Title

A genetics-guided approach to the clinical management of schizophrenia

Author

Besterman, Aaron D

Publication Date

2023-10-01

DOI

10.1016/j.schres.2023.09.042

Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

A genetics-guided approach to the clinical management of schizophrenia

Aaron D. Besterman *

University of California San Diego, Department of Psychiatry, San Diego, CA, USA
Rady Children's Hospital San Diego, Division of Behavioral Health Services, San Diego, CA, USA
Rady Children's Institute for Genomic Medicine, San Diego, CA, USA

ARTICLE INFO

Keywords:
Schizophrenia
Genetics
Genetics testing
Precision medicine
Pharmacogenetics

ABSTRACT

Schizophrenia is a highly heritable, severe mental illness characterized by hallucinations, delusions, social withdrawal, and cognitive dysfunction present in ~1% of populations across cultures. There have been recent major advancements in our understanding of the genetic architecture of schizophrenia. Both rare, highly penetrant genetic variants as well as common, low-penetrant genetic variants can predispose individuals to schizophrenia and can impact the way people metabolize psychoactive medications used to treat schizophrenia. However, the impact of these findings on the clinical management of schizophrenia remains limited. This review highlights the few places where genetics currently informs schizophrenia management strategies, discusses major limitations, and reviews promising areas of genetics research that are most likely to impact future schizophrenia care. Specifically, I focuss on psychiatric genetic counseling, genetic testing strategies, pharmacogenetics, polygenic risk, and genetics-guided treatment. Lastly, I emphasize important ethical considerations in the clinical use of genetics for schizophrenia management, including the exacerbation of healthcare inequalities and unintended consequences of new genetic technologies.

1. Introduction

Schizophrenia is a highly heritable, severe mental illness characterized by hallucinations, delusions, social withdrawal, and cognitive dysfunction present in ~1 % of populations across cultures (Kahn et al., 2015). Schizophrenia, or perhaps dimensional traits of schizophrenia (Ronald and Pain, 2018; Waszczuk et al., 2023), are highly heritable (Hilker et al., 2018), but until recently the specific genetic architecture was unknown. Due to the joint efforts of major consortia, we are beginning to uncover the genetic foundations of schizophrenia, though they are still not fully understood.

287 distinct genomic loci have been significantly associated with schizophrenia (Trubetskoy et al., 2022) through genome-wide association studies (GWAS). At each of these loci, multiple single nucleotide polymorphisms (SNPs) (i.e., single base pair changes that are common in the general population and typically have a mild individual effect) contribute to the observed signal. However, these genome-wide significant SNPs only account for a small percent of the variance in liability for schizophrenia (~2.4 %) (Trubetskoy et al., 2022). When all measured SNPs are considered, the proportion of variance in liability explained increases to ~24 % (Trubetskoy et al., 2022), suggesting that many SNPs that do not meet the stringent threshold for genome-wide significance still collectively contribute to the genetic liability for schizophrenia. This underscores the polygenic nature of schizophrenia, where numerous variants spread across the genome, each with a subtle effect, combine to confer risk for the disorder. Furthermore, several SNPs within the *CYP2D6* gene have been linked to the rate of metabolism of antipsychotic drugs used to treat schizophrenia (Islam et al., 2021), suggesting a complex genetic basis for treatment response, in addition to disease onset.

Rare, highly pathogenic variants have also been associated with an increased risk of developing schizophrenia (Singh et al., 2022). These variants include large genomic deletions and duplications known as copy number variants (CNVs) and rare pathogenic single nucleotide changes known as single nucleotide variants (SNVs) (Kato et al., 2023). Rare variants have been identified through both large schizophrenia case-control studies (Singh et al., 2022) as well as through the analysis of large, multiplex families (Li et al., 2021). Rare variants, such as the 22q11.2 deletion, can act in concert with SNP-based genetic liability for schizophrenia to contribute to disease onset (Cleynen et al., 2021).

Historically, genetics and genetic testing has had a very limited role in the clinical management of schizophrenia. This is gradually changing,

* 3020 Children's Way, San Diego, CA 92123, USA.
E-mail address: abesterman@health.ucsd.edu.

https://doi.org/10.1016/j.schres.2023.09.042
Received 14 May 2023; Received in revised form 27 September 2023; Accepted 29 September 2023

with a growing number of patients who may benefit from a genomics-guided approach, especially those individuals who possess a highly penetrant rare CNV or SNV. Below, I describe the ways in which genetics may inform schizophrenia management currently and attempt to highlight promising areas of psychiatric genetics research that may soon translate into novel management strategies, which are also briefly summarized in Table 1.

2. Genetic counseling and testing

Genetic counseling is often initiated in the context of schizophrenia due to a family member's concern or curiosity about the potential development of the condition. In this case, providing empiric data on recurrence risk may suffice without resorting to genetic testing (McGuffin et al., 2004). For clinicians uncomfortable with genetic

Table 1
Summary of Genetics-guided Approaches to Clinical Management of Schizophrenia.

Genetics-guided approach	Current clinical use	Example of current clinical use	Barriers to translation and implementation	Potential future directions	References
Psychiatric genetic counseling	Currently indicated for patients or families with schizophrenia who have an interest in better understanding causes of schizophrenia	Collaboration with mental health clinicians to counsel patients and families about causes of schizophrenia using "jar model" and risks and benefits of genetic testing	Limited number of genetic counselors with specialty training in psychiatric genetics	Expanded education of genetic counseling workforce in psychiatric genetics	(Austin, 2020)
Genetic testing	Consider CMA, exome, or genome testing for patients with schizophrenia, especially with comorbidities suggestive of a specific condition	Patient presents with schizophrenia and history of congenital cardiac malformations or cleft palate. Consider CMA or genome sequencing to test for 22q11.2 deletion syndrome	• Unclear diagnostic yield of genetic testing • No current professional guidelines • Limited number of psychiatrists extensively trained in genetics • Not always clear benefit > risk	Once guidelines are established, more widespread genetic testing for patients with schizophrenia. Yield will increase with larger genome sequencing studies.	(Finucane et al., 2021)
PGx testing					
Antipsychotic management	Possible use of *CYP2D6* genotype and metabolic phenotyping with patients with atypical responses	Consider *CYP2D6* genotyping for patients with dramatic side effects on low doses antipsychotics or no response on high doses	• Insufficient evidence of improved treatment outcomes with *CYP2D6* genotyping • Limited number of additional genes associated with antipsychotic treatment outcomes	Standard PGx testing for all patients with schizophrenia prior to antipsychotic initiation to guide medication selection and dose	(Caudle et al., 2020; Islam et al., 2021)
CIA	None	None	Insufficient evidence demonstrating improved clinical outcomes with *HLA-DRB1*04:02*	Large, consortia-based studies of CIA to strengthen evidence for variant association followed by outcome trials.	(Islam et al., 2022; Pardiñas et al., 2023)
Carbamazepine/ oxcarbazepine	*HLA-A*31:01* testing in patients of European ancestry and *HLA-B*15:02* in patients of Asian ancestry to reduce SCARs	*HLA-B*15:02* testing in a patient with schizoaffective disorder of Asian descent prior to starting carbamazepine	Tests less informative for patients of non-European or non-Asian ancestry	Larger studies in more diverse populations necessary to find additional risk variants	(Chen et al., 2011; McCormack et al., 2011)
Polygenic scores					
Conversion prediction	None	None	• Probabilistic risk difficult to explain • Insufficient for people of non-European ancestry • Use in pediatric populations for adult-onset disease	Improved schizophrenia PGS with larger, more diverse GWAS that can be combined with multiple non-genetic factors for more accurate conversion prediction	(Murray et al., 2021; Perkins et al., 2020)
Embryonic selection	None	None	Unknown effects on development and health	Unclear if this is a viable or ethical approach	(Lencz et al., 2022)
Genetics guided treatment					
Clinically Informed Treatment	A small number of genetic disorders with known psychiatric management modifications	AED co-initiation with clozapine for 22q11.2 deletion syndrome; Risperidone for psychosis in Prader-Willi syndrome	Many undiagnosed genetic conditions in schizophrenia and rarity of each individual disorder	Improved clinical insight as more patients with schizophrenia receive a genetic diagnosis	(Bonnot et al., 2016; Fung et al., 2015)
Preclinical models of schizophrenia	Brain organoid model with single schizophrenia genetic variant	Patient-derived three-dimensional cerebral cortical organoid model of 22q11.2 deletion syndrome	Validation that organoids recapitulate critical pathophysiology of schizophrenia	Complex assembloid libraries for high-throughput drug screening	(Khan et al., 2020; Levy and Paşca, 2023)
Targeted treatments	Extremely limited	Two patients with glycine decarboxylase triplication disorder improved with NMDA-R co-agonists	• Limited number of high-penetrance genes identified • Targeted therapies still in early phases of development	Schizophrenia treatment is based on underlying genetic architecture	(Bodkin et al., 2019; Casas-Alba et al., 2021)

Abbreviations: AED = antiepileptic drug; CIA = clozapine-induced agranulocytosis; CMA = chromosomal microarray; PGx = pharmacogenetic; NMDA-R = *N*-methyl-D-aspartate receptor; SCARs = serious cutaneous adverse reactions.

counseling, psychiatric genetic counselors may serve as especially helpful partners. They are trained to use a holistic approach to explain the interplay between genetic and environmental factors contributing to psychiatric disorders and to address the emotional concerns and questions of the patients (Austin, 2020). Topics such as guilt, blame, shame, fear, and stigma associated with mental illness are typically covered. Studies have shown that such counseling improves the understanding of disease recurrence risk, increases objective and subjective genetics knowledge, and reduces internalized stigma, worry, and self-blame in individuals with schizophrenia and their families (Costain et al., 2014a, 2014b).

