.H. Fatemi, who had presented results from a microarray study of olanzapine-treated rat brain at the 2005 meeting, presented in 2006 the results of a study of the reelin protein in rat prefrontal cortex. The results indicated that two antipsychotics, olanzapine and clozapine, increased and decreased reelin 410 and 180kDa protein isoforms respectively, and that investigating both gene and protein expression in response to drug administration might an important tool in uncovering the different modes of action.

Moving on to the area of whole genome association approach in pharmacogenetics, Lencz reviewed the advances that had been made so far, and both the advantages and the potential pitfalls. The advantages are the identification of novel candidates; however, he explained that these types of studies often suffer from lack of power due to small sample numbers. Nonetheless, he outlined some recent advances in psychiatric genetics using this technique, and gave some examples from current work he and colleagues are undertaking using the Affymetrix 500K SNP microarray system. He did, however, point out that candidate gene studies will continue to be the approach of choice for the near future, probably due to cost constraints imposed on microarray experiments.

H.S. Stassen (Psychiatric University Hospital, Zurich, now moved to [give affiliation in Basel], Switzerland) discussed the evidence for shared genetic factors in psychiatric disorders by presenting evidence from the study of 71 Swiss nuclear families that were subjected to a genome scan for both drug response and vulnerability to schizophrenia and BPD. Results suggested that there are co-existing vulnerability and resilience factors for both disorders, along with response to drugs. Interestingly, none of these factors were necessary or sufficient for the disorder, suggesting that the amount of individual variation in underlying genetic vulnerability to psychiatric disorder is very large, and that uncovering it will present researchers with many challenges for the future.

Finally, in a highly relevant but often overlooked area of pharmacogenetics, G. Javitt (Genetics and Public Policy Center, USA; www.DNApolicy.org) discussed the current regulations for pharmacogenetic tests, and the outlook for the ensuring future test quality. This was a very interesting topic for this type of meeting, since the one of the ultimate aims for pharmacogenetics include the development of accurate and reliable tests for individual drug response. The mission of the Genetics and Public Policy Center is to create an environment and tools needed by key decision makers in the private and public sector for genetic testing. Surprisingly, there are currently over 900 available genetic tests, although many of these tests

are not yet of clinical quality (only about a dozen having been approved by the FDA). The worrying fact of the current state of regulation is that many of these tests are available directly to the consumer, without the advice of qualified healthcare professionals. Additionally, the amount of regulation required depends on the type of test being performed; those using 'home brew' tests do not require FDA checks, simply checks that the 'recipe' is being followed. Therefore, the quality of these types of tests is not assured by any external regulating body. The ultimate aim is to ensure that there is government regulation and evaluation of all genetic tests to ensure accuracy, reliability and appropriateness.

Expert Opinion

Pharmacogenetics in psychiatry is on the brink of new breakthroughs in all aspects of the medication spectrum; dosage, maintenance and adverse effects. However, the over-riding message of the meeting was that we really need to get to the mechanisms behind these associations and figure out what is driving these genetic associations. This is not a problem confined to pharmacogenetics, but a genetics-wide problem, and we need to use other fields as examples of what can be done how to tackle it. We are beginning to do that with implementation of new techniques and approaches, and many of these techniques are becoming more accessible; for example, microarrays are becoming progressively cheaper.

Outlook

This conference was outstanding in addressing all of the relevant points in psychiatric pharmacogenetics that abound today. Attendees would have been left better able to not only approach their studies, and better equipped to deal with confounding factors that are inherent in this type of research, but also with clear ideas for the future. It is now obvious, for example, that not all antipsychotics work the same way, and that endophenotypes hold promise as drug-responsive intermediate phenotypes for treatment measurement. Of course, the ultimate aim is clinical relevance, and the overall message form the meetings was we are not quite there yet, but we are making real progress. In summary, in keeping with the tradition of this meeting, investigators presented their most recent work in the field, allowing participants to discuss their current research with established scientists in an atmosphere of healthy discussion and open disclosure, and fostering collaborative strategies for future pharmacogenetic research.

Highlights

1. Pharmacogenetics in psychiatry, is yielding some real promise for prediction of individual differences in drug response and averse side effects.
2. Newer approaches to assessing the role of genetic variation (e.g. functional imaging, whole genome association analysis) that have been employed in other fields are being employed with success.

3. Related endophenotypes can have a differential response to drugs; different endophenotypes might need to be looked at separately.
4. Some genes have been replicated consistently in this field (eg. 5-HTT, *DRD2, COMT*).
5. There are still issues of ethical, legal and social policy implications to be further studied and addressed.
6. Clinical application (diagnostics) is just emerging and likely to increase greatly with data emerging from WGA and other approaches.

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