GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 10 (355) Октябрь 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 10 (355) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 10 (355) 2024

GENETIC VARIANTS IN ANTIPSYCHOTIC METABOLISM: POLYMORPHISM PROFILES IN KAZAKH COHORT WITH PARANOID SCHIZOPHRENIA

Kovaleva Kristina[1], Zulfiya Kachiyeva[1]*, Aigulim Abetova[2], Natalia Raspopova[3].

[1]*S.D. Asfendiyarov Kazakh National Medical University; Kazakhstan, 050000 Almaty, Tole bi st., 94.*

[2]*Republican Scientific and Practical Center of Mental Health, Almaty, Kazakhstan.*

[3]*Kazakh Russian Medical University Almaty, Kazakhstan.*

Abstract.

Schizophrenia is a multifaceted psychiatric disorder characterized by hallucinations, delusions, cognitive impairments, and behavioral disturbances. Genetic factors significantly contribute to its pathogenesis, accounting for approximately 80% of the heritability. Globally, about 1% of the population is affected by schizophrenia, with 45,054 individuals in Kazakhstan receiving medical treatment for the condition, indicating a prevalence rate of 238,6 per 100,000 people. The rise in mental health disorders in Kazakhstan underscores the need for personalized treatment approaches to address these public health challenges. This study examines the influence of key polymorphisms—CYP2D6 (rs1135840), CYP3A5 (rs776746), COMT (rs4818, rs4680, rs9606186), CNR1 (rs1049353), HTR2A (rs6311, rs6313), and DRD2 (rs1799978, rs1800497)—on AP drug metabolism and therapeutic outcomes. The findings underscore the potential for genotype-guided AP dosage individualization in Kazakh individuals, laying a foundation for future research on optimizing AP therapy in this population.

Key words. Paranoid schizophrenia, SNPs, CYP2D6, DRD2, HTR2A, COMT, CNR1, pharmacogenetics, Kazakh ethnic group, antipsychotics, central Asian.

Abbreviation. BMI: Body Mass Index; SCZ: Schizophrenia; Snps: Single Nucleotide Polymorphisms; PANSS: Positive And Negative Syndrome Scale; AP: Antipsychotic; ASD: Autism Spectrum Disorders; UKU: Side Effect Rating Scale.

Introduction.

Schizophrenia (SCZ) remains a severe, progressively debilitating psychoneurological disorder, posing a significant burden on patients, their families, and global healthcare systems including in the regions of Central Asia, as they grapple with pharmacotherapeutic considerations for the disease. In 2020, Kazakhstan reported a prevalence of 238.6 cases per 100,000 people for SCZ and related disorders (Ministry of Health of the Republic of Kazakhstan, 2020). The disease affects 0.6-0.7% of the Kazakh population, representing 19% of the mentally ill population, with 215-245 new cases diagnosed annually [1-5]. Understanding the etiopathogenesis, clinical aspects, and treatment of SCZ in Kazakhstan is crucial.

SCZ is a chronic condition requiring long-term antipsychotic (AP) treatment, although side effects often impede adherence and contribute to relapses. Effective therapy involves biological interventions tailored to the individual, including psychopharmacotherapy, psychotherapy, and social rehabilitation [6]. Traditional APs, such as Haloperidol, were once the mainstay of treatment due to their effectiveness in reducing severe symptoms. Atypical APs, however, offer improved outcomes by targeting D2 dopamine receptors and 5-HT2A serotonin receptors, alleviating both positive and negative symptoms while minimizing side effects [6]. This genetically influenced mental disorder features disruptions in cognitive functioning, including disturbances in perception, comprehension, and the ability to meet life's demands [7].

The management of SCZ necessitates prolonged, often lifelong, AP drug use, which can lead to drug resistance and significant metabolic disturbances. Around 70% of individuals, particularly in the early treatment phases, fail to meet the minimum efficacy threshold for AP therapy [8].

Genetic variations play a key role in the effectiveness of APs. For typical APs, CYP2D6 is the main enzyme involved in metabolism, while for atypical APs, CYP3A4/A5, CYP2D6, and CYP1A2 are crucial [9]. SCZ's pathophysiology is linked to disruptions in dopaminergic and serotoninergic pathways. APs reduce positive symptoms by inhibiting dopamine receptors, but they can cause side effects like prolactin elevation, which leads to issues such as amenorrhea and sexual dysfunction. Genetic variations in dopamine-related genes like DRD2 and AKT1 influence drug dosage requirements [10,11]. Serotonin receptor genes, including HTR2A and HTR2C, also play a role in treatment responses [12]. Furthermore, the COMT gene's variants affect dopamine metabolism, influencing the response to APs [12,13].

The CNR1 gene, involved in the endocannabinoid system, has been linked to SCZ and its response to APs, though findings remain inconclusive [14]. This research focuses on genotype distributions related to drug metabolism and receptor genes in SCZ patients from Kazakhstan, including CYP2D6, CYP3A4/5, COMT, CNR1, HTR2A, and DRD2 [15,16]. The research covered in this article centers on the distribution of genotypes by polymorphisms within genes related to drug metabolism Risperidone and Haloperidol patients with paranoid SCZ in the Kazakh cohort, such as CYP2D6, CYP3A4/5, COMT, CNR1. Additionally, genes that code for the drug targets of AP medications, which encompass serotonin and dopamine receptors (such as HTR2A, and DRD2), also play a crucial role in how these medications interact with the patient's body, also will be covered [15,16].

Managing SCZ and associated psychotic disorders involves lifelong therapy with AP medications from different generations. Patients receive a combination of typical and atypical drugs at customized dosages based on their clinical history. The clinical response varies among individuals, with around half experiencing benefits and others facing adverse effects or insufficient efficacy. This highlights the importance of personalized treatment strategies and ongoing monitoring for optimal management.

Materials and Methods.

Participants:

The study utilized a case-control design, involving a total of 1200 individuals of the Kazakh population. This group included 708 individuals diagnosed with a clinically verified diagnosis of Paranoid Schizophrenia. Participants were gathered from diverse areas throughout Kazakhstan, with the investigation taking place in four regional centers of the Republic of Kazakhstan: Astana, Almaty, Shymkent, and Kyzylorda. A cohort of 1200 inpatients receiving AP therapy was assembled over a three-year period, specifically from multidisciplinary hospitals, within the Psychiatry Service of the Kazakh Clinic.

Patients in the experimental group fulfilled the criteria outlined in the ICD-10 F20.0 category, ranging in age from 18 to 65 years. Data collection employed clinical research methods, specifically clinical-psychopathological and psychometric approaches, utilizing the PANSS scale (Table 1).

During the examination, the mental condition of the patients was assessed by calculating cumulative scores for positive, negative, and general psychopathological symptoms using the PANSS (Positive and Negative Syndrome Scale) scale. The effectiveness of AP therapy over a

6-month observation period was also evaluated using the PANSS scale, categorizing effectiveness based on the main AP drug detailed in (Table 1).

The distribution of patients receiving specific AP medications in the Kazakh cohort of individuals diagnosed with Paranoid Schizophrenia is presented in (Table 2).

Additionally, an adapted version of the international UKU scale (Table 4) was utilized in this study to objectively evaluate the dynamics of mental disorder severity and the adverse effects associated with ongoing AP therapy using specific psychotropic drugs. This version of the UKU scale, tailored to the study's objectives, assessed the severity of side effects and the tolerability of AP therapy, with symptom severity rated on a scale from 0 to 3 points (Table 4).

Sample preparation and genotyping:

Genomic DNA was extracted from the whole blood samples with KingFisher Flex-Ready DNA Ultra 2.0 Prefilled Plates on the KingFisher Flex Purification System (ThermoFisher, USA) according to the manufacturer's protocol. The concentration of DNA was measured on a Qubit 4 Fluorometer (ThermoFisher, USA) instrument using reagents from the manufacturer according to the standard protocol. Polymorphisms for CYP2D6 (rs1135840), CYP3A5 (rs776746), COMT (rs4818, rs4680, rs9606186), CNR1 (rs1049353), HTR2A (rs6311, rs6313), and DRD2 (rs1799978, rs1800497) were detected and analyzed using the QuantStudio 12K Flex Real-Time PCR System (ThermoFisher, USA) using QuantStudio 12K Flex Accufill System.

Statistical Analysis:

Descriptive statistics were utilized for demographic data analysis. Genotype variations for Hardy-Weinberg equilibrium were tested using x^2 test. A P value of ≤ 05 denoted statistical significance and for the mutant allele was calculated using the Clopper-Pearson exact method [17].

Exclusion Criteria:

The comprehensive list of exclusion criteria is available on the ClinicalTrials.gov portal under trial registration NCT05090644. The main exclusion criteria include individuals who are non-Kazakh or lack confirmed Kazakh ethnicity up to the third generation, individuals younger than 18 or older than 65, those with diagnoses unrelated to ICD-10 F20.0 "Paranoid Schizophrenia," illness duration less than one year, the presence of severe somatic or neurological diseases, comorbid substance use disorders, and those who fail to provide signed informed consent.

Ethical issues:

The research received ethical clearance from the Local Ethics Committee of the S.D. Asfendiyarov Kazakh National Medical University, Almaty, Republic of Kazakhstan, under Protocol No. 12 118 dated September 28, 2021. Furthermore, it obtained approval from the Central Bioethics Commission of the Ministry of Healthcare of the Republic of Kazakhstan, per Protocol No. 14 dated November 24, 2021. The study was registered on ClinicalTrials.gov (NCT05090644), where detailed information on the exclusion and inclusion criteria can be accessed.

All procedures adhered to the appropriate protocols and standards. Informed consent was acquired from all participants or their legal representatives. During the assessment phase, all eligible participants provided written informed consent, signifying their voluntary engagement in the research, permission to collect biological samples (specifically, deoxygenated blood), and authorization for the potential publication of research findings.

Results and Discussion.

Clinical and biochemical data:

Recent research has focused on evaluating the effectiveness and safety of various antipsychotic (AP) medications to identify treatments that balance symptom control and side effect reduction. Atypical APs were developed to overcome limitations and adverse effects of typical APs, particularly reducing movement disorders such as tardive dyskinesia and elevated prolactin levels [18].

Typical APs include D2-dopamine receptor antagonists like Haloperidol and chlorpromazine, while second-generation APs, such as amisulpride and clozapine, also target serotonin and other receptors. However, individual responses to these medications can vary significantly, influencing treatment efficacy and adverse effects, including weight gain, sedation, orthostatic hypotension, and agranulocytosis [19].

In our study of Paranoid SCZ patients in Kazakhstan, Risperidone, Paliperidone, Clozapine, and Haloperidol were identified as the most frequently prescribed medications, in accordance with the clinical protocol for neuroleptic treatment (Table 2, Figure 1). Despite the popularity of Risperidone and Haloperidol, their effectiveness is often limited by variability in patient responses and adverse reactions. Our study focuses on analysing the distribution of six genes involved in the metabolism of these drugs in the Kazakh population.

In this research, the genetic, clinical, and psychopathological characteristics of the study cohort were summarized in (Table 3).