In schizophrenia, there are a number of known, schizophrenia-associated CNVs such as the 22q11.2 deletion, 3q29 deletion, 1q21.1 deletion, and 16p11.2 duplication (Marshall et al., 2016) and schizophrenia-associated ultra-rare coding SNVs (Singh et al., 2022) There are some unique properties of these variants and their correlation to schizophrenia such that the benefit of genetic testing may not always outweigh the risk, which is different than other neurodevelopmental disorders, such as intellectual disability (ID) or global developmental delay (GDD) (Morris et al., 2022). For example, unlike in ID or GDD, genetic variants associated with schizophrenia tend not to be causal in nature (i.e. not fully penetrant), have a more modest impact on medical management, rarely inform accurate recurrence risk on their own, and may create false beliefs that the state of active symptoms of the condition is permanent or immutable (Morris et al., 2022). Furthermore, in ID/GDD there is a well-established high (~20–40 %) diagnostic yield of pathogenic or likely pathogenic (P/LP) variants using chromosomal microarray for CNVs, exome sequencing for SNVs, and/or genome sequencing for both CNVs and SNVs (Manickam et al., 2021; Muhle et al., 2017). In contrast, the reported diagnostic yield for schizophrenia ranges from <1 % (Balakrishna and Curtis, 2020) to upwards of 15 % (Mojarad et al., 2021), with significant heterogeneity across study populations. The populations differ on psychosis age-of-onset, from childhood-onset (i.e., pre-pubescent) (Ambalavanan et al., 2019, 2016), to early-onset (i.e., adolescent) (Brownstein et al., 2022; Gregoric Kumperscak et al., 2021), to adult-onset (Balakrishna and Curtis, 2020; Costain et al., 2013). Additionally, the degree of comorbidity with other NDDs varies considerably, which can strongly impact diagnostic yield (Lowther et al., 2017). The uncertain benefit and variable diagnostic yield are two key factors leading to indeterminate recommendations for genetic testing in schizophrenia from professional psychiatric organizations like the American Psychiatric Association, Canadian Psychiatry Association, and International Society of Psychiatric Genetics are (Finucane et al., 2021; International Society of Psychiatric Genetics, 2019). Therefore, it is currently up to the discretion of clinicians in consultation with patients and families to decide whether to pursue genetic counseling and/or genetic testing for an individual with schizophrenia.

3. Pharmacogenetics

3.1. Antipsychotics

The effectiveness of antipsychotic medications for schizophrenia varies between individuals, with some patients experiencing significant symptom relief and others experiencing little to none. Similarly, the burden of side effects can differ, with certain individuals tolerating the medications and others experiencing severe or intolerable side effects, necessitating dose adjustments or medication switches. Pharmacogenetics (PGx) seeks to identify genetic factors that contribute to this variability in antipsychotic response and tolerability. Antipsychotics are metabolized by several cytochrome P450 genes that code for a group of liver-expressed detoxifying enzymes, with *CYP2D6* playing a central metabolic role for many (Islam et al., 2021). Variants within this gene and different copy numbers of the gene can alter an individual's rate of antipsychotic metabolism and subsequent serum level and drug exposure, resulting in metabolic phenotype classifications: Poor (i.e., very slow), intermediate (i.e., reduced), extensive (i.e, normal or wild-type), or ultrarapid (Islam et al., 2021).

In a meta-analysis of 33 studies, *CYP2D6* genetic variations significantly impacted the response to and side effects of antipsychotics (Milosavljević et al., 2021). Poor metabolizers experienced more side effects and required lower doses, while ultra-rapid metabolizers needed higher doses for therapeutic effects. Intermediate and extensive metabolizers showed mixed responses (Milosavljević et al., 2021). Similar finding were observed in a meta-analysis of antipsychotic treatment in youth (Maruf et al., 2021). While these studies highlight a correlation between metabolic phenotype and prescribed antipsychotic dose, it should be noted that without knowing PGx status of patients, clinicians naturally adjust antipsychotic dose or switch to a different medication at higher rates for patients with outlier metabolic phenotypes (i.e., poor and ultrarapid metabolizers) (Jukic et al., 2019). Therefore, it remains unclear if *CYP2D6* genotyping truly improves treatment outcomes for patients with schizophrenia on antipsychotics or not. Furthermore, *CYP2D6* is structurally complex, highly polymorphic, frequently impacted by CNVs, and prone to forming hybrid genes with the neighboring *CYP2D7* pseudogene (Gaedigk, 2013). This complexity has resulted in significant inconsistency in metabolic phenotyping between labs (Bousman and Dunlop, 2018). Recent expert consensus recommendations were published to harmonize genotype-to-metabolic phenotype translation (Caudle et al., 2020) and new bioinformatic approaches have been developed to improve *CYP2D6* sequencing (Chen et al., 2021; Lee et al., 2019). Therefore, while *CYP2D6* testing may provide some information about the rate of metabolism and exposure to antipsychotics in patients with schizophrenia, it is important to consider the technical challenges of genotyping and the subsequent variability in laboratory reporting in addition to the clinical limitations.

3.2. Clozapine

Clozapine is likely underutilized in the management of severe and treatment-refractory schizophrenia in part due the substantial concern about serious side effects (e.g., cardiomyopathy, seizures, metabolic syndrome, agranulocytosis) and the need for close monitoring (Kelly et al., 2018). This had led to significant interest in the use of PGx testing to identify patients at greatest risk for adverse outcomes, such as clozapine-induced agranulocytosis (CIA). In a meta-analyses of CIA, out of 13 variants across nine genes (*NQO2*, *CYBA*, *MPO*, *HLA-DRB1*, *HLA-DQB1*, *HLA-DRB4*, *HLA-DRB5*, *HLA-DR2*, and *HLA-B*), only the association between *HLA-DRB1*04:02* and CIA was found to be significant compared to non-carriers, with the risk allele associated with a sixfold higher odds of CIA (Islam et al., 2022; Teng et al., 2023).

Likewise, in a recent large-scale PGx study of clozapine response, two SNPs (rs2472297, rs3732218), in genes known to be associated with clozapine metabolism, *CYP1A2* and *UGT1A,* were found to be associated with peripheral concentrations of clozapine metabolites (Bousman, 2023; Pardiñas et al., 2023). When the effects of a large numbers of variants associated with clozapine metabolism were combined into polygenic scores, up to 7.26 % of the variance in drug metabolism could be explained (Pardiñas et al., 2023). The genetic associations with CIA and clozapine exposure suggest that further genetic studies of clozapine response are warranted and will likely yield fruitful results but are not yet strong enough to warrant clinical use.

3.3. Carbamazepine and oxcarbazepine

For individuals with schizoaffective disorder or an otherwise significant mood component to their psychosis, PGx testing can help guide the safe use of the mood stabilizers carbamazepine and oxcarbazepine. The *HLA-A*31:01* variant is associated with an increased risk of serious cutaneous adverse reactions (SCARs; e.g., Stevens–Johnson syndrome, toxic epidermal necrolysis) for individuals of European-ancestry (Fricke-

Galindo et al., 2018; McCormack et al., 2011). Currently, only the European Medicines Agency explicitly recommends regular *HLA-A*31:01* for patients of European ancestry, while other regulatory agencies such as the American Food and Drug Administration, the United Kingdom's Medicines and Healthcare products Regulatory Agency, and Japan's Pharmaceuticals and Medical Devices Agency acknowledge the risk but defer to clinical judgement on testing. The *HLA-B*15:02* variant is likewise associated with an increased risk of SCARs for individuals of Asian-ancestry (Chen et al., 2011; Fricke-Galindo et al., 2018). Per the Clinical Pharmacogenetics Implementation Consortium, both *HLA-A*31:01* and *HLA-B*15:02* PGx testing have level 1 A evidence supporting their clinical use (Phillips et al., 2018). Regulatory agencies in many places, including the United States, Europe, the United Kingdom, Australia, Japan, Taiwan, Singapore, and Thailand have explicit recommendations for HLA-B*15:02 testing in patients of Asian ancestry prior to carbamazepine initiation.

3.4. PGx implementation

Currently, only *HLA* genotyping for carbamazepine and oxcarbazepine to reduce SCARs has a clearly defined clinical role for PGx testing in the management of schizophrenia. There is insufficient evidence to guide the use of *CYP2D6* genotyping in clinical practice. One potential strategy is to consider is genotyping only for those patients with atypical responses to antipsychotics. This includes patients with extreme sensitivity to low dose antipsychotics or those without any response at high dose. *CYP2D6* genotyping may aid clinical decision making by confirming clinician suspicion of either particularly slow or rapid antipsychotic metabolism and proceed with dose adjustments more rapidly and reduce the number of medication switches, although this has not been definitively demonstrated. There is no clinical indication for PGx testing in the management of clozapine currently.

