WORLD PSYCHIATRIC ASSOCIATION

Highlights of the Recent Activities of the WPA Section

Genetics in Psychiatry

2020-2023

Impressum

This a publication of WPA Scientific Section on Genetics

WORLD PSYCHIATRIC ASSOCIATION

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Dear colleagues and friends,

It is a great pleasure and honor to welcome you to the 23rd World Congress of Psychiatry in beautiful Vienna, Austria. This is the second in-person World Congress after the end of the pandemic. After two difficult years for all of us, the world of global psychiatry met in Bangkok in August of last year. With close to 3,000 attendees, this was a testament to the energy and resilience in the face of hardships of the World Psychiatric Association (WPA), our association, YOUR association.

This year, we are looking at close to 4,000 attendees, with participants from all around the globe and more than 100 member societies actively taking part in the governance of WPA by electing a new leadership for the 2023-2026 triennium. The last two triennia have seen a consolidation of WPA as the global voice of psychiatry. We have made major headway towards modernizing and streamlining our infrastructural, communicational, and educational tools.

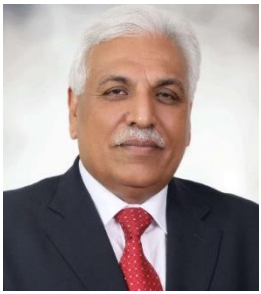
The Sections have proven that they are indeed WPA's scientific backbone. In fact, they have become a major motor of innovation for WPA: harnessing the strength that comes from their global diversity, they have blended scientific excellence with tangible actions in all corners of the world: the WPA Exchange Program, ESPRI (Education, Science, Publication, and Research Initiative) focusing on low- and middle-income countries, WPA's Education Portal, and many more initiatives would not have been possible without our Sections.

One of them you are holding in your hands right now: a booklet, entitled "World Psychiatric Association: Highlights of the Recent Activities of the Genetics in Psychiatry Section 2020-2023" produced by members of our Section on Genetics in Psychiatry. The idea for this booklet (which will also be made available online) was

born out of a large international research consortium funded by the European Union within the Horizon 2020 framework. It is spearheaded by members of our Section: "A New Intervention for Implementation of Pharmacogenetics in Psychiatry" (www.PSY-PGx.org).

WPA is honored to be a partner in the dissemination and education work package of this consortium. And we are happy that we can deliver! We hope that you will enjoy reading this booklet and that you will find its content useful in your daily clinical work. We would like to thank the authors and the Section on Genetics in Psychiatry for their effort and for their great intersectional spirit, demonstrated by numerous educational activities at WPA congresses in the past two triennia.

Yours sincerely,



Afzal Javed (UK & Pakistan)
President
World Psychiatric Association

Thomas G. Schulze (USA & Germany)
Secretary for Scientific Sections
World Psychiatric Association

Dear colleagues,

The Chairs of the WPA Genetics in Psychiatry Section along with the Principal Investigator of the WPA associated grant in pharmacogenetics are pleased to provide a brief highlight of our recent activities discussing the role of genetics in psychiatric practice. The aim of genetics and pharmacogenetic-based treatment is to benefit our patients by better understanding the causes of psychiatric disorders and increasing the effectiveness of treatment through assessing person-specific genetic factors that predict clinical response and side effects. Standing on the threshold of such a powerful change in psychiatric treatment requires, in our opinion, a comprehensive consideration of this approach from different perspectives to guarantee that the development and implementation will be fair, ethically sound and beneficial for patients, individuals at risk and their society - across all social classes, cultures, and ethnicities. We hope that this is a useful document to WPA members to understand the rapidly changing field of genetics and encourage any interested members to join our society.

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1. The Role of Genetics in Psychiatry:

Psychiatric genetics has the potential to inform prevention, diagnosis and treatment of psychiatric disorders. During the last two decades genetic research has made tremendous progress in identifying genetic risk factors at a molecular level and in shedding light on the complex etiology of psychiatric disorders. However, while many insights have been gained, there are very few instances where such discoveries have been translated into the clinic.