For instance, the mean age at primary SCZ was 28.74 (SD

Table 1. *Mental Status at the Time of Examination: Assessment Using the PANSS Scale.*

Positive Symptoms according to the PANSS scale (symptom severity from 1 to 7 points). The total score of positive symptoms.								
№	**Age**	**Mean**	**SD**	**Median**	**Items-total correlation**	**Average PANSS score**		
						initial examination	**after 12 weeks**	**after 24 weeks**
	Male							
1.	18-30	13.22	8.12	12	.83	72.71	62.51	43.92
2.	31-50	16.31	10.54	14	.87	79.83	68.33	46.43
3.	51 years and older	12.62	19	17	.89	87.15	72.68	49.35
4.	**Total**	16.38	10.8	14	.88	80.75	68.63	46.86
	Female							
1.	18-30	16.37	9.25	15	.78	81.36	63.45	47.11
2.	31-50	14.94	8.42	14	.75	79.24	67.17	45.36
3.	51 years and older	14.81	7.21	15	.73	83.45	66.13	44.25
4.	**Total**	15.11	8.1	15	.74	81.44	65.63	45.78
The Total Negative Symptoms Score according to the PANSS scale								
	Male							
1.	18-30	20.45	10.25	20	.75	68,33	59,80	41,22
2.	31-50	24.28	11.44	27	.82	82,08	70,59	47,58
3.	51 years and older	27.84	12.3	29	.88	97,91	82,5	56,39
4.	**Total**	24.44	11.65	27	.84	83,3	71,43	48,5
	Female							
1.	18-30	23.15	10.08	24	.71	65,32	58,4	43,31
2.	31-50	23.59	9.64	24	.61	76,89	65,44	44,96
3.	51 years and older	24.66	8.74	25.5	.63	79,10	65,45	44,32
4.	**Total**	24.01	9.37	25	.62	77,9	65,55	45,10
The Total Score of General Psychopathological Symptoms according to the PANSS scale								
	Male							
1.	18-30	35.65	17.68	33	.97	68,13	77,98	65,96
2.	31-50	41.11	21.28	33	.96	82	70,52	47,62
3.	51 years and older	51.34	25.36	48	.98	97,41	82,19	56,40
4.	**Total**	42.32	22.21	34	.97	83,23	71,5	49,5
	Female							
1.	18-30	39.29	17.08	37	.95	64,3	65,96	47,59
2.	31-50	38.19	15.47	38	.94	76,76	65,38	45,03
3.	51 years and older	41.09	15.47	39	.92	79,1	66,45	44,50
4.	**Total**	38.79	15.59	38	.95	73,4	65,93	45,5

Patients with Primary First-Generation AP Discontinued/Replaced due to inefficacy (Trifluoperazine and Haloperidol), during the observation period (6 months)				
№	**Age**	**The drug was discontinued (replaced)**	**PANSS <50%**	**PANSS >50%**
1.	18-30	0	23	4
2.	31-50	10	109	34
3.	51 years and older	6	49	15
4.	Total	16 (2.2%)	181 (25.5%)	53 (7.4%)
Patients with Primary Second-Generation AP Discontinued/Replaced (e.g., Risperidone) during the observation period (6 months)				
№	**Age**	**The drug was discontinued (replaced)**	**PANSS <50%**	**PANSS >50%**
1.	18-30	6	59	25
2.	31-50	17	158	59
3.	51 years and older	8	89	37
4.	Total	31 (4.4%)	306 (43.2%)	121 (17.1%)

Table 2. *The distribution of medications (Aps) administered to individuals diagnosed with Paranoid SCZ in the Kazakh cohort.*

Medication	**Quantity of patient intake**	**n (%)**
Haloperidol	212	42.4
Paliperidone (Invega, Xeplion, Trevicta)	141	28.2
Risperidone (Rispolept)	129	25.8
Clozapine	90	18
Olanzapine (Zyprexa, Ferzapine, Olfrex)	59	11.8
Trifluoperazine	38	7.6
Amisulpride	27	5.4
Cariprazine (Reagila)	7	1.4
Aripiprazole (Aripegis)	5	1

Table 3. *Summary of genetic, clinical and psychopathological characteristics of the study cohort.*

Genotype			
Variable		**Study Cohort (n = 708) n (%)**	**P Value**
Original Genotype	**GPVD**		
CYP2D6 (rs1135840)			
*1/*1 (wild-type, G/G)	BB	252 (35.6%)	0.117
*2/*1 (G/C)	AB	300 (42.3%)	0.0027
*2/*2 (C/C)	AA	144 (20.3%)	0.053
Unknown (“no call”)		11 (1.5%)	
CYP3A5 (rs776746)			
*1/*1 (wild-type, C/C)	BB	534 (75.4%)	0.825
*3/*1 (C/T)	AB	161 (22.7%)	0.650
*3/*3 (T/T)	AA	9 (1.3%)	0.652
Unknown (“no call”)		4 (0.56%)	
COMT (rs4680)			
G/G (wild-type)	BB	254 (35.8%)	0.480
G/A	AB	341 (48.2%)	0.156
A/A	AA	89 (12.6%)	0.327
Unknown (“no call”)		24 (3.4%)	
COMT (rs9606186)			
G/G (wild-type)	BB	308 (43.5%)	0.595
G/C	AB	307 (43.4%)	0.291
C/C	AA	77 (10.8%)	0.328
Unknown (“no call”)		16 (2.2%)	
COMT (rs4818)			
G/G (wild-type)	BB	111 (15.6%)	1.000
G/C	AB	356 (49.8%)	0.940
C/C	AA	237 (33.4%)	0.012
Unknown (“no call”)		4 (0.56%)	
CNR1 (rs1049353)			
C/C (wild-type)	BB	475 (67.09%)	0.169
C/T	AB	188 (26.5%)	0.004
T/T	AA	18 (2.5%)	0.078
Unknown (“no call”)		27 (3.8%)	
HTR2A (rs6311)			
C/C (wild-type)	BB	291 (41.1%)	0.970
C/T	AB	327 (46.1%)	0.910
T/T	AA	80 (11.2%)	0.238
Unknown (“no call”)		10 (1.4%)	
HTR2A (rs6313)			
C/C (wild-type)	BB	298 (42%)	0.879
C/T	AB	324 (45.8%)	0.762
T/T	AA	83 (11.7%)	0.862
Unknown (“no call”)		3 (0.42%)	
DRD2 (rs1799978)			
A/A (wild-type)	BB	575 (81.2%)	0.918
A/G	AB	110 (15.5%)	0.834
G/G	AA	4 (0.6%)	0.824
Unknown (“no call”)		19 (2.6%)	
DRD2 (rs1800497)			
G/G (wild-type)	BB	381 (53.8%)	0.821
G/A	AB	256 (36.1%)	0.083
A/A	AA	63 (8.9%)	0.096
Unknown (“no call”)		8 (1.1%)	
Demographic data			
Sex (M/F)		369 (52,1%) /339 (47,8%)	
Age (years) (mean ± SD)		43 ± 11.31	

Age of Onset of Mental Disorders	Up to 18 years 18 to 30 years 31 to 50 years 51 to 60 years	63 (12.6%) 317 (63.4%) 114 (22.8%) 6 (1.2%)	
Frequency of Hospitalizations over the past 5 years	First-time More than 1 times 1 or 2 times 3 or 4 times 5 or more times	26 (5.2%) 474 (66,9%) 267 (53.4%) 121 (24.2%) 86 (17.2%)	0.4768 0.00001 0.0187 0.4090 0.2742
Alcohol Consumption	Do not use Uses occasionally Alcohol addiction	603 (85.1%) 95 (13.41%) 10 (1.41%)	 0.0001
Use of Psychoactive Substances (Drugs)	Does not use Uses occasionally Drug addict	673 (95.3%) 25 (3.53%) 10 (1.4%)	 0.0001
Clinical-psychopathological data			
Psychopathological heredity burden	No Yes (no additional instructions) Yes, Schizophrenia Yes, Affective Disorder Yes, Alcoholism Yes, Other Psychoses Other non-psychotic illnesses Yes, Mental Retardation Yes, (drug addiction/ substance abuse)	421 (59.5%) 113 (15.9%) 88 (12.4%) 3 (0.4%) 66 (9.32%) 6 (0.84%) 4 (0.56%) 2 (0.28%) 5 (0.7%)	 0.5955 0.1596 0.1243 0.0042 0.0932 0.0085 0.0056 0.0028 0.0071
Premorbid personality traits	Sociability Closedness Independence Dependence Confidence Uncertainty Activity Passivity Altruism Selfishness Goodwill Hostility Tendency to Feel Guilty Tendency to Self-Justification	270 (38.1%) 437 (61.7%) 276 (38.9%) 432 (61.01%) 262 (37%) 446 (62.3%) 275 (38.8%) 433 (61.1%) 227 (32%) 481 (68%) 376 (53.1%) 332 (46.9%) 227 (32.06%) 481 (67.9%)	8.5×10^{-19} 1.1×10^{-16} 1.4×10^{-22} 4.5×10^{-17} 1.5×10^{-41} 0.019 1.5×10^{-41}
Presence of Mental Illness Disability	No First Group Second Group Third Group	122 (17.2%) 16 (2.25%) 549 (77.5%) 21 (3%)	4.9×10^{-9} 1.2×10^{-53} 1.6×10^{-68} 1.8×10^{-49}

**It should be mentioned that in this cohort the indicated SNPs have been accessed separately (1 SNP = 1 panel), which does not exclude the possibility of presence of several SNPs in the same patient (compound heterozygous carriers). GPVD = Genetic Profile from Visual Data.*

7.9; age range = 18-65 years). Based on the phenotypic data, the most common manifestation of Paranoid Schizophrenia occurs at the age of 18 to 30 years among men (41.2%) and women (22.2%) in the Republic of Kazakhstan. Particularly, at the age of 21 to 30 years among men, the onset of the mental disorder Schizophrenia predominates (47.6%). The frequency of hospitalizations more than once also prevails among men (53.4%), while among women, it is observed much less often (32.4%). Episodic use of alcohol/psychoactive substances as well as alcohol/drug addiction is also more common in men. Having analyzed the questionnaire data of patients according to psychopathological heredity, Schizophrenia (10.2%) and Alcoholism (10%) prevailed, as well as burden without additional instructions (18.2%) in the cohort of Ethnic Kazakhs. In terms of premorbid personality traits, the prevailing number of patients noted Confidence (66.8%), Addiction (64.6%), Uncertainty (66.8%), Passivity (65.8%), Selfishness (70.4%) and a tendency to Self-Justification (69.4%).