4. Polygenic risk

One of the longstanding goals in psychiatric research is to better predict who will develop severe mental disorders like schizophrenia. Cohorts of young patients with early, subthreshold, psychotic symptoms who are deemed "clinically high-risk (CHR)" for psychosis have been tracked to identify risk factors for converting to fully-manifested schizophrenia (Carrión et al., 2016). This effort has led to the development of risk calculators that predict (imperfectly) an individual's risk of conversion (Carrión et al., 2016) based on clinical factors. There has been a hope that genetics can improve these risk predictions. Polygenic score (PGS) (i.e., the cumulative effect of many SNPs associated with a disease or trait) for schizophrenia were incorporated into the risk calculator, conversion prediction modestly improved, with greater benefit for individuals of European ancestry than non-European ancestry (Perkins et al., 2020), a well-documented problem due to an overemphasis of genetics research in populations of European ancestry (Martin et al., 2019). This case highlights the potential for genetics research to exacerbate disparities in psychiatry if not conducted thoughtfully and equally (Martin et al., 2019).

Schizophrenia PGS also have the potential to inform genetic counseling, as demonstrated for breast cancer (McGuinness et al., 2021) and diabetes (Huvinen et al., 2022). However, unlike monogenic disorders where disease variants are highly penetrant, disease risk due to PGS must be understood in the context of probabilities, which may be more difficult for some patients to fully grasp and appropriately weigh in medical decision making (Peck et al., 2022). Furthermore, schizophrenia PGS have the clearest application for pediatric CHR populations who must defer to their guardians as proxy decision makers, although the genetic test is for a mostly adult-onset condition. Whether guardians should make such decisions remains controversial (Botkin, 2016), as the American Academy of Pediatrics (Caga-anan et al., 2012) and others have recommended that testing should be deferred until adulthood or until an adolescent interested in testing has developed mature decision-making capacities if there is no immediate medical benefit. There has also been speculation that elevated schizophrenia PGS might create a vulnerability to the effects of environmental factors associated with schizophrenia, such as cannabis exposure (Elkrief et al., 2023). However, recent studies have not supported this theory, and have instead indicated that cannabis use remains a risk factor for schizophrenia, over and above genetic vulnerability for schizophrenia (Elkrief et al., 2023). This suggests that schizophrenia PGS would not be a helpful biomarker of vulnerability to the psychosis-inducing properties of cannabis.

Ethical use of schizophrenia PGS must also be carefully considered in the new field of polygenic embryo screening, where embryos are selected for based on their genetic profile, such as low schizophrenia PGS (Lencz et al., 2022). There are several potential unintended consequences of this approach, such as selecting for adverse traits, altering population demographics, exacerbating inequalities in society, and devaluing certain traits (Turley et al., 2021). Clinicians should proceed with great caution to avoid ushering in a new era of genetics-based stigma and discrimination, especially around psychiatric disorders. In the specific case of sperm or egg donation, it is common practice for donors to complete a family history and sperm and eggs to undergo basic genetic screening to assess for genetic conditions including cystic fibrosis, spinal muscular atrophy, haemoglobinopathies, Tay-Sachs disease and Fragile X syndrome (Amor et al., 2018). However, both donors and recipients are wary of expanding genetic screening beyond current levels (Amor et al., 2018) and there is scant evidence to suggest that genetic screening improves the likelihood of live birth for recipients of donor oocytes (Doyle et al., 2020).

To summarize, there is currently no clinical indication for schizophrenia PGS, but there is promise that they may be used, in combination with other factors, to improve individual risk prediction of schizophrenia onset (Murray et al., 2021). Careful consideration should be given to the ethical implications of using schizophrenia PGS, given the potential to exacerbate healthcare inequalities, the challenges of properly communicating their probabilistic nature to patients, the potential for unintended harm and genetic discrimination, and their future potential to predict the onset of an adult disorder in a pediatric population. Given the uncertainty around clinical benefit, tests for schizophrenia PRS are not readily available through insurance, so if clinicians felt there was a strong clinical indication for such testing, cash payment would likely be necessary through a direct-to-consumer company.

5. Genetics-guided treatment

There are no current clinical practice guidelines recommending the use of genetics to guide psychiatric management for any disorder. There are, however, several rare neurogenetics conditions associated with schizophrenia where adjustments to pharmacologic treatment can be considered based on the genetic diagnosis. For individuals with 22q11.2 deletion syndrome, psychotropic management can be adjusted based on known drug sensitives, but not based on a genetics-informed understanding of pathophysiology. For example, it has been observed that individuals with 22q11.2 deletion syndrome are particularly susceptible to the seizure-lowering effects of antipsychotics and great care should be taken when starting antipsychotics that significantly lower the threshold, such as clozapine (Butcher et al., 2015; Fung et al., 2015). In fact, co-initiation with antiepileptic drugs should be considered in these cases. Likewise, risperidone has been observed to be particularly effective in treating psychosis in patients with Prader-Willi syndrome due to uniparental disomy (Bonnot et al., 2016). In contrast, there are certain neurogenetic conditions associated with schizophrenia where the genetic mechanism of disease may directly inform treatment. Two individuals with schizophrenia associated with glycine decarboxylase triplication disorder in n-of-1 placebo-controlled trials were responsive to the psychotropic augmentation with *N*-methyl-D-aspartate receptor (NMDA-R) co-agonists, glycine and D-cycloserine (Bodkin et al., 2019).

Both psychotic and mood symptoms improved significantly in response to the co-agonists, which were selected based on presumed NMDA-R hypofunction. Similarly, there are reports of individuals with 15q13.3 deletion syndrome associated with schizophrenia, intellectual disability, epilepsy, aggression and autism spectrum disorders (ASD) where *CHRNA7*, the gene encoding the α7-nicotinic acetylcholine receptor subunit, is deleted (Casas-Alba et al., 2021; Cubells et al., 2011). The acetylcholinesterase inhibitor, galantamine, was observed to reduce aggression in one adult with psychosis and intellectual disability (Cubells et al., 2011) and improve fluid reasoning, working memory, and processing speed in one youth with ASD (Casas-Alba et al., 2021).

The reality remains that for most patients with schizophrenia a genetic diagnosis will not impact psychotropic management. But there has been progress in leveraging our current knowledgebase on the genetics of schizophrenia to advance therapeutic development. For example, genome-wide association data was combined with gene expression data to identify subgroups of individuals with schizophrenia that could respond to repurposed drugs (Reay et al., 2022). The repurposed drugs normalized aberrant gene expression associated with the specific genomic subtype of schizophrenia (Reay et al., 2022). New preclinical in vitro methods hold promise as neuropsychiatric disease models for drug screening. For example, a patient-derived three-dimensional cerebral cortical organoid model of 22q11.2 deletion syndrome was developed that recapitulates many aspects of human pathophysiology (Khan et al., 2020). However, current organoid models of neuropsychiatric disease contain limited cell types, tend to recapitulate very early stages of brain development, and can be hard to reliably reproduce (Levy and Paşca, 2023). More complex assembloid models may offer additional promise as in vitro disease models, perhaps even allowing for high-throughput drug screening (Levy and Paşca, 2023). Gene modifying therapies are being actively pursued for neuropsychiatric disorders, although most efforts are currently in neurodevelopmental genetic disorders, such as Angelman's syndrome (Markati et al., 2021) and Rett syndrome (Shao et al., 2021). Another potential therapeutic strategy is isoform-specific targeting of dysregulated gene expression in schizophrenia using antisense oligonucleotides or related technologies (Gandal et al., 2018).

6. Conclusion

This review highlights the complex role of genetics in schizophrenia management and the challenges in developing genetically-informed, effective treatments. Despite progress in identifying genetic risk factors, their translation into improved clinical outcomes remains limited. The growing prevalence of patients with known genetic conditions necessitates that mental health clinicians enhance their genetic expertise and collaborate with professionals like psychiatric genetic counselors (Besterman et al., 2019). Further research on the potential of PGS is crucial, with emphasis on establishing a strong ethical framework to ensure equitable benefits and informed understanding of genetic implications. Further advances in PGx may enable personalized dosing and medication selection, contributing to better prevention, treatment, and quality of life for those with schizophrenia. Genetics-informed disease modeling and treatments hold great promise in revolutionizing the therapeutic landscape, paving the way for more targeted and personalized approaches to alleviate the burdens of schizophrenia, but many challenges remain. As our understanding of genetic factors associated with schizophrenia deepens, it is vital to remain attentive to the social implications of clinical translation, striving for the benefit of all patients.

Declaration of competing interest

None.

Acknowledgements

No acknowledgements.

Role of funding sources

Dr. Besterman receives funding from the Rady Children's Institute for Genomic Medicine and the Rady Children's Hospital San Diego Transforming Mental Health Initiative to support his research time. Neither funding source had any role in the development or writing of this manuscript.