Currently, the use of genetic testing in clinical practice is limited to subjects suspected of having Mendelian Disorders (for example, Huntington's disease or other rare forms of early onset-dementia) or in specific neurodevelopmental conditions such as intellectual disability or severe autism (for more detail see: https://ispg.net/genetic-testing-statement). In common psychiatric disorders (such as schizophrenia, bipolar disorder or severe depression), there are no current genetic (or other) biomarkers available to guide psychiatric diagnoses, inform prognosis, or guide treatment selection.

With the advent of new technologies in genomic and phenomics analyses such as a broader measurement of potential biomarkers ("omics") and larger-scale phenotypic data capture through longitudinal ecological momentary assessment, there is hope that emerging insights will be more directly applicable to specific clinical concerns in diverse and representative populations. Although we are not there yet, we provide a short update of the present state-of the art of genetic research and testing in psychiatry below.

We know that genetic factors play a significant role in the etiology of all psychiatric disorders because family-based and twin studies have shown that most psychiatric disorders are significantly heritable. Although not as simple or intuitive as it sounds, the statistical concept of heritability provides us with confidence that genes are involved, even though heritability can change under

different environments, and heritability, by itself does not mean that the phenotypes themselves cannot be changed. Using this information in genetic counselling is helpful and can correct misbeliefs of genetic determinism that often lead to unnecessary worry and guilt.

Genetic studies are of two major types: those focusing on common genetic variants (GWAS) and those focused on rare variation that require sequencing either at the exome or whole genome level (Rare variation association studies or RVAS).

Genome Wide Association Studies (GWAS): Common variant studies focus on variations in the genome that occur approximately in 1% or more of the population. Because these variations are common, they have essentially all been discovered, allowing us to design cost-effective microarray chips that can determine what type of variation (or allele) is present in these known locations. Eventually, as whole genome sequencing becomes cheaper and more feasible, it will be the genetic test of choice; however, for the time being the vast majority of GWAS studies utilize microarray chips.

An important consideration in the study of common variants is that because they are common, it is unlikely that they are associated with a particularly severe effect, either at the levels of molecules or at the level of the phenotype. This is because if they were associated with a severe effect, natural selection would probably prevent them from being common and we would instead expect them to be rare (see below). There are, as always, a few exceptions, the most widely known being the common APOE4 allele that is associated with Alzheimer's disease. Here the risk allele has a much bigger effect (odds ratio ~ 8) than we usually see in common variant studies, but natural selection has "allowed" for such an effect because the disease occurs late in life after individuals have been able to have children.

However, except for very few such examples, common variant studies tend to find variants with effect sizes in the 1.01 to 1.2 range. This means that we need large sample sizes to confidently detect their presence in a population and it also means that individually, a single common variant is likely to have a very subtle effect on disease related biology or risk. GWAS studies have now been carried out at sufficiently large sample sizes for all the major disorders, and numerous significant genome-wide associations have been discovered (Figure 1).

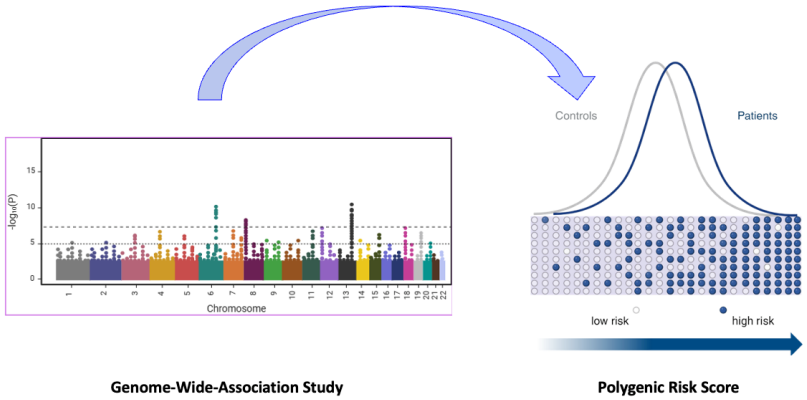
The major focus now is to maximize this effort so that we discover essentially all common variants associated with a disorder so as to better characterize them biologically and clinically. These associations still have all the caveats of any biomarker study and they need to be interpreted cautiously, because they may still be influenced by confounding factors and because they rarely point directly to actionable biology. This does not mean that they are not useful, or that they do not provide insights, but that they must be considered with care. Indeed, GWAS findings have begun to shed light on the genetic structure and the etiology of these disorders, as well as their genetic heterogeneity, their genetic overlap, and, most importantly, the genes, pathways, tissues and cells involved.