Table 4. *Adapted UKU Scale for Symptom Severity Assessment.*

Monitoring Side Effects from taking Antipsychotics (tolerance to AP therapy)				
Side Effects after taking Antipsychotics	**The quality of being expressive**			
	0	**1**	**2**	**3**
Hyperprolactinemia	606	92	7	3
Weight gain	553	137	13	5
Other side effects	589	108	10	1
Extrapyramidal symptoms (neuroleptic syndrome)	477	159	47	25
Cancellation of the main AP due to the severity of side effects	32 (4,5%) yes		676 (95,4 %) no	
The main AP was canceled/replaced due to insufficient effectiveness	n=47 (6.6%) patients			
Low efficiency (decrease in PANSS score < 50% of points)	n=487 (68.7%) patients			
High (decrease in PANSS score > 50% of points)	n=174 (24.6%) patients			
Level of Compliance (adherence to therapy)				
Full compliance	283 (39.9%)			
Partial non-compliance	343 (48.4%)			
Complete non-compliance	82 (11,58%)			
The Primary AP was changed due to ineffectiveness				
Age of onset of mental disorders	**n (%)**			
Before 18	n=10 ((1.4%)			
From 18 to 30	n=30 (4.23%)			
From 31 to 50	n=7 (0.98%)			
51 and older	n=2 (0.28%)			

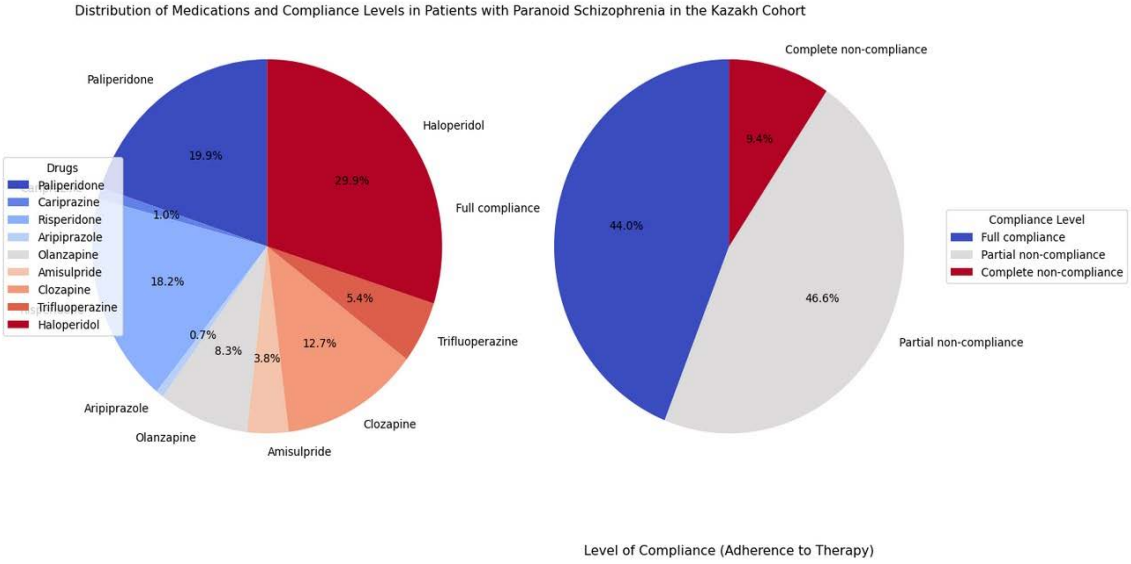

Figure 1. *Paliperidone (19,9%), Risperidone (18,2%) and Haloperidol (29,9%) are the predominant pharmacological agents for the treatment of individuals diagnosed with Paranoid Schizophrenia and are commonly prescribed in clinical practice in the Republic of Kazakhstan. The images were created using the JupyterLab program, based on the Anaconda 4.0.16 platform.*

Although not the main objective of this paper, these data were presented since they may help establish the genotype-phenotype correlation and may provide a solid base for prospective research on the individualization of AP dosage in the affected Kazakh individuals shortly.

The monitoring of side effects from AP medication (tolerability of antipsychotic therapy) is detailed in (Table 4), which is an adapted version of the UKU scale. This scale evaluates symptom severity on a 0 to 3-point scale and is visually represented in the as (Figure 2).

The prevailing drugs in AP therapy were Paliperidone (19.9%), Risperidone (18.2%) and Haloperidol (29.9%). In the process of psychopharmacotherapy in patients with paranoid schizophrenia, partial and complete non-compliance with APs was observed, predominating in both men (27.8%) and women (28.2%) of cases in Kazakhs.

Genetic Polymorphism/Genotyping.

1. rs1135840 of the gene CYP2D6:

CYP2D6 enzymatic activity plays a key role in the metabolism of several AP medications used in treating SCZ, including Haloperidol, Risperidone, and Aripiprazole. Genetic variations in CYP2D6 can influence both the efficacy and tolerability of these drugs. Polymorphisms resulting in reduced or enhanced enzyme activity may require dose adjustments or alter the risk of adverse effects. Genotyping CYP2D6 can help optimize AP

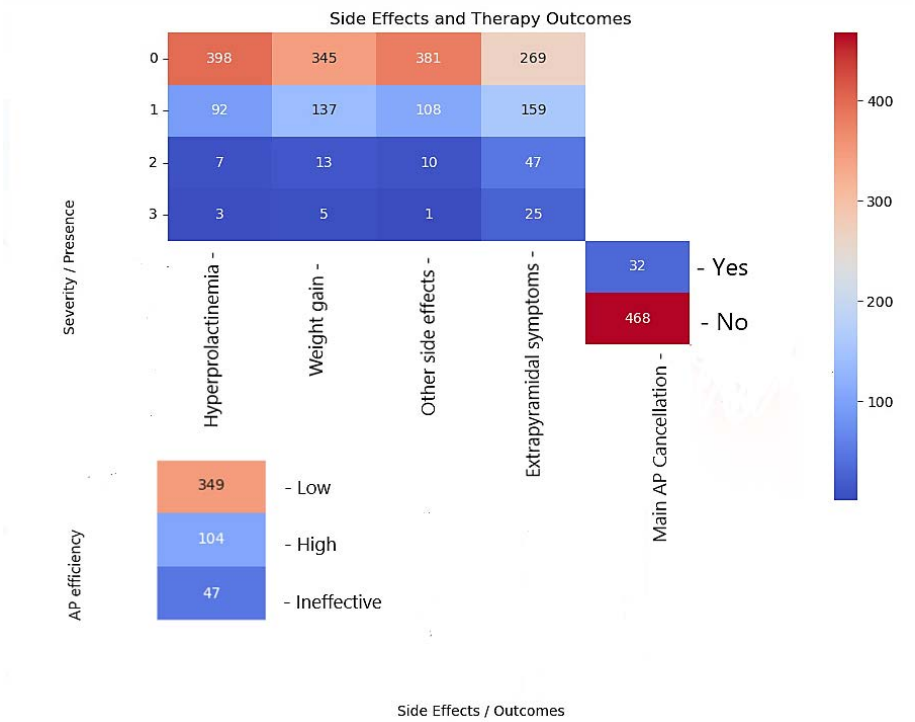

Figure 2. *This heatmap reflects the data from (Table 4) on the effectiveness and tolerability of AP therapy over a 6-month observation period for patients with Paranoid SCZ. In most cases, patients reported good adherence to and tolerance to AP treatment. On average, 348 patients had zero side effects on the UKU scale. However, 18,4% of patients experienced mild hyperprolactinemia, 27,4% had weight gain, 31,8% had mild extrapyramidal symptoms, and 21,6% experienced other side effects from taking APs. A total of 22,2% of patients exhibited moderate to severe symptoms from AP therapy. The images were created using the JupyterLab program, based on the Anaconda 4.0.16 platform.*

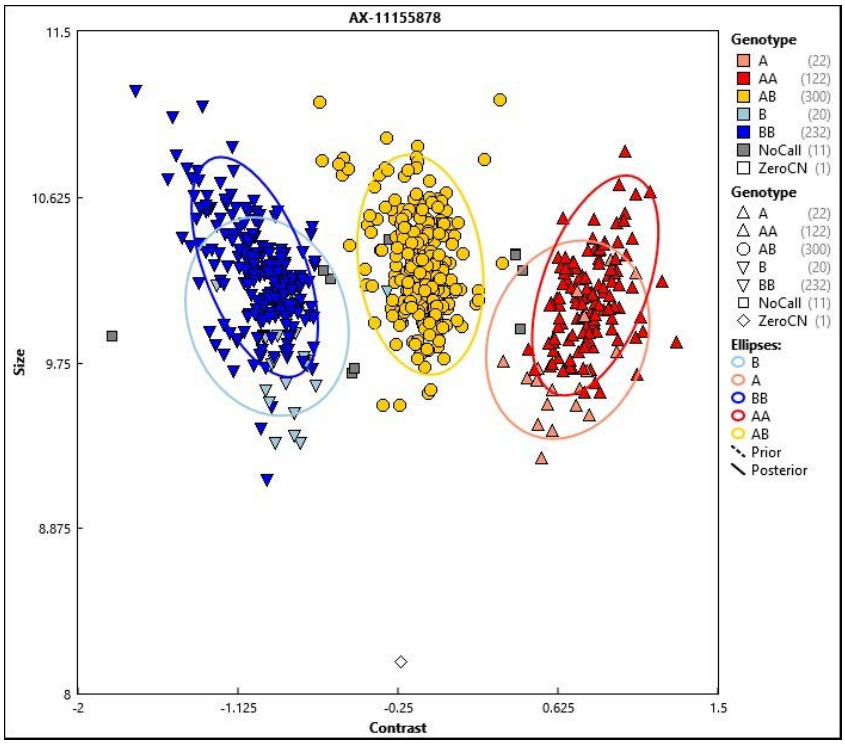

Figure 3. *Allele frequency distribution of* ***CYP2D6*2 (rs1135840)*** *in the Kazakh population.*
*1) Homozygous wild-type CYP2C9*1/*1 G/G (indicated as* ***BB****, n = 252) allele carriers.*
*2) Heterozygous CYP2C9*2/*1 G/C (indicated as* ***AB****, n = 300) allele carriers.*
*3) Homozygous CYP2C9*2/*2 C/C (indicated as* ***AA****, n = 144) allele carriers.*
4) "No call" signal (n = 11).

drug selection and dosing, identifying patients at higher risk of side effects or those needing specific adjustments based on their genotype. For instance, CYP2D6 genotype impacts Risperidone plasma levels and clinical outcomes [20].

Preliminary research suggests that individuals with the CYP2D6*2 (rs1135840) allele may metabolize Haloperidol more slowly, leading to higher drug levels and an increased risk of side effects. The clinical impact of CYP2D6 polymorphisms depends on the drug, the individual's genetic profile, and health conditions [21].

CYP2D6 activity is essential for the effectiveness of APs like Haloperidol, Risperidone, and Aripiprazole. Genetic variations can significantly influence drug metabolism and patient responses. Incorporating CYP2D6 genotyping into clinical practice in Kazakhstan could improve personalized treatment by identifying patients at risk of adverse effects or those needing dose adjustments. However, the use of genotyping in psychiatry is still debated and requires consultation with experienced healthcare providers.

The CYP2D6 gene shows significant polymorphism, with drug metabolism influenced by the specific allele combinations present. Individuals with the *2 (B) allele and a normal function allele typically metabolize Haloperidol slower than ultra-rapid metabolizers. Poor metabolizers (*4/*4) should receive 60% of the standard Haloperidol dose, while ultra-rapid metabolizers *1/*1 (BB), *1/*2 (AB), are shown in blue and yellow in (Figure 3), may need 1.5 times the usual dose or an alternative AP [21,22].

Within the examined Kazakh cohort, a notable prevalence of heterozygous AB genotypes is evident among those diagnosed with Paranoid SCZ, while homozygous BB allele carriers, represented in blue in the accompanying illustration, are classified as normal metabolizers of Haloperidol. Understanding this polymorphic locus within the CYP2D6 gene family is essential for elucidating the metabolic profile of a given AP.

The genetic variant rs1135840, known as CYP2D62, has been extensively linked to altered Risperidone metabolism and treatment outcomes. This polymorphism, characterized by a guanine to cytosine substitution at position 4181 in the CYP2D6 gene, results in distinct metabolic profiles and drug responses. Lu et al. reported a significant association between the G4181C polymorphism and variations in plasma Risperidone levels and the R/9-OH ratio.