References

Ambalavanan, A., Girard, S.L., Ahn, K., Zhou, S., Dionne-Laporte, A., Spiegelman, D., Bourassa, C.V., Gauthier, J., Hamdan, F.F., Xiong, L., Dion, P.A., Joober, R., Rapoport, J., Rouleau, G.A., 2016. De novo variants in sporadic cases of childhood onset schizophrenia. Eur. J. Hum. Genet. 24, 944–948. https://doi.org/10.1038/ejhg.2015.218.

Ambalavanan, A., Chaumette, B., Zhou, S., Xie, P., He, Q., Spiegelman, D., Dionne-Laporte, A., Bourassa, C.V., Therrien, M., Rochefort, D., Xiong, L., Dion, P.A., Joober, R., Rapoport, J.L., Girard, S.L., Rouleau, G.A., 2019. Exome sequencing of sporadic childhood-onset schizophrenia suggests the contribution of X-linked genes in males. Am. J. Med. Genet. B Neuropsychiatr. Genet. 180, 335–340. https://doi.org/10.1002/ajmg.b.32683.

Amor, D.J., Kerr, A., Somanathan, N., McEwen, A., Tome, M., Hodgson, J., Lewis, S., 2018. Attitudes of sperm, egg and embryo donors and recipients towards genetic information and screening of donors. Reprod. Health 15, 26. https://doi.org/10.1186/s12978-018-0468-9.

Austin, J.C., 2020. Evidence-based genetic counseling for psychiatric disorders: a road map. Cold Spring Harb. Perspect. Med. 10, a036608 https://doi.org/10.1101/CSHPERSPECT.A036608.

Balakrishna, T., Curtis, D., 2020. Assessment of potential clinical role for exome sequencing in schizophrenia. Schizophr. Bull. 46, 328–335. https://doi.org/10.1093/schbul/sbz057.

Besterman, A.D., Moreno-De-Luca, D., Nurnberger, J.I., 2019. 21st-century genetics in psychiatric residency training: how do we get there? JAMA Psychiatry 76, 231–232. https://doi.org/10.1001/jamapsychiatry.2018.3872.

Bodkin, J.A., Coleman, M.J., Godfrey, L.J., Carvalho, C.M.B., Morgan, C.J., Suckow, R.F., Anderson, T., Öngür, D., Kaufman, M.J., Lewandowski, K.E., Siegel, A.J., Waldstreicher, E., Grochowski, C.M., Javitt, D.C., Rujescu, D., Hebbring, S., Weinshilboum, R., Rodriguez, S.B., Kirchhoff, C., Visscher, T., Vuckovic, A., Fialkowski, A., McCarthy, S., Malhotra, D., Sebat, J., Goff, D.C., Hudson, J.I., Lupski, J.R., Coyle, J.T., Rudolph, U., Levy, D.L., 2019. Targeted treatment of individuals with psychosis carrying a copy number variant containing a genomic triplication of the glycine decarboxylase gene. Biol. Psychiatry 86, 523–535. https://doi.org/10.1016/j.biopsych.2019.04.031.

Bonnot, O., Cohen, D., Thuilleaux, D., Consoli, A., Cabal, S., Tauber, M., 2016. Psychotropic treatments in Prader-Willi syndrome: a critical review of published literature. Eur. J. Pediatr. 175, 9–18. https://doi.org/10.1007/s00431-015-2670-x.

Botkin, J.R., 2016. Ethical issues in pediatric genetic testing and screening for current opinion in pediatrics. Curr. Opin. Pediatr. 28, 700–704. https://doi.org/10.1097/MOP.0000000000000418.

Bousman, C.A., 2023. Pharmacogenomics-informed clozapine therapy. Lancet Psychiatry 10, 160–162. https://doi.org/10.1016/S2215-0366(23)00032-9.

Bousman, C.A., Dunlop, B.W.Genotype, 2018. Phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. Pharmacogenomics J. 18, 613–622. https://doi.org/10.1038/s41397-018-0027-3.

Brownstein, C.A., Douard, E., Mollon, J., Smith, R., Hojlo, M.A., Das, A., Goldman, M., Garvey, E., Cabral, K., Li, J., Bowen, J., Rao, A.S., Genetti, C., Carroll, D., Knowles, E. E.M., Deaso, E., Agrawal, P.B., Beggs, A.H., D'Angelo, E., Almasy, L., Alexander-Bloch, A., Saci, Z., Moreau, C.A., Huguet, G., Deo, A.J., Jacquemont, S., Glahn, D.C., Gonzalez-Heydrich, J., 2022. Similar rates of deleterious copy number variants in early-onset psychosis and autism spectrum disorder. AJP 179, 853–861. https://doi.org/10.1176/appi.ajp.21111175.

Butcher, N.J., Fung, W.L.A., Fitzpatrick, L., Guna, A., Andrade, D.M., Lang, A.E., Chow, E.W.C., Bassett, A.S., 2015. Response to clozapine in a clinically identifiable subtype of schizophrenia. Br. J. Psychiatry 206, 484–491. https://doi.org/10.1192/bjp.bp.114.151837.

Caga-anan, E.C.F., Smith, L., Sharp, R.R., Lantos, J.D., 2012. Testing children for adult-onset genetic diseases. Pediatrics 129, 163–167. https://doi.org/10.1542/peds.2010-3743.

Carrión, R.E., Cornblatt, B.A., Burton, C.Z., Tso, I.F., Auther, A.M., Adelsheim, S., Calkins, R., Carter, C.S., Niendam, T., Sale, T.G., Taylor, S.F., McFarlane, W.R., 2016. Personalized prediction of psychosis: external validation of the NAPLS-2 psychosis risk calculator with the EDIPPP project. AJP 173, 989–996. https://doi.org/10.1176/appi.ajp.2016.15121565.

Casas-Alba, D., Nolasco, G.A., Díez-Juan, M., Mezzatesta, M., Balañá, G., Fons, C., 2021. Targeted therapy with galantamine in a pediatric patient with 15q13.3 deletion syndrome. Am. J. Med. Genet. Pt. A 185, 3897–3899. https://doi.org/10.1002/ajmg.a.62425.

Caudle, K.E., Sangkuhl, K., Whirl-Carrillo, M., Swen, J.J., Haidar, C.E., Klein, T.E., Gammal, R.S., Relling, M.V., Scott, S.A., Hertz, D.L., Guchelaar, H.-J., Gaedigk, A., 2020. Standardizing CYP2D6 genotype to phenotype translation: consensus recommendations from the Clinical Pharmacogenetics Implementation Consortium

and Dutch Pharmacogenetics Working Group. Clin. Transl. Sci. 13, 116–124. https://doi.org/10.1111/cts.12692.

Chen, P., Lin, J.-J., Lu, C.-S., Ong, C.-T., Hsieh, P.F., Yang, C.-C., Tai, C.-T., Wu, S.-L., Lu, C.-H., Hsu, Y.-C., Yu, H.-Y., Ro, L.-S., Lu, C.-T., Chu, C.-C., Tsai, J.-J., Su, Y.-H., Lan, S.-H., Sung, S.-F., Lin, S.-Y., Chuang, H.-P., Huang, L.-C., Chen, Y.-J., Tsai, P.-J., Liao, H.-T., Lin, Y.-H., Chen, C.-H., Chung, W.-H., Hung, S.-I., Wu, J.-Y., Chang, C.-F., Chen, L., Chen, Y.-T., Shen, C.-Y., 2011. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N. Engl. J. Med. 364, 1126–1133. https://doi.org/10.1056/NEJMoa1009717.

Chen, X., Shen, F., Gonzaludo, N., Malhotra, A., Rogert, C., Taft, R.J., Bentley, D.R., Eberle, M.A., 2021. Cyrius: accurate CYP2D6 genotyping using whole-genome sequencing data. Pharmacogenomics J. 2021 21:2 21, 251–261. doi:https://doi.org/10.1038/s41397-020-00205-5.