Although the effect sizes of each of these variants are small, they can be summed up into a so-called polygenic risk score to increase their predictive ability. Polygenic risk scores are first constructed from a large scale GWAS study to identify which variants should be used in their score and how to weigh them based on the strength of their association. They are then applied to an independent dataset with GWAS data to determine how associated or predictive they are in individuals with the phenotype in question. As with any other risk factors, there is usually a slightly increased distribution of polygenic risks in affected subjects versus normal controls (see Figure 1).

However, this pattern is seen at a group level, and there is usually marked variability at the individual level, which currently limits their utility in clinical practice. As GWAS studies become larger, the accuracy of the initial training dataset should increase (all other factors being equal) and therefore the expectation is that the predictive ability of polygenic risk scores should also increase in the next several years.

One important consideration is that polygenic risk scores tend to fare poorly when tested in different populations relative to population where the initial GWAS study was conducted. Hence, the major focus of current GWAS studies is to increase their populational diversity so that they are sufficiently predictive of an outcome, and that they are predictive for all global populations. Although a few direct-to-consumer tests are already offering genome-wide association tests, almost all current guidelines (for example, https://ispg.net/genetic-testing-statement/) consider their use to be premature and not yet tested with rigorous clinical trials. However, stay tuned, because such trials are likely to occur in the near future and their results will likely be available.

Figure1. Genome-wide Association Studies and Polygenic Risk Scores



Rare Variant Association Study (RVAS): The other major study of genetic variation in psychiatric disorders is the RVAS. In principle, this is very similar to GWAS, except that it is focused on variants that are much less common, and sometimes seen only once in the entire sample.

The rarest form of variation is the one that arises a new or *de novo* from minor replication errors during fertilization. *De novo* variants occur in all births, but the vast majority of such variants are neutral and have no detrimental effect. However, in certain severe early-onset disorders like autism and intellectual disability, these *de novo* variants have been found to affect functioning in genes that are likely to be causal. Rare variants are likely to play less of a central role in other disorders such as schizophrenia and bipolar disorder. Nevertheless, disorder associated rare variants can still provide potentially important knowledge to both the individual and for biological insights, since rare variants are usually easier to interpret and can have a more pronounced role in gene functioning.

RVAS studies are still in their infancy compared to the common variant GWAS, but they are rapidly increasing in sample size. When whole genome sequencing studies become economically feasible, essentially all genetic studies will include both rare variant and common variant studies at the same time. Ultimately, the best estimates of risk will be to combine both common and rare variants studies – such studies are currently being performed and already show that both types of variation can influence clinically relevant phenotypes.

2. Pharmacogenetics (PGx) in Psychiatry

The study of the role of heritable genetic variation on drug response is referred to as pharmacogenetics (PGx). Knowledge of an individual's genetic background for drug-metabolizing enzymes, drug transporters, receptors or effector proteins can be used to guide pharmacological treatment. However, the value of PGx in most areas of clinical care remains controversial, and its implementation in daily clinical practice remains challenging, including in psychiatry. In practice, there are many questions about the application of pharmacogenetics. For which patient can pharmacogenetic testing be beneficial, how to order, what genes to test for, and how can a clinician translate the results into clinical actions when prescribing medication?

There are several pharmacogenetic guidelines as (for example from the Dutch Pharmacogenetics Working Group (DPWG), the US-based Clinical Pharmacogenetics Implementation Consortium

(CPIC), the Canadian Pharmacogenomics Networks for Drug Safety (CPNDS) or the French National Network for Pharmacogenetics (RNPGx), including a recent report on the use of pharmacogenetics guideline for daily psychiatric practice by the principal investigator of the WPA affiliated pharmacogenetic study (van Westrhenen et al. 2021, see below). For psychiatric medications, the guideline focuses on genetic variation in pharmacokinetic determinants (CYP enzymes), where most of the current evidence for potential clinical utility exists. Currently, our knowledge of pharmacodynamic variation is too limited to have clinical utility. The strongest evidence for genetic variations in the metabolism of psychiatric medications are found in the CYP2D6 or CYP2C19 genes, which can help assign individuals into several phenotypic categories.