Notably, individuals with the CYP2D6*10 genotype showed different changes in glucose and triglyceride levels compared to AB carriers, suggesting a potential influence on Risperidone's metabolic effects. Additionally, individuals with the AA allele, which is associated with reduced enzyme activity, exhibited increased Risperidone concentrations and R/9-OH ratios, highlighting a possible interactive effect on Risperidone metabolism and therapeutic response [20,22,23].

In summary, the rs1135840 polymorphism, particularly in conjunction with alleles like CYP2D6*10, significantly influences Risperidone plasma concentrations and may affect its metabolic and therapeutic effects [24].

These findings suggest that the AA genotype (illustrated in red) in the Kazakh cohort may affect the metabolic response to Risperidone, leading to variations in drug efficacy and side effects. Individuals with the AA genotype for rs1135840 may process Risperidone differently, resulting in unique plasma concentrations and metabolic ratios compared to those with the AB genotype.

This underscores the importance of incorporating genetic variations, such as the rs1135840 polymorphism, into personalized medicine strategies to optimize Risperidone treatment for individuals with schizophrenia. Notably, the CYP2D6 *2/*2 (AA) genotype has been linked to elevated Haloperidol concentrations in individuals diagnosed with SCZ compared to those with the CYP2D6 *1/*1 (BB) or *1/*2 (AB) genotypes [25].

2. rs776746 of the gene CYP3A5:

The rs776746 A>G variant, known as 6986A>G, defines the CYP3A53 haplotype. In CYP3A5 3/*3 individuals, the A>G change creates a cryptic splice site in intron 3, leading to alternative splicing. This results in a nonfunctional protein due to a premature termination codon. Unlike the T allele, the C allele isn't linked to Risperidone dose, but *3/*3 carriers exhibit higher serum Risperidone levels and a greater Risperidone/9-hydroxy Risperidone ratio, indicating altered pharmacokinetics [26].

The examination of the Kazakh sample reveals a discernible prevalence of BB and AB genotypes (Figure 4). Individuals harboring the AB genotype exhibit elevated serum levels of Risperidone, as highlighted in yellow within the accompanying image. Conversely, those possessing the allele B and the BB genotype, denoted in blue on the image, demonstrate typical metabolization patterns of Risperidone [27].

The CYP3A5 rs776746 variant *3 (A) affects Olanzapine metabolism, with *3/*3 (AA) carriers showing lower drug exposure compared to those with at least one *1 (B) allele. Patients with the *1 (B) allele may have higher Olanzapine levels than those with two non-functional alleles, while *3 (A) carriers with a normal-function allele may also show increased exposure [28,29].

Based on genotyping results and observed distributions, it is assumed that AB and AA genotypes are prevalent in the Kazakh cohort, with AA carriers potentially showing reduced Olanzapine response, lower plasma concentrations, and poorer adherence compared to AB carriers, who may demonstrate better therapeutic outcomes.

3. rs4680 of the gene COMT:

The Val158Met (rs4680) variant in the COMT gene, characterized by the substitution of a high-activity Val allele (rs4680G) with a low-activity Met allele (rs4680A), COMT plays a significant role in SCZ treatment responses [30].

Several research investigations propose that specific individuals carrying methylated alleles, such as the "L" allele synonymous with rs4680A and identified in scholarly works as a low-activity allele, may be more susceptible to the onset of negative symptoms [31].

The deductions regarding the polymorphic loci and variations in genotypes influencing both metabolism and the occurrence of side effects during the prescription of APs were drawn from a thorough analysis of data derived from prior research endeavors within this specific domain [29-31].

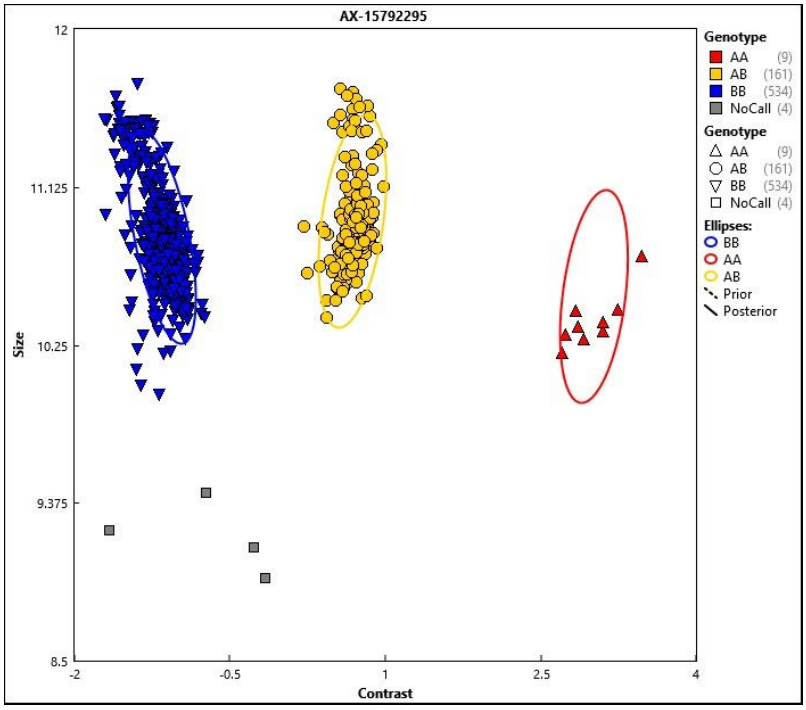

Figure 4. *Allele frequency distribution of* ***CYP3A5 (rs776746)*** *in the Kazakh population.*
1) Homozygous wild-type ***CYP3A5*1/*1****, C/C (indicated as* ***BB****, n = 534) allele carriers.*
2) Heterozygous ***CYP3A5*3/*1*** *C/T (indicated as* ***AB****, n = 161) allele carriers.*
3) Homozygous ***CYP3A5*3/*3*** *T/T (indicated as* ***AA****, n = 9) allele carriers.*
4) "No call" signal (n = 4).

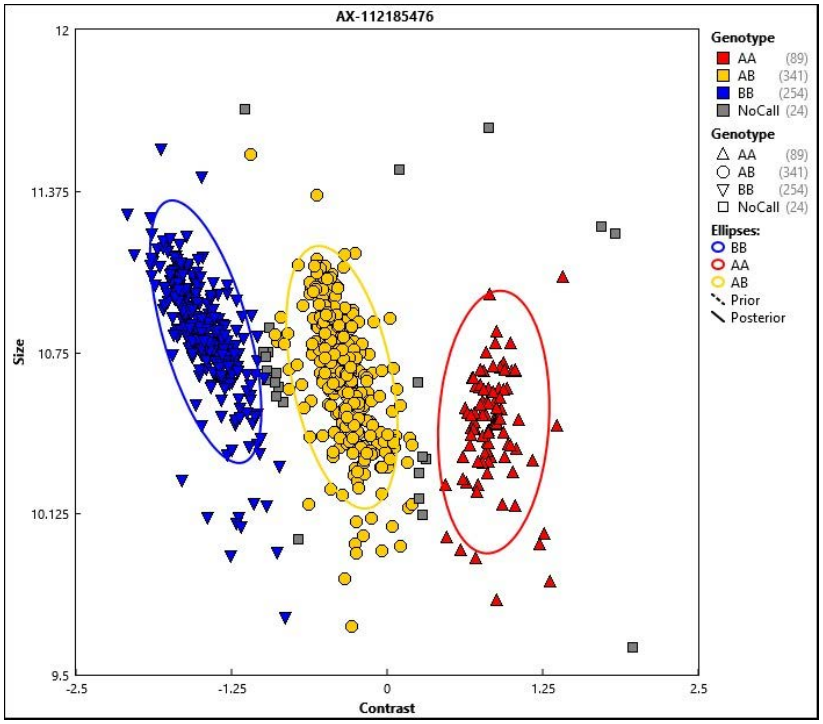

Figure 5. *Allele frequency distribution of* ***COMT (rs4680)*** *in the Kazakh population.*
1) Homozygous wild-type ***COMT*** *G/G (indicated as* ***BB****, n = 254) allele carriers.*
2) Heterozygous ***COMT*** *G/A (indicated as* ***AB****, n = 341) allele carriers.*
3) Homozygous ***COMT*** *A/A (indicated as* ***AA****, n = 89) allele carriers.*
4) "No call" signal (n = 24).

Upon examination of the Kazakh sample, it becomes evident that the prevalence of genotypes is skewed towards AB and BB (Figure 5). Individuals with the BB genotype display reduced manifestations of metabolic syndrome and a diminished susceptibility to extrapyramidal syndromes compared to the higher-risk AB genotype carriers, indicating a favorable distribution of genotypes in relation to these manifestations of side effects when prescribing Haloperidol [31].

Individuals diagnosed with SCZ possessing the AA genotype, when subjected to AP treatment, may encounter heightened methylation within the promoter regions of the COMT gene in contrast to those with the BB genotype. Additionally, an association has been established between increased methylation and the occurrence of metabolic syndrome [32].

Carriers possessing the AA and AB genotypes demonstrate a comparatively attenuated response to Risperidone when contrasted with those bearing the BB genotype, indicating a notably diminished level of responsiveness within the former genotypic cohorts. Based on this, it can be assumed that the genotypes depicted in blue in the illustration (BB) are best adherent to treatment with Risperidone [33].

4. rs9606186 of the gene COMT:

The rs9606186 polymorphism is another significant genetic factor discussed in the study of Risperidone treatment efficacy in SCZ patients. This polymorphism is located in the COMT gene, which encodes an enzyme involved in the degradation of catecholamines such as dopamine, epinephrine, and norepinephrine [34].

Upon examination of the Kazakh sample, it is evident that the prevalence of genotypes tilts towards AB and BB (Figure 6). Based on various sources, it can be argued that individuals with the BB genotype demonstrate an elevated responsiveness to Risperidone in patients with SCZ in comparison to those with AA and AB genotypes.

In addition, the recent investigation identified rs9606186, along with additional COMT polymorphisms, as a pivotal determinant of Risperidone treatment efficacy. This finding corroborates earlier observations in Chinese patients, underscoring the substantial involvement of COMT gene variations in shaping responses to Risperidone treatment. The rs9606186 variant was linked to improved clinical outcomes in male patients treated with Risperidone. The presence of rs9606186 underscores the intricate interplay of genetic factors in influencing individual treatment outcomes for individuals with SCZ [35,36].

5. rs4818 of the gene COMT:

The haplotypes associated with the COMT gene, responsible for encoding catechol-O-methyltransferase—a key player in dopamine metabolism—have been demonstrated to impact the efficacy of Risperidone treatment in patients. For individuals possessing the AA genotype in the context of SCZ, there is a potential for a diminished response to Risperidone when compared to those with AB or BB genotypes [36].

The rs4818 variant of the COMT gene is associated with psychiatric disorders and a familial predisposition to such conditions. Individuals with these traits are more likely to carry the B allele, indicating its potential involvement in the genetic risk for psychiatric illnesses [37].