Cleynen, I., Engchuan, W., Hestand, M.S., Heung, T., Holleman, A.M., Johnston, H.R., Monfeuga, T., McDonald-McGinn, D.M., Gur, R.E., Morrow, B.E., Swillen, A., Vorstman, J.A.S., Bearden, C.E., Chow, E.W.C., van den Bree, M., Emanuel, B.S., Vermeesch, J.R., Warren, S.T., Owen, M.J., Chopra, P., Cutler, D.J., Duncan, R., Kotlar, A.V., Mulle, J.G., Voss, A.J., Zwick, M.E., Diacou, A., Golden, A., Guo, T., Lin, J.-R., Wang, T., Zhang, Z., Zhao, Y., Marshall, C., Merico, D., Jin, A., Lilley, B., Salmons, H.I., Tran, O., Holmans, P., Pardinas, A., Walters, J.T.R., Demaerel, W., Boot, E., Butcher, N.J., Costain, G.A., Lowther, C., Evers, R., van Amelsvoort, T.A.M. J., van Duin, E., Vingerhoets, C., Breckpot, J., Devriendt, K., Vergaelen, E., Vogels, A., Crowley, T.B., McGinn, D.E., Moss, E.M., Sharkus, R.J., Unolt, M., Zackai, E.H., Calkins, M.E., Gallagher, R.S., Gur, R.C., Tang, S.X., Fritsch, R., Ornstein, C., Repetto, G.M., Breetvelt, E., Duijff, S.N., Fiksinski, A., Moss, H., Niarchou, M., Murphy, K.C., Prasad, S.E., Daly, E.M., Gudbrandsen, M., Murphy, C. M., Murphy, D.G., Buzzanca, A., Fabio, F.D., Digilio, M.C., Pontillo, M., Marino, B., Vicari, S., Coleman, K., Cubells, J.F., Ousley, O.Y., Carmel, M., Gothelf, D., Mekori-Domachevsky, E., Michaelovsky, E., Weinberger, R., Weizman, A., Kushan, L., Jalbrzikowski, M., Armando, M., Eliez, S., Sandini, C., Schneider, M., Béna, F.S., Antshel, K.M., Fremont, W., Kates, W.R., Belzeaux, R., Busa, T., Philip, N., Campbell, L.E., McCabe, K.L., Hooper, S.R., Schoch, K., Shashi, V., Simon, T.J., Tassone, F., Arango, C., Fraguas, D., García-Miñaúr, S., Morey-Canyelles, J., Rosell, J., Suñer, D.H., Raventos-Simic, J., Epstein, M.P., Williams, N.M., Bassett, A. S., 2021. Genetic contributors to risk of schizophrenia in the presence of a 22q11.2 deletion. Mol. Psychiatry 26, 4496–4510. https://doi.org/10.1038/s41380-020-0654-3.

Costain, G., Lionel, A.C., Merico, D., Forsythe, P., Russell, K., Lowther, C., Yuen, T., Husted, J., Stavropoulos, D.J., Speevak, M., Chow, E.W.C., Marshall, C.R., Scherer, S. W., Bassett, A.S., 2013. Pathogenic rare copy number variants in community-based schizophrenia suggest a potential role for clinical microarrays. Hum. Mol. Genet. 22, 4485–4501. https://doi.org/10.1093/hmg/ddt297.

Costain, G., Esplen, M.J., Toner, B., Hodgkinson, K.A., Bassett, A.S., 2014a. Evaluating genetic counseling for family members of individuals with schizophrenia in the molecular age. Schizophr. Bull. 40, 88–99. https://doi.org/10.1093/schbul/sbs124.

Costain, G., Esplen, M.J., Toner, B., Scherer, S.W., Meschino, W.S., Hodgkinson, K.A., Bassett, A.S., 2014b. Evaluating genetic counseling for individuals with schizophrenia in the molecular age. Schizophr. Bull. 40, 78–87. https://doi.org/10.1093/schbul/sbs138.

Cubells, J.F., Deoreo, E.H., Harvey, P.D., Garlow, S.J., Garber, K., Adam, M.P., Martin, C. L., 2011. Pharmaco-genetically guided treatment of recurrent rage outbursts in an adult male with 15q13.3 deletion syndrome. Am. J. Med. Genet. A 155, 805–810. https://doi.org/10.1002/ajmg.a.33917.

Doyle, N., Gainty, M., Eubanks, A., Doyle, J., Hayes, H., Tucker, M., Devine, K., DeCherney, A., Levy, M., Jahandideh, S., Hill, M., 2020. Donor oocyte recipients do not benefit from preimplantation genetic testing for aneuploidy to improve pregnancy outcomes. Hum. Reprod. 35, 2548–2555. https://doi.org/10.1093/humrep/deaa219.

Elkrief, L., Lin, B., Marchi, M., Afzali, M.H., Banaschewski, T., Bokde, A.L.W., Quinlan, E. B., Desrivières, S., Flor, H., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.-L., Martinot, M.-L.P., Nees, F., Orfanos, D.P., Paus, T., Poustka, L., Hohmann, S., Fröhner, J.H., Smolka, M.N., Walter, H., Whelan, R., Schumann, G., Luykx, J., Boks, M.P., Conrod, P.J., 2023. Independent contribution of polygenic risk for schizophrenia and cannabis use in predicting psychotic-like experiences in young adulthood: testing gene × environment moderation and mediation. Psychol. Med. 53, 1759–1769. https://doi.org/10.1017/S0033291721003378.

Finucane, B.M., Ledbetter, D.H., Vorstman, J.A., 2021. Diagnostic genetic testing for neurodevelopmental psychiatric disorders: closing the gap between recommendation and clinical implementation. Curr. Opin. Genet. Dev. 68, 1–8. https://doi.org/10.1016/J.GDE.2020.12.016.

Fricke-Galindo, I., LLerena, A., Jung-Cook, H., López-López, M., 2018. Carbamazepine adverse drug reactions. Expert. Rev. Clin. Pharmacol. 11, 705–718. https://doi.org/10.1080/17512433.2018.1486707.

Fung, W.L.A., Butcher, N.J., Costain, G., Andrade, D.M., Boot, E., Chow, E.W.C., Chung, B., Cytrynbaum, C., Faghfoury, H., Fishman, L., García-Miñaúr, S., George, S., Lang, A.E., Repetto, G., Shugar, A., Silversides, C., Swillen, A., Van Amelsvoort, T., Mcdonald-Mcginn, D.M., Bassett, A.S., 2015. Practical guidelines for managing adults with 22q11.2 deletion syndrome. Genet. Med. 17, 599–609. https://doi.org/10.1038/gim.2014.175.

Gaedigk, A., 2013. Complexities of CYP2D6 gene analysis and interpretation. Int. Rev. Psychiatry 25, 534–553. https://doi.org/10.3109/09540261.2013.825581.

Gandal, M.J., Zhang, P., Hadjimichael, E., Walker, R.L., Chen, C., Liu, S., Won, H., van Bakel, H., Varghese, M., Wang, Y., Shieh, A.W., Haney, J., Parhami, S., Belmont, J., Kim, M., Moran Losada, P., Khan, Z., Mleczko, J., Xia, Y., Dai, R., Wang, D., Yang, Y. T., Xu, M., Fish, K., Hof, P.R., Warrell, J., Fitzgerald, D., White, K., Jaffe, A.E., PsychENCODE Consortium, Peters, M.A., Gerstein, M., Liu, C., Iakoucheva, L.M., Pinto, D., Geschwind, D.H., 2018. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science 362, eaat8127. https://doi.org/10.1126/science.aat8127.

Gregoric Kumperscak, H., Krgovic, D., Drobnic Radobuljac, M., Senica, N., Zagorac, A., Kokalj Vokac, N., 2021. CNVs and chromosomal aneuploidy in patients with early-onset schizophrenia and bipolar disorder: genotype-phenotype associations. Front. Psychiatry 11.

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T.M., Nordentoft, M., Glenthøj, B., 2018. Heritability of schizophrenia and schizophrenia spectrum based on the Nationwide Danish twin register. Biol. Psychiatry Novel Mech. Schizophr. Pathophysiol. 83, 492–498. https://doi.org/10.1016/j.biopsych.2017.08.017.

Huvinen, E., Lahti, J., Klemetti, M.M., Bergman, P.H., Räikkönen, K., Orho-Melander, M., Laivuori, H., Koivusalo, S.B., 2022. Genetic risk of type 2 diabetes modifies the effects of a lifestyle intervention aimed at the prevention of gestational and postpartum diabetes. Diabetologia 65, 1291–1301. https://doi.org/10.1007/s00125-022-05712-7.

International Society of Psychiatric Genetics, 2019. Genetic Testing Statement. https://ispg.net/genetic-testing-statement/. (Accessed 22 September 2023).

Islam, F., Men, X., Yoshida, K., Zai, C.C., Müller, D.J., 2021. Pharmacogenetics-guided advances in antipsychotic treatment. Clin. Pharma. Ther. 110, 582–588. https://doi.org/10.1002/cpt.2339.

Islam, F., Hain, D., Lewis, D., Law, R., Brown, L.C., Tanner, J.-A., Müller, D.J., 2022. Pharmacogenomics of clozapine-induced agranulocytosis: a systematic review and meta-analysis. Pharmacogenomics J. 22, 230–240. https://doi.org/10.1038/s41397-022-00281-9.

Jukic, M.M., Smith, R.L., Haslemo, T., Molden, E., Ingelman-Sundberg, M., 2019. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. Lancet Psychiatry 6, 418–426. https://doi.org/10.1016/S2215-0366(19)30088-4.

Kahn, R.S., Sommer, I.E., Murray, R.M., Meyer-Lindenberg, A., Weinberger, D.R., Cannon, T.D., O'Donovan, M., Correll, C.U., Kane, J.M., Van Os, J., Insel, T.R., 2015. Schizophrenia. Nat. Rev. Disease Prim. 1, 1–23. https://doi.org/10.1038/nrdp.2015.67.

Kato, H., Kimura, H., Kushima, I., Takahashi, N., Aleksic, B., Ozaki, N., 2023. The genetic architecture of schizophrenia: review of large-scale genetic studies. J. Hum. Genet. 68, 175–182. https://doi.org/10.1038/s10038-022-01059-4.