First, there is a group with normal metabolism: these are the normal metabolizers (NM, also known in the old nomenclature as extensive metabolizers (EM) that have normal degradation capacity. Second, there is a group with delayed metabolism due to mutations leading to minimal degradation capacity: these are the poor metabolizers (PM). The third group is formed by a group in which metabolism is accelerated by, among other things, duplications of a gene, the so-called ultrarapid metabolizers (UM). Finally, there is a group with a metabolic capacity between an NM and a PM; the intermediate metabolizers (IM). Based on these phenotypes several groups, listed above, have formulated medication dosing guidelines.

Despite the presence of these mostly concordant guidelines, their uptake in clinical care has so far been limited. Reasons for this are that these current guidelines are not easily accessible, in many cases inconsistent and not user-friendly, hampering clinical uptake of pharmacogenetics in real-life patient settings. Moreover, the pharmacogenetic guidelines only provide advice for pharmacogenetic metabolizer status for one gene and one drug, whereas clinical reality often includes complicated polypharmacy.

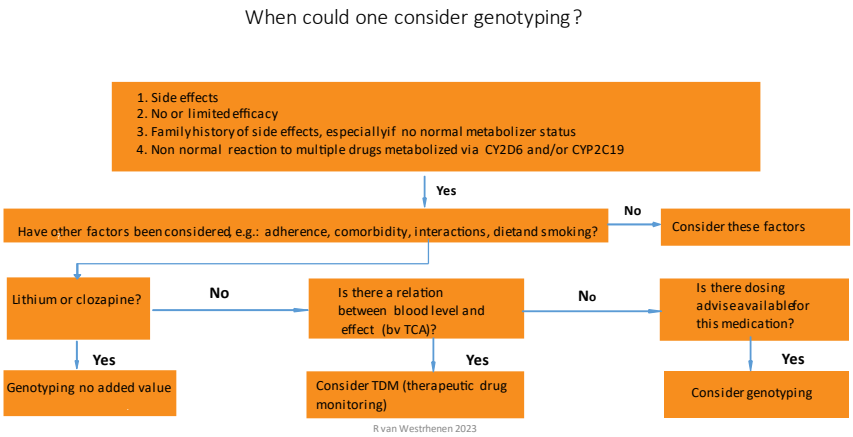
In 2020 the Dutch Psychiatric Association produced an open-access clinical guideline for psychiatrists (van Westrhenen e.a. 2021), This guideline helps to bridge the gap between the already available more technical guidelines, to practical application in clinical practice, as simple and easy-to-apply information is available that clinicians can adopt in their clinical practice without having to read through full texts on different websites or scientific publications. A short outline of this guideline for psychiatrists is provided below.

When to request pharmacogenetic tests:

Consider genotyping a person if there are side effects at a normal dose or with insufficient efficacy. This is particularly important if a patient reacts unexpectedly to multiple drugs that are metabolized in the same way. Pharmacogenetic testing has the advantage that it provides information on the degradation capacity of multiple drugs and in principle only needs to be performed once because the pharmacogenetic profile does not change.

See Figure 2 Flowchart Pharmacogenetics in psychiatry (van Westrhenen e.a. 2021) for a representation of the considerations that can be made before proceeding to request pharmacogenetic testing. The guidance expresses that a request for pharmacogenetic testing can be limited for the time being to genotyping CYP2D6 and CYP2C19. In principle, there is currently no role for genotyping CYP1A2, CYP3A4, CYP2C9 or other pharmacogenetic variants, other than after thorough pharmacological analysis and/or consultation with a clinical pharmacologist or (hospital) pharmacist experienced in the field of pharmacogenetics.

Figure 2



What to do with the results of pharmacogenetic testing

It is important that the results of pharmacogenetic testing, after proper patient consent, should be shared with other healthcare providers including their general practitioner and pharmacist. Information from pharmacogenetic testing may be important for drugs other than the specific psychopharmaceutical for which the study was requested. The pharmacogenetic profile can be used for selecting and dosing medications already in use but also for newly prescribed medications. Ideally, a medical provider or pharmacist can record the pharmacogenetic information in the patient's record so that an alert is automatically generated if the patient is prescribed a drug where the pharmacogenetic information is relevant (van Westrhenen e.a. 2021).