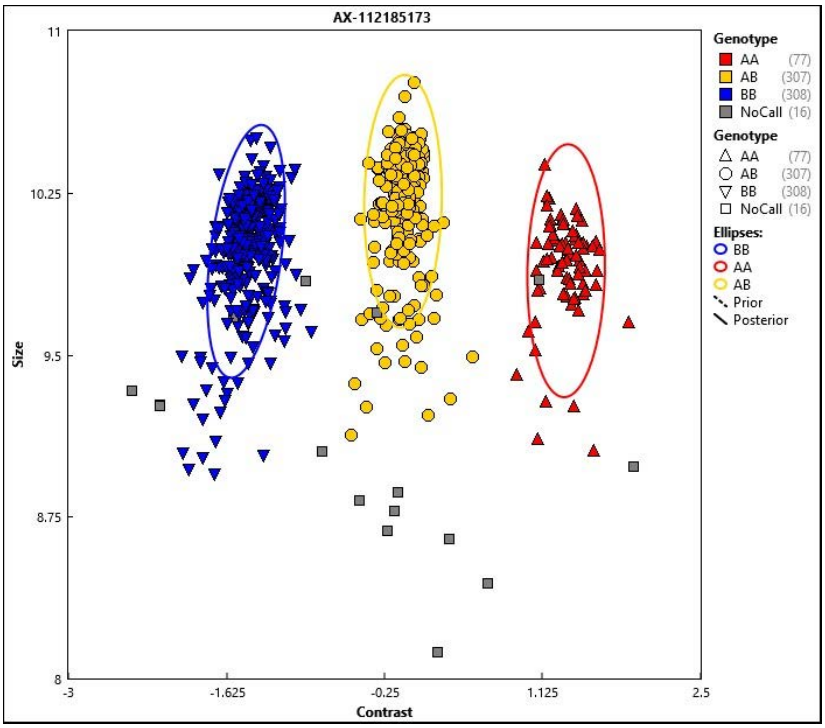

Figure 6. *Allele frequency distribution of* ***COMT (rs9606186)*** *in the Kazakh population.*
1) Homozygous wild-type ***COMT*** *G/G (indicated as* ***BB****, n = 308) allele carriers.*
2) Heterozygous ***COMT*** *G/C (indicated as* ***AB****, n = 307) allele carriers.*
3) Homozygous ***COMT*** *C/C (indicated as* ***AA****, n = 77) allele carriers.*
4) "No call" signal (n = 16).

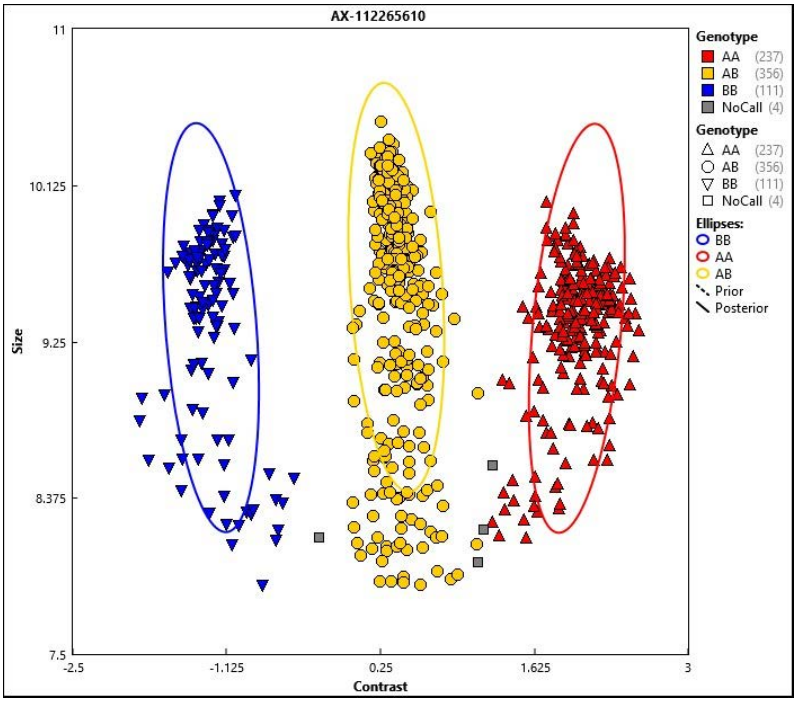

Figure 7. *Allele frequency distribution of* ***COMT (rs4818)*** *in the Kazakh population.*
1) Homozygous wild-type ***COMT*** *G/G (indicated as* ***BB****, n = 111) allele carriers.*
2) Heterozygous ***COMT*** *G/C (indicated as* ***AB****, n = 356) allele carriers.*
3) Homozygous ***COMT*** *C/C (indicated as* ***AA****, n = 237) allele carriers.*
4) "No call" signal (n = 4).

Upon analysis of the Kazakh sample, it becomes evident that the prevalence of genotypes leans notably towards AB and AA (Figure 7). Individuals bearing the AA genotype, highlighted in red within the visual representation, exhibit a substantially diminished responsiveness to Risperidone treatment when contrasted with carriers of the AB and BB genotypes, such patients may require an increase in the daily dose of the drug or a change to an alternative medication. Individuals diagnosed with SCZ who possess the AA genotype exhibit the most diminished response to Risperidone therapy when juxtaposed with those carrying the AB and BB genotypes. Individuals diagnosed with paranoid SCZ and possessing the BB genotype exhibit higher adherence to Risperidone and Quetiapine treatment compared to carriers of alternative genotypes, marked by a decrease in scores on the PANSS Scale ≥ 50% [34,37,38].

6. rs1049353 of the gene CNR1:

The endocannabinoid system assumes a crucial role in modulating dopamine transmission and various metabolic pathways. The endocannabinoid receptor type 1 gene (CNR1) is recognized as a candidate gene implicated in both SCZ and metabolic disorders [39].

The rs1049353 variant of the CNR1 gene has been linked to treatment response and side effects associated with Aripiprazole, Clozapine, Haloperidol, Olanzapine, quetiapine, and Risperidone in ASD, psychotic disorders, and SCZ. Patients with the AB genotype show a higher risk of weight gain when treated with these APs compared to AA genotype carriers. Studies investigating the rs1049353 variant's role in Haloperidol response suggest potential influences on drug efficacy and side effect susceptibility.

However, the relationship is complex, as it can be affected by genetic, environmental, and individual factors. Drug effects may also vary based on the specific psychiatric condition being treated [40].

In the context of Risperidone, allele (B) has been associated with an elevated risk of weight gain in children with ASD compared to allele (A). BMI increases over an eight-week treatment period were highest in patients with the AB genotype, identifying it as a "risk allele" for Risperidone-induced weight gain. Risk scores based on the presence of alleles, including rs806378 and rs7799039, were used to predict weight gain severity in patients [41].

Among Kazakh patients with Paranoid Schizophrenia, the rs1049353 polymorphism was predominantly represented by the homozygous genotype BB (67%) and heterozygous AB (26.5%), (Figure 8). Individuals with psychotic disorders such as SCZ or ASD who possess the AB genotype exhibit a heightened vulnerability to weight gain when undergoing treatment with APs, including Haloperidol and Risperidone, as opposed to carriers of the BB and AA genotypes. According to the UKU scale for evaluating AP therapy tolerability, 21.9% of Kazakh patients reported weight gain following neuroleptic treatment.

On the other hand, the BB (67%) genotype is linked to a lower risk of weight gain during Clozapine or Olanzapine treatment in individuals with SCZ compared to the AB genotype.

Some investigations focused on the rs1049353 variant within the CNR1 gene concerning its correlation with Haloperidol in terms of treatment response and potential adverse effects. Several studies suggest that this genetic variant might impact the efficacy of Haloperidol and an individual's susceptibility to its side effects [42].

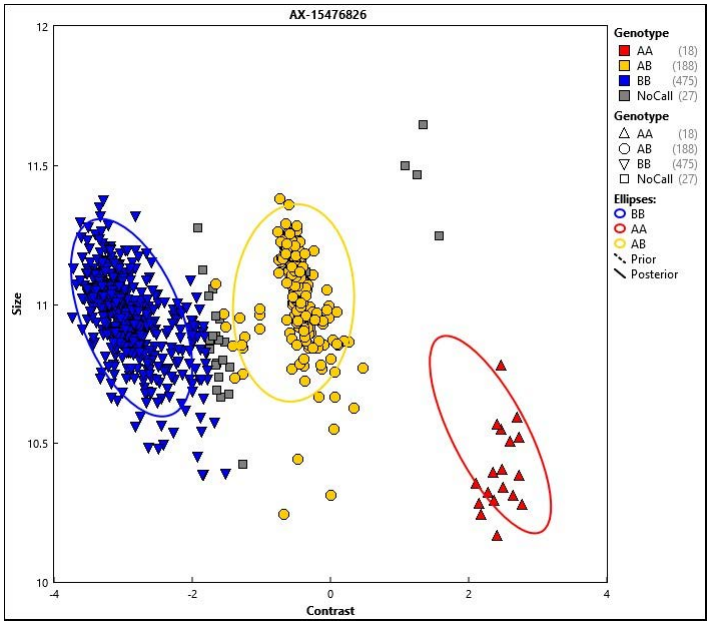

Figure 8. *Allele frequency distribution of* ***CNR1 (rs1049353)*** *in the Kazakh population.*
1) Homozygous wild-type ***CNR1*** *C/C (indicated as* ***BB****, n = 475) allele carriers."*
2) Heterozygous ***CNR1*** *C/T (indicated as* ***AB****, n = 188) allele carriers.*
3) Homozygous ***CNR1*** *T/T (indicated as* ***AA****, n = 18) allele carriers.*
4) "No call" signal (n = 27).

Nevertheless, it is imperative to acknowledge the intricate nature of the association between the rs1049353 genetic variant and the response to Haloperidol, a complexity that additional genetic factors, environmental variables, and individual differences may influence.

7. rs6311 of the gene HTR2A:

HTR2A encodes a receptor protein crucial for serotonin neurotransmission. This variant, also known as -1438G/A, is a single nucleotide polymorphism involving a substitution of guanine (G) for adenine (A) at position -1438. Research suggests that rs6311 may influence HTR2A receptor expression or function, affecting neurotransmission and responses to receptor-targeting drugs. The rs6311 variant, linked to medication response and studied in psychiatric conditions, was examined by Chen et al. regarding its impact on aripiprazole efficacy. Two significant polymorphisms, 1438G (rs6311) and T102C (rs6313), revealed that the BB genotype predicted poorer improvement in negative symptoms [34,43].

The rs6311 polymorphism of the HTR2A gene has been associated with variability in treatment outcomes among patients undergoing AP therapy. Specifically, the AB genotype may act as a potential marker for reduced treatment resistance, indicating that individuals with this genotype might experience a more favorable therapeutic response compared to other genotypes. Additionally, the polymorphism has been linked to differing responses to medications like Risperidone, potentially due to shared receptor targets with antidepressants, further underscoring its significance in influencing treatment efficacy [44].

While the AB genotype is suggested to correlate with lower resistance to AP therapy, including Risperidone, the evidence remains inconclusive, necessitating further investigation to validate this relationship. These findings highlight the intricate role of genetic factors in shaping treatment responses, emphasizing the need for more comprehensive studies to clarify these associations and their clinical implications [44].

In the Kazakh sample under scrutiny, the predominant genotypes identified are BB (41.1%), which exhibit a reduced likelihood of experiencing side effects associated with tardive dyskinesia when subjected to AP treatments. The red-highlighted AA (11.2%) genotype is correlated with an elevated susceptibility to tardive dyskinesia in individuals with SCZ undergoing AP drug treatment, in contrast to those with BB and AB (46.2%) genotypes (Figure 9).

Based on the analyzed data, it can be inferred that within the Kazakh population, the BB genotype may correspond to a limited response to Aripiprazole, showing insufficient improvement in negative symptoms. In contrast, carriers of the AB genotype may exhibit a better response to Risperidone, potentially serving as an indicator of reduced treatment resistance.