Kelly, D.L., Freudenreich, O., Sayer, M.A., Love, R.C., 2018. Addressing barriers to clozapine underutilization: a national effort. PS 69, 224–227. https://doi.org/10.1176/appi.ps.201700162.

Khan, T.A., Revah, O., Gordon, A., Yoon, S.-J., Krawisz, A.K., Goold, C., Sun, Y., Kim, C. H., Tian, Y., Li, M.-Y., Schaepe, J.M., Ikeda, K., Amin, N.D., Sakai, N., Yazawa, M., Kushan, L., Nishino, S., Porteus, M.H., Rapoport, J.L., Bernstein, J.A., O'Hara, R., Bearden, C.E., Hallmayer, J.F., Huguenard, J.R., Geschwind, D.H., Dolmetsch, R.E., Paşca, S.P., 2020. Neuronal defects in a human cellular model of 22q11.2 deletion syndrome. Nat. Med. 26, 1888–1898. https://doi.org/10.1038/s41591-020-1043-9.

Lee, S. been, Wheeler, M.M., Patterson, K., McGee, S., Dalton, R., Woodahl, E.L., Gaedigk, A., Thummel, K.E., Nickerson, D.A., 2019. Stargazer: a software tool for calling star alleles from next-generation sequencing data using CYP2D6 as a model. Genet. Med. 21, 361–372. https://doi.org/10.1038/s41436-018-0054-0.

Lencz, T., Sabatello, M., Docherty, A., Peterson, R.E., Soda, T., Austin, J., Bierut, L., Crepaz-Keay, D., Curtis, D., Degenhardt, F., Huckins, L., Lazaro-Munoz, G., Mattheisen, M., Meiser, B., Peay, H., Rietschel, M., Walss-Bass, C., Davis, L.K., 2022. Concerns about the use of polygenic embryo screening for psychiatric and cognitive traits. Lancet Psychiatry 9, 838–844. https://doi.org/10.1016/S2215-0366(22)00157-2.

Levy, R.J., Paşca, S.P., 2023. What have organoids and assembloids taught us about the pathophysiology of neuropsychiatric disorders? Biol. Psychiatry 93, 632–641. https://doi.org/10.1016/j.biopsych.2022.11.017.

Li, S., DeLisi, L.E., McDonough, S.I., 2021. Rare germline variants in individuals diagnosed with schizophrenia within multiplex families. Psychiatry Res. 303, 114038 https://doi.org/10.1016/j.psychres.2021.114038.

Lowther, C., Merico, D., Costain, G., Waserman, J., Boyd, K., Noor, A., Speevak, M., Stavropoulos, D.J., Wei, J., Lionel, A.C., Marshall, C.R., Scherer, S.W., Bassett, A.S., 2017. Impact of IQ on the diagnostic yield of chromosomal microarray in a community sample of adults with schizophrenia. Genome Med. 9, 105. https://doi.org/10.1186/s13073-017-0488-z.

Manickam, K., McClain, M.R., Demmer, L.A., Biswas, S., Kearney, H.M., Malinowski, J., Massingham, L.J., Miller, D., Yu, T.W., Hisama, F.M., 2021. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet. Med. 1–9 https://doi.org/10.1038/s41436-021-01242-6.

Markati, T., Duis, J., Servais, L., 2021. Therapies in preclinical and clinical development for Angelman syndrome. Expert Opin. Investig. Drugs 30, 709–720. https://doi.org/10.1080/13543784.2021.1939674.

Marshall, C.R., Howrigan, D.P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D.S., Antaki, D., Shetty, A., Holmans, P.A., Pinto, D., Gujral, M., Brandler, W.M., Malhotra, D., Wang, Z., Fajarado, K.V.F., Maile, M.S., Ripke, S., Agartz, I., Albus, M., Alexander, M., Amin, F., Atkins, J., Bacanu, S.A., Belliveau, R.A., Bergen, S.E., Bertalan, M., Bevilacqua, E., Bigdeli, T.B., Black, D.W., Bruggeman, R., Buccola, N. G., Buckner, R.L., Bulik-Sullivan, B., Byerley, W., Cahn, W., Cai, G., Cairns, M.J., Campion, D., Cantor, R.M., Carr, V.J., Carrera, N., Catts, S.V., Chambert, K.D., Cheng, W., Cloninger, C.R., Cohen, D., Cormican, P., Craddock, N., Crespo-Facorro, B., Crowley, J.J., Curtis, D., Davidson, M., Davis, K.L., Degenhardt, F., Del Favero, J., DeLisi, L.E., Dikeos, D., Dinan, T., Djurovic, S., Donohoe, G., Drapeau, E., Duan, J.,

Dudbridge, F., Eichhammer, P., Eriksson, J., Escott-Price, V., Essioux, L., Fanous, A. H., Farh, K.-H., Farrell, M.S., Frank, J., Franke, L., Freedman, R., Freimer, N.B., Friedman, J.I., Forstner, A.J., Fromer, M., Genovese, G., Georgieva, L., Gershon, E.S., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I., Gratten, J., de Haan, L., Hamshere, M.L., Hansen, M., Hansen, T., Haroutunian, V., Hartmann, A.M., Henskens, F.A., Herms, S., Hirschhorn, J.N., Hoffmann, P., Hofman, A., Huang, H., Ikeda, M., Joa, I., Kähler, A.K., Kahn, R.S., Kalaydjieva, L., Karjalainen, J., Kavanagh, D., Keller, M.C., Kelly, B.J., Kennedy, J.L., Kim, Y., Knowles, J.A., Konte, B., Laurent, C., Lee, P., Lee, S.H., Legge, S.E., Lerer, B., Levy, D.L., Liang, K.-Y., Lieberman, J., Lönnqvist, J., Loughland, C.M., Magnusson, P.K.E., Maher, B.S., Maier, W., Mallet, J., Mattheisen, M., Mattingsdal, M., McCarley, R.W., McDonald, C., McIntosh, A.M., Meier, S., Meijer, C.J., Melle, I., Mesholam-Gately, R.I., Metspalu, A., Michie, P.T., Milani, L., Milanova, V., Mokrab, Y., Morris, D.W., Müller-Myhsok, B., Murphy, K.C., Murray, R.M., Myin-Germeys, I., Nenadic, I., Nertney, D.A., Nestadt, G., Nicodemus, K.K., Nisenbaum, L., Nordin, A., O'Callaghan, E., O'Dushlaine, C., Oh, S.-Y., Olincy, A., Olsen, L., O'Neill, F.A., Van Os, J., Pantelis, C., Papadimitriou, G.N., Parkhomenko, E., Pato, M.T., Paunio, T., Perkins, D.O., Pers, T.H., Pietiläinen, O., Pimm, J., Pocklington, A.J., Powell, J., Price, A., Pulver, A.E., Purcell, S.M., Quested, D., Rasmussen, H.B., Reichenberg, A., Reimers, M.A., Richards, A.L., Roffman, J.L., Roussos, P., Ruderfer, D.M., Salomaa, V., Sanders, A.R., Savitz, A., Schall, U., Schulze, T.G., Schwab, S.G., Scolnick, E.M., Scott, R.J., Seidman, L.J., Shi, J., Silverman, J.M., Smoller, J.W., Söderman, E., Spencer, C.C.A., Stahl, E.A., Strengman, E., Strohmaier, J., Stroup, T.S., Suvisaari, J., Svrakic, D.M., Szatkiewicz, J.P., Thirumalai, S., Tooney, P.A., Veijola, J., Visscher, P.M., Waddington, J., Walsh, D., Webb, B.T., Weiser, M., Wildenauer, D.B., Williams, N.M., Williams, S., Witt, S. H., Wolen, A.R., Wormley, B.K., Wray, N.R., Wu, J.Q., Zai, C.C., Adolfsson, R., Andreassen, O.A., Blackwood, D.H.R., Bramon, E., Buxbaum, J.D., Cichon, S., Collier, D.A., Corvin, A., Daly, M.J., Darvasi, A., Domenici, E., Esko, T., Gejman, P. V., Gill, M., Gurling, H., Hultman, C.M., Iwata, N., Jablensky, A.V., Jönsson, E.G., Kendler, K.S., Kirov, G., Knight, J., Levinson, D.F., Li, Q.S., McCarroll, S.A., McQuillin, A., Moran, J.L., Mowry, B.J., Nöthen, M.M., Ophoff, R.A., Owen, M.J., Palotie, A., Pato, C.N., Petryshen, T.L., Posthuma, D., Rietschel, M., Riley, B.P., Rujescu, D., Sklar, P., St Clair, D., Walters, J.T.R., Werge, T., Sullivan, P.F., O'Donovan, M.C., Scherer, S.W., Neale, B.M., Sebat, J., 2016. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nat. Genet. 2016 49:1 49, 27–35. doi:https://doi.org/10.1038/ng.3725.

Martin, A.R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B.M., Daly, M.J., 2019. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat. Genet. 2019 51:4 51, 584–591. doi:https://doi.org/10.1038/s41588-019-0379-x.

Maruf, A.A., Stein, K., Arnold, P.D., Aitchison, K.J., Müller, D.J., Bousman, C., 2021. CYP2D6 and antipsychotic treatment outcomes in children and youth: a systematic review. J. Child Adolesc. Psychopharmacol. https://doi.org/10.1089/cap.2020.0093.