3. Conclusion: Key messages for applying genetics in psychiatry

Routine genetic screening for psychiatric disorders is currently not recommended for most psychiatric disorders, although exceptions exist e.g. for subjects with prominent intellectual disability, severe autism and certain types of dementia. Genetic counselling should be mandatory whenever genetic testing is considered. Genetic counselling can often be most beneficial and informative even without genetic testing because it can explain why the disease occurred and help limit the stigma that families and individuals may experience. Counselling may also help parents understand the risk of recurrence of the disorder in their other offspring.

For pharmacogenetics, begin with the basics: clinicians should familiarize themselves with the pharmacokinetic pathways of drugs they prescribe as well as interactions with other drugs used for common comorbidities. This will aid in evaluating the feasibility and need for pharmacogenetic testing and how the results can affect treatment.

Consider genotyping of CYP2C19 and CYP2D6 in clinical practice in patients taking antidepressants or antipsychotics when there are side effects or ineffectiveness after starting treatment with a selective serotonin reuptake inhibitor (SSRI) or selective serotonin and noradrenalin reuptake inhibitor (SNRI). This applies especially if the patient has experienced side effects or ineffectiveness with multiple drugs with similar CYP metabolism.

However, we must acknowledge that the promise of pharmacogenetics whereby a drug and dosage are chosen based on a genetic passport prior to prescription is not yet fulfilled. Ongoing research will show whether evidence exists for the routine (rather

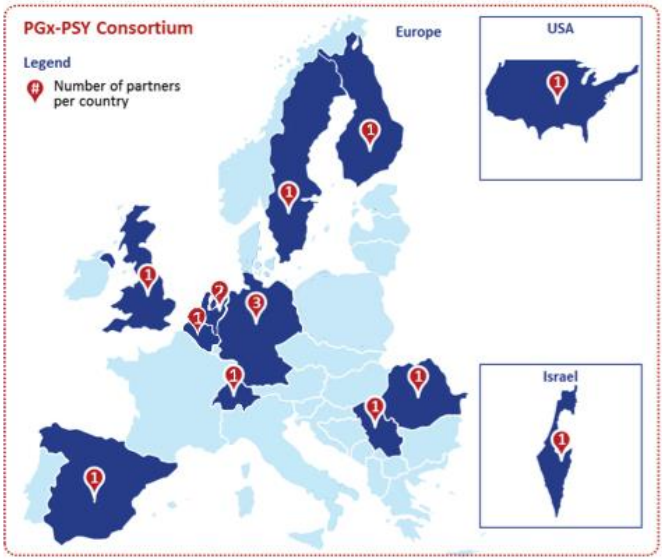
than case specific) application of pharmacogenetic testing in psychiatric patients.

4. WPA supported project: PSY-PGx

The **PSY-PGx Consortium**, funded by the European Union's Horizon 2020 Program is the first investigator initiated (Prof. R. van Westrhenen) initiative to propose a multi-center large-scale non-industry sponsored randomized clinical study that systematically researches the clinical benefits and potential of pharmacogenetic-based interventions for psychiatric patients.

Patients with depression (unipolar and bipolar), anxiety or psychotic disorders, who experience an acute illness episode with the need for a medication change, can enroll in the clinical study at nine inclusion sites across seven countries. All participants receive treatment with well-established medications but are randomly assigned to a pharmacogenetics-testing group (dosing based on pharmacogenetic information) or a dosing-as-usual group. In parallel, biobank data from Finland and the UK are investigated to search for additional pharmacogenetic associations that influence medication response.

This information will be integrated with existing knowledge and the results of the clinical study to develop an algorithm for personalized medication prescriptions.



The PSY-PGx consortium unites 16 partners from 11 European (and related) countries and the US. This large consortium is required for a variety of reasons:

Multidisciplinary: As PSY-PGx is a holistic personal medicine approach, a truly multidisciplinary expertise is needed. The PSY-PGx consortium includes experts in genetics/ pharmacogenetics, ICT (computing, IT infrastructures, smart tools), psychiatric clinical practice and research.