8. rs6313 of the gene HTR2A:

The HTR2A gene encodes the 5-HT2A receptor, a G protein-coupled receptor crucial in the central nervous system, mediating serotonin's effects on mood, cognition, and perception, and playing a key role in the action of antipsychotic drugs. The rs6313 polymorphism, also known as the T102C polymorphism, is a SNP located in the first exon of the HTR2A gene. Specifically, it involves a substitution of thymine (T) with cytosine (C) at nucleotide position 102.

This polymorphism results in three possible genotypes: AA, AB, and BB [45-47].

Upon examination of the Kazakh sample, it is evident that the prevalence of genotypes leans towards AB (45.7%) and BB (42%). Individuals with the AA genotype may exhibit

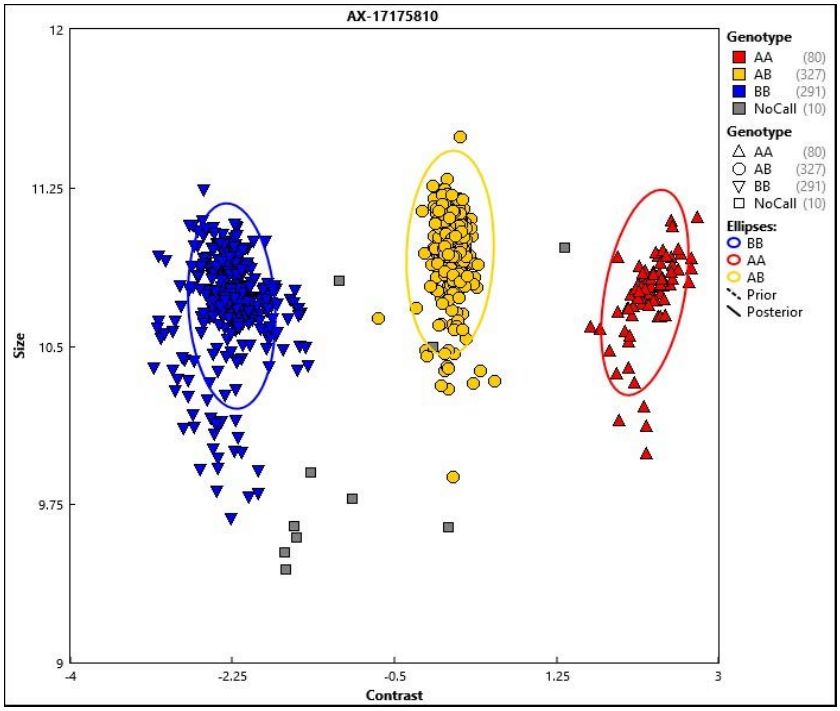

Figure 9. *Allele frequency distribution of* ***HTR2A (rs6311)*** *in the Kazakh population.*
1) Homozygous wild-type ***HTR2A*** *C/C (indicated as* ***BB****, n = 291) allele carriers.*
2) Heterozygous ***HTR2A*** *C/T (indicated as* ***AB****, n = 327) allele carriers.*
3) Homozygous ***HTR2A*** *T/T (indicated as* ***AA****, n = 80) allele carriers.*
4) "No call" signal (n = 10).

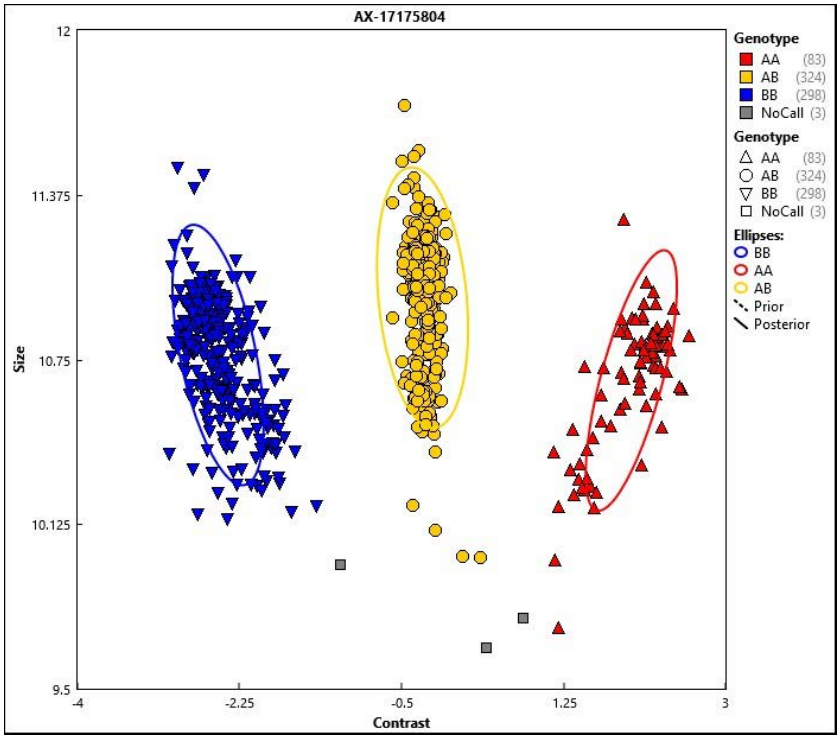

Figure 10. *Allele frequency distribution of* ***HTR2A (rs6313)*** *in the Kazakh population.*
1) Homozygous wild-type ***HTR2A*** *C/C (indicated as* ***BB****, n = 298) allele carriers.*
2) Heterozygous ***HTR2A*** *C/T (indicated as* ***AB****, n = 324) allele carriers.*
3) Homozygous ***HTR2A*** *T/T (indicated as* ***AA****, n = 83) allele carriers.*
4) "No call" signal (n = 3).

a diminished response to Risperidone therapy, whereas heterozygous AB carriers manifest an intermediate response and display a favorable reaction to Risperidone when compared to those with the BB genotype (Figure 10).

Homozygotes with the BB variant of HTR2A rs6313 showed improved treatment adherence for negative symptoms compared to those with at least one (A) allele. Maffioletti et al. found that the presence of the (A) allele could predict a better response to Risperidone or Olanzapine monotherapy. In vitro, pharmacogenetic research indicated that various HTR2A gene variants influenced the activity of Aripiprazole, Clozapine, Quetiapine, and Risperidone, while serotonin receptor gene variants HTR3E and HTR3A had minimal impact on the early response to Haloperidol or Risperidone treatment. According to this research, it was uncovered the association between the rs6313 polymorphism, and the efficacy of AP drugs was found to be mainly influenced by drug and ethnicity. Caucasian patients with the (A) allele responded better to drug therapy, and Asian patients with the AB genotype showed better treatment response [45,46].

When Olanzapine is administered, individuals with this polymorphism and heterozygous AB carriage are noted for experiencing weight gain [47].

The rs6313 polymorphism in the HTR2A gene has been studied for its potential influence on AP drug efficacy, but findings have varied across different populations and studies.

A meta-analysis by Wang et al., encompassing 18 studies, found no significant overall association between rs6313 allele or genotype polymorphisms and the response rate or scale score reduction following antipsychotic treatment. However, the analysis highlighted that ethnicity and specific drug regimens may play a role in modifying treatment outcomes associated with this polymorphism.

Ethnicity appears to be a critical factor influencing treatment efficacy. For example, Caucasian patients carrying the (A) allele demonstrated a more favorable response to AP therapy, whereas Indian patients with the AA genotype exhibited the poorest treatment outcomes, reflected in a lower scale score reduction rate. In East Asian populations, individuals with the AB genotype showed better treatment responses, while those with the BB genotype experienced less favorable outcomes. These findings underscore the importance of considering genetic and ethnic variability when evaluating the clinical implications of rs6313 in AP therapy [48].

Studying the Kazakh population, we emphasize that the distribution of the rs6313 polymorphism is more common in heterozygous AB and homozygous wild-type BB genotypes. As the Kazakh population includes various Eurasian ethnic groups, the mixing of these races may explain the higher prevalence of heterozygosity and the presence of allele A. This supports findings that ethnicity plays a crucial role in the response to AP treatment, with populations like Caucasians showing better outcomes with the (A) allele, while East Asians with the AB genotype tend to respond more favourably compared to those with BB.

9. rs1799978 of the gene DRD2:

The DRD2 gene encodes the Dopamine Receptor D2, a G protein-coupled receptor essential to the dopaminergic system, influencing mood, motivation, reward, and motor control. Located on chromosome 11 (11q22.1), it is linked to neurological and psychiatric conditions, including schizophrenia, bipolar disorder, and addiction [49].

Polymorphisms in the DRD2 gene, including rs1800497 and rs1799978, have been extensively studied for their impact on receptor function, density, and dopaminergic signalling. These genetic variations are particularly relevant to AP treatments, as the D2 receptor is a primary target for these medications. Variations can influence the efficacy and side effect profiles of APs, highlighting the potential for DRD2-related genetic testing to inform personalized treatment strategies.

As reported by Taheri et al. in BMC Psychiatry, the G allele (AA genotype, highlighted in red in Figure 11) of the DRD2 A-241G (rs1799978) polymorphism shows a notable correlation with resistance to AP treatment among SCZ patients. This indicates that individuals carrying the AA genotype might face an elevated risk of poor response to AP therapy [50].

As per the genotyping of the Kazakh sample, it is evident that the prevalence of genotypes tilts towards AA (81.2%), (Figure 11). Individuals carrying the AA genotype may experience an extended biotransformation period for medications such as Olanzapine and Risperidone, leading to a delay in the attainment of therapeutic effects, heterozygotes for this polymorphism are less resistant to the drugs Risperidone and Olanzapine; against homozygotes BB are characterized by a normal biotransformation time. According to the analyzed sample, this polymorphism is associated with an increased risk of poor adherence to medications such as Olanzapine and Risperidone in the Kazakh cohort, with carriers of the risk allele potentially requiring an extended duration to attain a therapeutic effect.

10. rs1800497 of the gene DRD2:

Upon scrutinizing the analyzed Kazakh sample, it becomes apparent that the distribution of genotypes is predominantly inclined toward BB (53.8%) (Figure 12). Individuals carrying the BB genotype demonstrate lower prolactin levels when subjected to Risperidone treatment compared to those with genotypes AA (8.9%) and AB (36.1%), indicated in yellow and red, respectively. The latter genotypes may be susceptible to experiencing the side effects of hyperprolactinemia when administered this medication.

Ikeda's study identified rs1800497 in the DRD2 gene as a significant predictor of Risperidone treatment response in SCZ patients. Along with that, other DRD2 and AKT1 variants were also found to influence treatment outcomes, emphasizing their potential role in guiding personalized therapeutic strategies [51].

According to the study by Antonio Del Casale et.al, the rs1800497 polymorphism in the DRD2 gene is linked to variations in AP treatment response. Patients carrying the A allele, in either the AA or AB genotype, showed greater sensitivity to AP medications, with improved symptom relief and fewer side effects. Conversely, the BB genotype was associated with higher treatment resistance and poorer therapeutic outcomes, often requiring alternative approaches. These findings emphasize the potential of rs1800497 as a predictive marker for personalized AP therapy [44,51].