McCormack, M., Alfirevic, A., Bourgeois, S., Farrell, J.J., Kasperavičiūtė, D., Carrington, M., Sills, G.J., Marson, T., Jia, X., de Bakker, P.I.W., Chinthapalli, K., Molokhia, M., Johnson, M.R., O'Connor, G.D., Chaila, E., Alhusaini, S., Shianna, K. V., Radtke, R.A., Heinzen, E.L., Walley, N., Pandolfo, M., Pichler, W., Park, B.K., Depondt, C., Sisodiya, S.M., Goldstein, D.B., Deloukas, P., Delanty, N., Cavalleri, G. L., Pirmohamed, M., 2011. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N. Engl. J. Med. 364, 1134–1143. https://doi.org/10.1056/NEJMoa1013297.

McGuffin, P., Owen, M.J., Gottesman, I.I., 2004. Psychiatric Genetics and Genomics. OUP Oxford.

McGuinness, M., Fassi, E., Wang, C., Hacking, C., Ellis, V., 2021. Breast cancer polygenic risk scores in the clinical cancer genetic counseling setting: current practices and impact on patient management. J. Genet. Couns. 30, 588–597. https://doi.org/10.1002/jgc4.1347.

Milosavljević, F., Bukvić, N., Pavlović, Z., Miljević, Č., Pešić, V., Molden, E., Ingelman-Sundberg, M., Leucht, S., Jukić, M.M., 2021. Association of CYP2C19 and CYP2D6 poor and intermediate metabolizer status with antidepressant and antipsychotic exposure: a systematic review and meta-analysis. JAMA Psychiatry 78, 270–280. https://doi.org/10.1001/jamapsychiatry.2020.3643.

Mojarad, B.A., Yin, Y., Manshaei, R., Backstrom, I., Costain, G., Heung, T., Merico, D., Marshall, C.R., Bassett, A.S., Yuen, R.K.C.C., 2021. Genome sequencing broadens the range of contributing variants with clinical implications in schizophrenia. Transl. Psychiatry 11, 84. https://doi.org/10.1038/s41398-021-01211-2.

Morris, E., O'Donovan, M., Virani, A., Austin, J., 2022. An ethical analysis of divergent clinical approaches to the application of genetic testing for autism and schizophrenia. Hum. Genet. 141, 1069–1084. https://doi.org/10.1007/s00439-021-02349-1.

Muhle, R.A., Reed, H.E., Vo, L.C., Mehta, S., McGuire, K., Veenstra-VanderWeele, J., Pedapati, E., 2017. Clinical diagnostic genetic testing for individuals with developmental disorders. J. Am. Acad. Child Adolesc. Psychiatry 56, 910–913. https://doi.org/10.1016/j.jaac.2017.09.418.

Murray, G.K., Lin, T., Austin, J., McGrath, J.J., Hickie, I.B., Wray, N.R., 2021. Could polygenic risk scores be useful in psychiatry?: a review. JAMA Psychiatry 78, 210–219. https://doi.org/10.1001/JAMAPSYCHIATRY.2020.3042.

Pardiñas, A.F., Kappel, D.B., Roberts, M., Tipple, F., Shitomi-Jones, L.M., King, A., Jansen, J., Helthuis, M., Owen, M.J., O'Donovan, M.C., Walters, J.T.R., 2023. Pharmacokinetics and pharmacogenomics of clozapine in an ancestrally diverse sample: a longitudinal analysis and genome-wide association study using UK clinical monitoring data. Lancet Psychiatry 10, 209–219. https://doi.org/10.1016/S2215-0366(23)00002-0.

Peck, L., Borle, K., Folkersen, L., Austin, J., 2022. Why do people seek out polygenic risk scores for complex disorders, and how do they understand and react to results? Eur. J. Hum. Genet. 30, 81–87. https://doi.org/10.1038/s41431-021-00929-3.

Perkins, D.O., Olde Loohuis, L., Barbee, J., Ford, J., Jeffries, C.D., Addington, J., Bearden, C.E., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Mathalon, D.H., McGlashan, T.H., Seidman, L.J., Tsuang, M., Walker, E.F., Woods, S.W., 2020. Polygenic risk score contribution to psychosis prediction in a target population of persons at clinical high risk. AJP 177, 155–163. https://doi.org/10.1176/appi.ajp.2019.18060721.

Phillips, E.J., Sukasem, C., Whirl-Carrillo, M., Müller, D.J., Dunnenberger, H.M., Chantratita, W., Pirmohamed, M., 2018. Clinical pharmacogenetics implementation consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. Clin. Pharmacol. Ther. 103 (4), 574–581.

Reay, W.R., Geaghan, M.P., Atkins, J.R., Carr, V.J., Green, M.J., Cairns, M.J., 2022. Genetics-informed precision treatment formulation in schizophrenia and bipolar disorder. Am. J. Hum. Genet. 109, 1620–1637. https://doi.org/10.1016/j.ajhg.2022.07.011.

Ronald, A., Pain, O., 2018. A systematic review of genome-wide research on psychotic experiences and negative symptom traits: new revelations and implications for psychiatry. Hum. Mol. Genet. 27, R136–R152. https://doi.org/10.1093/hmg/ddy157.

Shao, Y., Sztainberg, Y., Wang, Q., Bajikar, S.S., Trostle, A.J., Wan, Y.-W., Jafar-nejad, P., Rigo, F., Liu, Z., Tang, J., Zoghbi, H.Y., 2021. Antisense oligonucleotide therapy in a humanized mouse model of MECP2 duplication syndrome. Sci. Transl. Med. 13, eaaz7785. https://doi.org/10.1126/scitranslmed.aaz7785.

Singh, T., Poterba, T., Curtis, D., Akil, H., Al Eissa, M., Barchas, J.D., Bass, N., Bigdeli, T. B., Breen, G., Bromet, E.J., Buckley, P.F., Bunney, W.E., Bybjerg-Grauholm, J., Byerley, W.F., Chapman, S.B., Chen, W.J., Churchhouse, C., Craddock, N., Cusick, C. M., DeLisi, L., Dodge, S., Escamilla, M.A., Eskelinen, S., Fanous, A.H., Faraone, S.V., Fiorentino, A., Francioli, L., Gabriel, S.B., Gage, D., Gagliano Taliun, S.A., Ganna, A., Genovese, G., Glahn, D.C., Grove, J., Hall, M.H., Hämäläinen, E., Heyne, H.O., Holi, M., Hougaard, D.M., Howrigan, D.P., Huang, H., Hwu, H.G., Kahn, R.S., Kang, H.M., Karczewski, K.J., Kirov, G., Knowles, J.A., Lee, F.S., Lehrer, D.S., Lescai, F., Malaspina, D., Marder, S.R., McCarroll, S.A., McIntosh, A.M., Medeiros, H., Milani, L., Morley, C.P., Morris, D.W., Mortensen, P.B., Myers, R.M., Nordentoft, M., O'Brien, N.L., Olivares, A.M., Ongur, D., Ouwehand, W.H., Palmer, D.S., Paunio, T., Quested, D., Rapaport, M.H., Rees, E., Rollins, B., Satterstrom, F.K., Schatzberg, A., Scolnick, E., Scott, L.J., Sharp, S.I., Sklar, P., Smoller, J.W., Sobell, J.L., Solomonson, M., Stahl, E.A., Stevens, C.R., Suvisaari, J., Tiao, G., Watson, S.J., Watts, N.A., Blackwood, D.H., Børglum, A.D., Cohen, B.M., Corvin, A.P., Esko, T., Freimer, N.B., Glatt, S.J., Hultman, C.M., McQuillin, A., Palotie, A., Pato, C.N., Pato, M.T., Pulver, A.E., St. Clair, D., Tsuang, M.T., Vawter, M.P., Walters, J.T., Werge, T.M., Ophoff, R. A., Sullivan, P.F., Owen, M.J., Boehnke, M., O'Donovan, M.C., Neale, B.M., Daly, M. J., 2022. Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature 2022 604:7906 604, 509–516. doi:https://doi.org/10.1038/s41586-022-04556-w.

Teng, Y., Sandhu, A., Liemburg, E.J., Naderi, E., Alizadeh, B.Z., 2023. The progress and pitfalls of pharmacogenetics-based precision medicine in schizophrenia spectrum disorders: a systematic review and meta-analysis. J. Personalized Med. 13, 471. https://doi.org/10.3390/jpm13030471.