The WPA, as a member of this Consortium- has been tasked with the dissemination of its findings. Such results will inform our members on how to use pharmacogenetic-based treatment personalization in real-life psychiatric care for mood, anxiety or psychotic disorder patients. (PSY-PGx Website).

The Genetics Section of the WPA is included in the project for dissemination of the undertakings of PSY-PGX as well as education of

its members on pharmacogenetics. To that end, we organized symposia at several WPA regional meetings in partnership with local experts, describing various aspects of genetics and pharmacogenetics. This booklet is an additional step in that direction.

5. Activities of the WPA Section in Genetics and Pharmacogenetics

The symposia organized by the WPA genetics section are as follows:

1. WPA World Congress in Bangkok, Thailand (August 3, 2022): **Course on Genetics & Pharmacogenetics and Symposium**; Chair: Thomas G. Schulze (Germany/USA), Speakers: Fernando Goes (US), Roos van Westrhenen (Netherlands/UK/India)

2. WPA Thematic Congress in La Valetta, Malta (November 11, 2022) “New Horizons in Psychiatric Practice: Creative Ideas and Innovative Interventions”: **Discussion Panel;** Chair: Thomas G. Schulze (German/USA); Participants: Marcella Rietschel (Germany), Urs Heilbronner (Germany), Ramona Moldovan (Romania), Daniel Mueller (Canada), Fernando Goes (USA) , Roos van Westrhenen (Netherlands/UK/India), Smita Deshpande (India; via videolink)

3. WPA Regional Congress in Kolkata, West Bengal, India (April 14, 2023) "Building Awareness, Bridging Treatment Gaps": **How to optimally implement genetics and pharmacogenetics in psychiatry – an international panel discussion;** Chairs: Thomas G. Schulze (Germany/USA) & Marcella Rietschel (Germany); Participants: Smita Deshpande (India), Sanjeev Jain (India), Biju Viswanath (India), Roos van Westrhenen (Netherlands/UK/India).

4. WPA Thematic Congress in Abu Dhabi, UAE (May 6, 2023) "Innovations in Treatment & Psychosocial Rehabilitation": **How to optimally implement genetics and pharmacogenetics in psychiatry;** Chairs: Thomas G. Schulze (Germany/USA) & Marcella Rietschel (Germany); Participants: Smita Deshpande (India), Fernando Goes (USA), Maha Mohamed Saber-Ayad (UAE), Hamid Alhaj (UAE), Roos van Westrhenen (Netherlands, UK, India).

5. WPA Regional Congress in Yerevan, Armenia (June 9, 2023) "Innovations in the Practice of Psychiatry in XXI Century": **How to optimally implement genetics and pharmacogenetics in psychiatry: a panel discussion**. Chair: Thomas G. Schulze (Germany/USA): Participants: Fernando Goes (USA), Roksana Zakharyan (Armenia) , Robert Ostrander (USA), Roos van Westrhenen (Netherlands/UK/India).

6. WPA Teaching Programme aimed at early career psychiatrists from Ukraine and Poland in Kraków, Poland (August 30, 2023) "Recent advances in psychiatry": **The WPA Genetics Section – Promoting Research in Genetics**. Participants: Thomas G. Schulze (Germany/USA), Fernando Goes (USA), Roos van Westrhenen (Nethelands/UK/India).

7. WPA **World Congress of Psychiatry** in Vienna, Austria (September 29, 2023):

   A. Scientific Session: **When research experts meet patient experts: Pharmacogenetics in psychiatry.** Chairs: Roos van Westrhenen (Netherlands/UK/India) & Thomas G. Schulze (Germany/USA); Speakers: Urs Heilbronner (Germany), Ramona Moldovan (Romania/UK), Erik van der Eycken (GAMIAN, Belgium), Roos van Westrhenen (Netherlands/UK/India).

   B. State-of-the-Art Symposium: **Equity in genetics and pharmacogenetics: talking the talk and walking the walk.** Chair: Marcella Rietschel (Germany; Speakers: Fernando Goes (USA), Smita Deshpande (India), Roos van Westrhenen (Netherlands/UK/India).

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