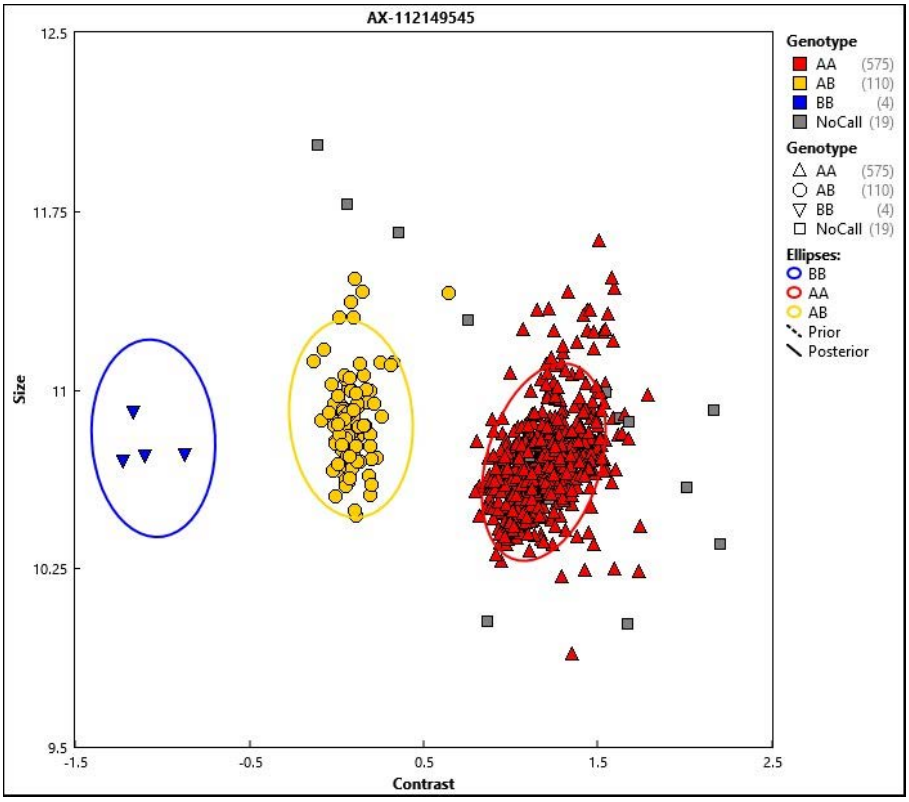

Figure 11. *Allele frequency distribution of* ***DRD2 (rs1799978)*** *in the Kazakh population.*
1) Homozygous wild-type ***DRD2*** *A/A (indicated as* ***BB****, n = 4) allele carriers.*
2) Heterozygous ***DRD2*** *A/G (indicated as* ***AB****, n = 110) allele carriers.*
3) Homozygous ***HTR2A*** *G/G (indicated as* ***AA****, n = 575) allele carriers.*
4) "No call" signal (n = 19).

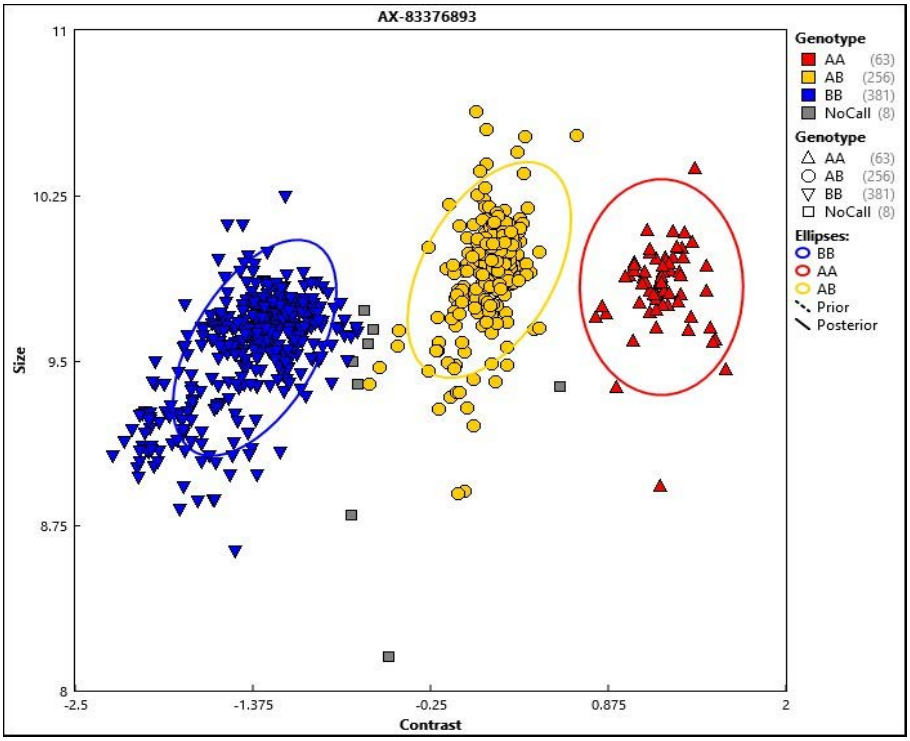

Figure 12. *Allele frequency distribution of* ***DRD2 (rs1800497)*** *in the Kazakh population.*
1) Homozygous wild-type ***DRD2*** *G/G (indicated as* ***BB****, n = 381) allele carriers.*
2) Heterozygous ***DRD2*** *G/A (indicated as* ***AB****, n = 256) allele carriers.*
3) Homozygous ***HTR2A*** *A/A (indicated as* ***AA****, n = 63) allele carriers.*
4) "No call" signal (n = 8).

Conclusion.

The genetic variants analyzed in this study, including CYP2D62 (rs1135840), CYP3A53/3 (rs776746), and polymorphisms in COMT, CNR1, HTR2A, and DRD2 genes, were evaluated within a sample of the Kazakh population with schizophrenia. This analysis highlights associations between specific genotypes and variations in antipsychotic drug metabolism, treatment adherence, and susceptibility to side effects. Notably, genotypes such as CYP2D62, linked to Haloperidol metabolism, and CYP3A5 *3/*3, associated with slower Risperidone metabolism, illustrate the potential for pharmacogenetic insights to guide therapy.

The findings are based on the analyzed cohort and should be further validated in larger and more diverse samples. It is crucial to emphasize that this represents the first investigation into antipsychotic-related genotypes within the Kazakh population. These initial insights provide a foundation for future research but must be interpreted with caution until broader studies confirm their applicability.

Pharmacogenetic testing for SNPs (rs1135840, rs776746, rs4680, rs9606186, rs4818, rs1049353, rs6311, rs6313, rs1799978, rs1800497) could play a pivotal role in optimizing SCZ treatment in Kazakhstan. Personalized approaches based on genetic profiles hold promise for improving therapeutic outcomes and reducing adverse effects, but further studies are required to refine these strategies and validate their effectiveness across larger cohorts.

Author Contributions: Z.K. conceived and planned the experiments. K.D. carried out the experiments. A.A. contributed to sample preparation. K.D., contributed to the interpretation of the results. K.D. took the lead in writing the manuscript. Z.K. made appropriate adjustments to the manuscript. A.A. and N.R. provided a phenotypic database of patients. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Funding: The research was supported by the grant of the Ministry of Healthcare of the Republic of Kazakhstan "National Program for the Introduction of Personalized and Preventive Medicine in the Republic of Kazakhstan (2021–2023)" (Grant Number OR12165486).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of S.D. Asfendiyarov Kazakh National Medical University.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Acknowledgments: The authors express their gratitude for the administrative and technical support provided by S.D. Asfendiyarov Kazakh National Medical University.

REFERENCES

1. Altynbekov K, Raspopova N, Abetova A. Analysis of social and demographic and clinical characteristics of patients with paranoid schizophrenia of the Kazakh ethnic group in the Republic of Kazakhstan. Georgian Medical News. 2023;338:6-13.

2. Pharm Reviews. Schizophrenia: relevance of the problem for Kazakhstan and modern therapy methods. Pharm Reviews. Available from: https://pharm.reviews/ru/stati/aktualnye-intervyu/item/6492-shizofreniy aktualnost-problemy-dlya-kazakhstana-i-sovremennye-metody-terapii. Accessed June 12, 2024.

3. Negay N, Altynbekov K, Raspopova N, et al. Genetic predictors of schizophrenia and their features in individual ethnic populations (review article). Georgian Medical News. 2022;331:6-11.

4. Bitter I, Mohr P, Raspopova N, et al. Assessment and treatment of negative symptoms in schizophrenia: a regional perspective. Front Psychiatry. 2022;12:820801.

5. Vijayan NN, Mukherjee O, Pal PK, et al. Antipsychotic drug dosage and therapeutic response in schizophrenia is influenced by ABCB1 genotypes: a study from a south Indian perspective. Pharmacogenomics. 2012;13:1119-1127.

6. Abetova A, Raspopova N, Yessimov N, et al. Clinical and genetic features of personalized antipsychotic therapy of patients with paranoid schizophrenia of the Kazakh ethnic group in the Republic of Kazakhstan. Georgian Medical News. 2023;342:80-90.

7. Mas S, Gassò P, Alvarez S, et al. Intuitive pharmacogenetics: spontaneous risperidone dosage is related to CYP2D6, CYP3A5, and ABCB1 genotypes. Pharmacogenomics J. 2012;12:255-259.

8. Prestwood TR, Asgariroozbehani R, Wu S, et al. Roles of inflammation in intrinsic pathophysiology and antipsychotic drug-induced metabolic disturbances of schizophrenia. Behav Brain Res. 2021;402:113101.

9. Soria-Chacartegui P, Villapalos-García G, Zubiaur P, et al. Genetic polymorphisms associated with the pharmacokinetics, pharmacodynamics, and adverse effects of olanzapine, aripiprazole, and risperidone. Front Pharmacol. 2021;12:711940.

10. Williams HJ, Owen MJ, O'Donovan MC. Is COMT a susceptibility gene for schizophrenia? Schizophr Bull. 2007;33:635-641.

11. Balu DT, Carlson GC, Talbot K, et al. Akt1 deficiency in schizophrenia and impairment of hippocampal plasticity and function. Hippocampus. 2012;22:230-240.

12. Sofronov AG, Dobrovolskaya AE, Morozova AY, et al. Association of gene polymorphisms DRD3 rs6280, COMT rs4680, and HTR2A rs7322347 with schizophrenia. Zh Nevrol Psikhiatr Im S S Korsakova. 2022;122:115-120.

13. Sagud M, Tudor L, Nedic Erjavec G, et al. Genotypic and haplotypic association of catechol-O-methyltransferase rs4680 and rs4818 gene polymorphisms with particular clinical symptoms in schizophrenia. Genes. 2023;14:1358.

14. Gouvêa ES, Santos AF, Filho OV, et al. The role of the CNR1 gene in schizophrenia: a systematic review including unpublished data. Rev Bras Psiquiatr. 2017;39:160-171.

15. Suzuki Y, Tsuneyama N, Fukui N, et al. Effect of risperidone metabolism and
P-glycoprotein gene polymorphism on QT interval in patients with schizophrenia. Pharmacogenomics J. 2014;14:452-456.

16. Hattori S, Suda A, Kishida I, et al. Effects of ABCB1 gene polymorphisms on autonomic nervous system activity during atypical antipsychotic treatment in schizophrenia. BMC Psychiatry. 2018;18:231.