Trubetskoy, V., Pardiñas, A.F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T.B., Bryois, J., Chen, C.-Y., Dennison, C.A., Hall, L.S., Lam, M., Watanabe, K., Frei, O., Ge, T., Harwood, J.C., Koopmans, F., Magnusson, S., Richards, A.L., Sidorenko, J., Wu, Y., Zeng, J., Grove, J., Kim, M., Li, Z., Voloudakis, G., Zhang, W., Adams, M., Agartz, I., Atkinson, E.G., Agerbo, E., Al Eissa, M., Albus, M., Alexander, M., Alizadeh, B.Z., Alptekin, K., Als, T.D., Amin, F., Arolt, V., Arrojo, M., Athanasiu, L., Azevedo, M.H., Bacanu, S.A., Bass, N.J., Begemann, M., Belliveau, R.A., Bene, J., Benyamin, B., Bergen, S.E., Blasi, G., Bobes, J., Bonassi, S., Braun, A., Bressan, R.A., Bromet, E.J., Bruggeman, R., Buckley, P.F., Buckner, R.L., Bybjerg-Grauholm, J., Cahn, W., Cairns, M.J., Calkins, M.E., Carr, V.J., Castle, D., Catts, S.V., Chambert, K. D., Chan, R.C.K., Chaumette, B., Cheng, W., Cheung, E.F.C., Chong, S.A., Cohen, D., Consoli, A., Cordeiro, Q., Costas, J., Curtis, C., Davidson, M., Davis, K.L., de Haan, L., Degenhardt, F., DeLisi, L.E., Demontis, D., Dickerson, F., Dikeos, D., Dinan, T., Djurovic, S., Duan, J., Ducci, G., Dudbridge, F., Eriksson, J.G., Fañanás, L., Faraone, S.V., Fiorentino, A., Forstner, A., Frank, J., Freimer, N.B., Fromer, M., Frustaci, A., Gadelha, A., Genovese, G., Gershon, E.S., Giannitelli, M., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I., González Peñas, J., González-Pinto, A., Gopal, S., Gratten, J., Green, M.F., Greenwood, T.A., Guillin, O., Gülöksüz, S., Gur, R.E., Gur, R.C., Gutiérrez, B., Hahn, E., Hakonarson, H., Haroutunian, V., Hartmann, A.M., Harvey, C., Hayward, C., Henskens, F.A., Herms, S., Hoffmann, P., Howrigan, D.P., Ikeda, M., Iyegbe, C., Joa, I., Julià, A., Kähler, A.K., Kam-Thong, T., Kamatani, Y., Karachanak-Yankova, S., Kebir, O., Keller, M.C., Kelly, B.J., Khrunin, A., Kim, S.-W., Klovins, J., Kondratiev, N., Konte, B., Kraft, J., Kubo, M., Kučinskas, V., Kučinskiene, Z.A., Kusumawardhani, A., Kuzelova-Ptackova, H., Landi, S., Lazzeroni, L.C., Lee, P.H., Legge, S.E., Lehrer, D.S., Lencer, R., Lerer, B., Li, M., Lieberman, J., Light, G.A., Limborska, S., Liu, C.-M., Lönnqvist, J., Loughland, C.M., Lubinski, J., Luykx, J.J., Lynham, A., Macek, M., Mackinnon, A., Magnusson, P.K.E., Maher, B.S., Maier, W., Malaspina, D., Mallet, J., Marder, S.R., Marsal, S., Martin, A.R., Martorell, L., Mattheisen, M., McCarley, R.W., McDonald, C., McGrath, J.J., Medeiros, H., Meier, S., Melegh, B., Melle, I., Mesholam-Gately, R.I., Metspalu, A., Michie, P.T., Milani, L., Milanova, V., Mitjans, M., Molden, E., Molina, E., Molto, M.D., Mondelli, V., Moreno, C., Morley, C.P., Muntané, G., Murphy, K.C., Myin-Germeys, I., Nenadić, I., Nestadt, G., Nikitina-Zake, L., Noto, C., Nuechterlein, K.H., O'Brien, N.L., O'Neill, F.A., Oh, S.-Y., Olincy, A., Ota, V.K., Pantelis, C., Papadimitriou, G.N., Parellada, M., Paunio, T., Pellegrino, R., Periyasamy, S., Perkins, D.O., Pfuhlmann, B., Pietiläinen, O., Pimm, J., Porteous, D., Powell, J., Quattrone, D., Quested, D., Radant, A.D., Rampino, A., Rapaport, M.H., Rautanen, A., Reichenberg, A., Roe, C., Roffman, J.L., Roth, J., Rothermundt, M., Rutten, B.P.F., Saker-Delye, S., Salomaa, V., Sanjuan, J.,

Santoro, M.L., Savitz, A., Schall, U., Scott, R.J., Seidman, L.J., Sharp, S.I., Shi, J., Siever, L.J., Sigurdsson, E., Sim, K., Skarabis, N., Slominsky, P., So, H.-C., Sobell, J. L., Söderman, E., Stain, H.J., Steen, N.E., Steixner-Kumar, A.A., Stögmann, E., Stone, W.S., Straub, R.E., Streit, F., Strengman, E., Stroup, T.S., Subramaniam, M., Sugar, C.A., Suvisaari, J., Svrakic, D.M., Swerdlow, N.R., Szatkiewicz, J.P., Ta, T.M. T., Takahashi, A., Terao, C., Thibaut, F., Toncheva, D., Tooney, P.A., Torretta, S., Tosato, S., Tura, G.B., Turetsky, B.I., Üçok, A., Vaaler, A., van Amelsvoort, T., van Winkel, R., Veijola, J., Waddington, J., Walter, H., Waterreus, A., Webb, B.T., Weiser, M., Williams, N.M., Witt, S.H., Wormley, B.K., Wu, J.Q., Xu, Z., Yolken, R., Zai, C.C., Zhou, W., Zhu, F., Zimprich, F., Atbaşoğlu, E.C., Ayub, M., Benner, C., Bertolino, A., Black, D.W., Bray, N.J., Breen, G., Buccola, N.G., Byerley, W.F., Chen, W.J., Cloninger, C.R., Crespo-Facorro, B., Donohoe, G., Freedman, R., Galletly, C., Gandal, M.J., Gennarelli, M., Hougaard, D.M., Hwu, H.-G., Jablensky, A. V., McCarroll, S.A., Moran, J.L., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Neil, A.L., Nordentoft, M., Pato, M.T., Petryshen, T.L., Pirinen, M., Pulver, A.E., Schulze, T.G., Silverman, J.M., Smoller, J.W., Stahl, E.A., Tsuang, D.W., Vilella, E., Wang, S.-H., Xu, S., Indonesia Schizophrenia Consortium, PsychENCODE, Psychosis Endophenotypes International Consortium, SynGO Consortium, Adolfsson, R., Arango, C., Baune, B.T., Belangero, S.I., Børglum, A.D., Braff, D., Bramon, E., Buxbaum, J.D., Campion, D., Cervilla, J.A., Cichon, S., Collier, D.A., Corvin, A., Curtis, D., Forti, M.D., Domenici, E., Ehrenreich, H., Escott-Price, V., Esko, T., Fanous, A.H., Gareeva, A., Gawlik, M., Gejman, P.V., Gill, M., Glatt, S.J., Golimbet, V., Hong, K.S., Hultman, C.M., Hyman, S.E., Iwata, N., Jönsson, E.G., Kahn, R.S., Kennedy, J.L., Khusnutdinova, E., Kirov, G., Knowles, J.A., Krebs, M.-O., Laurent-Levinson, C., Lee, J., Lencz, T., Levinson, D.F., Li, Q.S., Liu, J., Malhotra, A. K., Malhotra, D., McIntosh, A., McQuillin, A., Menezes, P.R., Morgan, V.A., Morris, D.W., Mowry, B.J., Murray, R.M., Nimgaonkar, V., Nöthen, M.M., Ophoff, R. A., Paciga, S.A., Palotie, A., Pato, C.N., Qin, S., Rietschel, M., Riley, B.P., Rivera, M., Rujescu, D., Saka, M.C., Sanders, A.R., Schwab, S.G., Serretti, A., Sham, P.C., Shi, Y., St Clair, D., Stefánsson, H., Stefansson, K., Tsuang, M.T., van Os, J., Vawter, M.P., Weinberger, D.R., Werge, T., Wildenauer, D.B., Yu, X., Yue, W., Holmans, P.A., Pocklington, A.J., Roussos, P., Vassos, E., Verhage, M., Visscher, P.M., Yang, J., Posthuma, D., Andreassen, O.A., Kendler, K.S., Owen, M.J., Wray, N.R., Daly, M.J., Huang, H., Neale, B.M., Sullivan, P.F., Ripke, S., Walters, J.T.R., O'Donovan, M.C., Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2022. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604, 502–508. https://doi.org/10.1038/s41586-022-04434-5.

Turley, P., Meyer, M.N., Wang, N., Cesarini, D., Hammonds, E., Martin, A.R., Neale, B.M., Rehm, H.L., Wilkins-Haug, L., Benjamin, D.J., Hyman, S., Laibson, D., Visscher, P.M., 2021. Problems with using polygenic scores to select embryos. N. Engl. J. Med. 385, 78–86. https://doi.org/10.1056/NEJMsr2105065.

Waszczuk, M.A., Jonas, K.G., Bornovalova, M., Breen, G., Bulik, C.M., Docherty, A.R., Eley, T.C., Hettema, J.M., Kotov, R., Krueger, R.F., Lencz, T., Li, J.J., Vassos, E., Waldman, I.D., 2023. Dimensional and transdiagnostic phenotypes in psychiatric genome-wide association studies. Mol. Psychiatry 1–11. https://doi.org/10.1038/s41380-023-02142-8.