17. Clopper CJ, Pearson S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404-413.
18. Remington G, Hahn MK, Agarwal SM, et al. Schizophrenia: antipsychotics and drug development. Behav Brain Res. 2021;414:113507.
19. Rognoni C, Bertolani A, Jommi C. Second-generation antipsychotic drugs for patients with schizophrenia: systematic literature review and meta-analysis of metabolic and cardiovascular side effects. Clin Drug Investig. 2021;41:303-319.
20. Wang X, Huang J, Lu J, et al. Risperidone plasma level, and its correlation with CYP2D6 gene polymorphism, clinical response, and side effects in chronic schizophrenia patients. BMC Psychiatry. 2024;24:41.
21. Someya T, Shimoda K, Suzuki Y, et al. Effect of CYP2D6 genotypes on the metabolism of haloperidol in a Japanese psychiatric population. Neuropsychopharmacology. 2003;28:1501-1505.
22. Beunk L, Nijenhuis M, Soree B, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4 and CYP1A2 and antipsychotics. Eur J Hum Genet. 2023.
23. Kane M. CYP2D6 Overview: Allele and phenotype frequencies. In: Pratt VM, Scott SA, Pirmohamed M, et al., editors. Medical Genetics Summaries. Bethesda (MD): National Center for Biotechnology Information. 2012.
24. Lu J, Yang Y, Lu J, et al. Effect of CYP2D6 polymorphisms on plasma concentration and therapeutic effect of risperidone. BMC Psychiatry. 2021;21:70.
25. Inada T, Shimoda K, Suzuki Y, et al. Cytochrome P450 II D6 gene polymorphisms and the neuroleptic-induced extrapyramidal symptoms in Japanese schizophrenic patients. Psychiatr Genet. 2003;13:163-168.
26. Mas S, Gassò P, Alvarez S, et al. Intuitive pharmacogenetics: spontaneous risperidone dosage is related to CYP2D6, CYP3A5, and ABCB1 genotypes. Pharmacogenomics J. 2012;12:255-259.
27. Shi Y, Li M, Song C, et al. Combined study of genetic and epigenetic biomarkers of risperidone treatment efficacy in Chinese Han schizophrenia patients. Transl Psychiatry. 2017;7.
28. Cabaleiro T, López-Rodríguez R, Ochoa D, et al. Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects. Hum Psychopharmacol. 2013;28:205-214.
29. Belmonte C, Ochoa D, Román M, et al. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers. Basic Clin Pharmacol Toxicol. 2018;122:596-605.
30. Xu Q, Wu X, Li M, et al. Association studies of genomic variants with treatment response to risperidone, clozapine, quetiapine, and chlorpromazine in the Chinese Han population. Pharmacogenomics J. 2016;16:357-365.
31. Nikolac Perkovic M, Sagud M, Zivkovic M, et al. Catechol-O-methyltransferase rs4680 and rs4818 haplotype association with treatment response to olanzapine in patients with schizophrenia. Sci Rep. 2020;10:10049.
32. Zivković M, Jovanović M, Nikolić T, et al. The association study of polymorphisms in DAT, DRD2, and COMT genes and acute extrapyramidal adverse effects in male schizophrenic patients treated with haloperidol. J Clin Psychopharmacol. 2013;33:593-599.
33. Cote AT, Panagiotopoulos C, Devlin AM. Interaction between the Val158Met catechol-O-methyltransferase gene variant and second-generation antipsychotic treatment on blood pressure in children. Pharmacogenomics J. 2015;15:95-100.
34. Shi Y, Li M, Song C, et al. Combined study of genetic and epigenetic biomarker risperidone treatment efficacy in Chinese Han schizophrenia patients. Transl Psychiatry. 2017;7.
35. Zhao QZ, Wang X, Gao Y, et al. Association between a COMT polymorphism and clinical response to risperidone treatment: a pharmacogenetic study. Psychiatr Genet. 2012;22:298-299.
36. Soria-Chacartegui P, Villapalos-García G, Zubiaur P, et al. Genetic polymorphisms associated with pharmacokinetics, pharmacodynamics, and adverse effects of olanzapine, aripiprazole, and risperidone. Front Pharmacol. 2021;12:711940.
37. Vieira AR, Barros MS, Soares MS, et al. COMT rs4818 less common allele is associated with psychological and psychiatric worse indicators in a cohort of individuals born with cleft lip and palate. Orthod Craniofac Res. 2023;26:387-392.
38. Spiros A, Geerts H. Toward predicting impact of common genetic variants on schizophrenia clinical responses with antipsychotics: a quantitative systems pharmacology study. Front Neurosci. 2021;15:738903.
39. Yu W, De Hert M, Moons T, et al. CNR1 gene and risk of metabolic syndrome in patients with schizophrenia. J Clin Psychopharmacol. 2013;33:186-192.
40. Jimeno N, Velasco-Gonzalez V, Fierro I, et al. Association of CNR1 and INSIG2 polymorphisms with antipsychotics-induced weight gain: a prospective nested case-control study. Sci Rep. 2021;11:15304.
41. Nurmi EL, Spanos M, Geller E, et al. Moderation of antipsychotic-induced weight gain by energy balance gene variants in the RUPP autism network risperidone studies. Transl Psychiatry. 2013;3.
42. Tiwari AK, Zai CC, Likhodi O, et al. A common polymorphism in the cannabinoid receptor 1 (CNR1) gene is associated with antipsychotic-induced weight gain in schizophrenia. Neuropsychopharmacology. 2010;35:1315-1324.
43. Boke O, Gunes S, Kara N, et al. Association of serotonin 2A receptor and lack of association of CYP1A2 gene polymorphism with tardive dyskinesia in a Turkish population. DNA Cell Biol. 2007;26:527-531.
44. Del Casale A, Simmaco M, Modesti MN, et al. DRD2, DRD3, and HTR2A single-nucleotide polymorphisms involvement in high treatment resistance to atypical antipsychotic drugs. Biomedicines. 2023;11:2088.
45. Sujitha SP, Nair A, Banerjee M, et al. 5-Hydroxytryptamine (serotonin) 2A receptor gene polymorphism is associated with schizophrenia. Indian J Med Res. 2014;140:736-743.
46. Maffioletti E, Polimeni G, Minelli A, et al. Association study between HTR2A rs6313 polymorphism and early response to risperidone and olanzapine in schizophrenia patients. Drug Dev Res. 2020;81:537-544.

47. Zubiaur P, Koller D, Zanger UM, et al. Impact of polymorphisms in transporter and metabolizing enzyme genes on olanzapine pharmacokinetics and safety in healthy volunteers. Biomed Pharmacother. 2021;138:111497.
48. Wang Y, Tan X, Chen Z, et al. Association between the rs6313 polymorphism in the 5-HTR2A gene and the efficacy of antipsychotic drugs. BMC Psychiatry. 2023;23:682.
49. Calarge CA, Nicol G, Best L, et al. Variants of the dopamine D2 receptor gene and risperidone-induced hyperprolactinemia in children and adolescents. Pharmacogenet Genomics. 2009;19:373-382.
50. Taheri N, Pirboveiri R, Sayyah M, et al. Association of DRD2, DRD4, and COMT genes variants and their gene-gene interactions with antipsychotic treatment response in patients with schizophrenia. BMC Psychiatry. 2023;23:781.
51. Ikeda M, Hongo M, Yamanouchi Y, et al. Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia. Pharmacogenomics. 2008;9:1437-1443.

АННОТАЦИЯ

Шизофрения — многогранное психиатрическое расстройство, характеризующееся галлюцинациями, бредом, когнитивными нарушениями и поведенческими расстройствами. Генетические факторы играют значительную роль в патогенезе заболевания, составляя около 80% наследственности. В глобальном масштабе шизофрения затрагивает примерно 1% населения, при этом в Казахстане медицинское лечение получают 45 054 человека, что соответствует заболеваемости 238,6 на 100 000 человек. Увеличение числа психических заболеваний в Казахстане подчеркивает необходимость персонализированного подхода к лечению для решения этих проблем в сфере здравоохранения. Это исследование посвящено влиянию ключевых полиморфизмов — CYP2D6 (rs1135840), CYP3A5 (rs776746), COMT (rs4818, rs4680, rs9606186), CNR1 (rs1049353), HTR2A (rs6311, rs6313) и DRD2 (rs1799978, rs1800497) — на метаболизм антипсихотических препаратов и терапевтические результаты. Полученные данные подчеркивают потенциал индивидуализации дозировки антипсихотических препаратов с учетом генотипа среди казахов, закладывая основу для будущих исследований, направленных на оптимизацию терапии АП в этой популяции.

Ключевые слова: Параноидальная Шизофрения, SNP, CYP2D6, DRD2, HTR2A, COMT, CNR1, фармакогенетика, Казахская Этническая Группа, Антипсихотики, Центральная Азия.

Сокращение: ИМТ: индекс массы тела; ШИЗ: шизофрения; SNP: однонуклеотидные полиморфизмы; PANSS: шкала положительных и отрицательных синдромов; АП: антипсихотический препарат; РАС: расстройства аутистического спектра; UKU: шкала оценки побочных эффектов.

აბსტრაქტი

შიზოფრენია არის მრავალმხრივი ფსიქიატრიული აშლილობა, რომელსაც ახასიათებს ჰალუცინაციები, ბოდვები, კოგნიტური დაქვეითება და ქცევითი დარღვევები. გენეტიკური ფაქტორები მნიშვნელოვან როლს თამაშობენ დაავადების პათოგენეზში, რაც მემკვიდრეობითობის დაახლოებით 80%-ს შეადგენს. გლობალურად, შიზოფრენია აზიანებს მოსახლეობის დაახლოებით 1%-ს, ყაზახეთში 45,054 ადამიანი მკურნალობს, რაც შეესაბამება 238,6 შემთხვევას 100,000 ადამიანზე. ყაზახეთში ფსიქიკური დაავადებების მზარდი შემთხვევა ხაზს უსვამს მკურნალობის პერსონალიზებული მიდგომის საჭიროებას ჯანდაცვის ამ გამოწვევების გადასაჭრელად. ეს კვლევა განიხილავს საკვანძო პოლიმორფიზმის გავლენას - CYP2D6 (rs1135840), CYP3A5 (rs776746), COMT (rs4818, rs4680, rs9606186), CNR1 (rs1049353), HTR2A (rs6329, rs6313, 497) - მეტაბოლიზმზე ფსიქოზური წამლებისა და თერაპიული შედეგების შესახებ. დასკვნები ხაზს უსვამს ყაზახებს შორის გენოტიპზე დაფუძნებული ანტიფსიქოზური დოზირების ინდივიდუალიზაციის პოტენციალს, რაც საფუძველს უყრის მომავალ კვლევებს, რომლებიც მიზნად ისახავს ამ პოპულაციაში ანტიფსიქოზური მკურნალობის ოპტიმიზაციას.

საკვანძო სიტყვები: პარანოიდული შიზოფრენია, SNP, CYP2D6, DRD2, HTR2A, COMT, CNR1, ფარმაკოგენეტიკა, ყაზახური ეთნიკური ჯგუფი, ანტიფსიქოტიკა, ცენტრალური აზია.

აბრევიატურები: BMI: სხეულის მასის ინდექსი; SCZ: შიზოფრენია; SNP: ერთი ნუკლეოტიდური პოლიმორფიზმი; PANSS: დადებითი და უარყოფითი სინდრომის სკალა; AP: ანტიფსიქოზური პრეპარატი; ASD: აუტისტური სპექტრის აშლილობა; UKU: არასასურველი მოვლენის შეფასების სკალა.