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The effect of ethnicity and immigration on treatment resistance in schizophrenia

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ABSTRACT

Background: Treatment resistance is a common issue among schizophrenia patients undergoing antipsychotic treatment. According to the American Psychiatric Association (APA) guidelines, treatment-resistant status is defined as little or no symptom reduction to at least two antipsychotics at a therapeutic dose for a trial of at least six weeks. The aim of the current study is to determine whether ethnicity and migration are associated with treatment resistance.
Methods: In a sample of 251 participants with schizophrenia spectrum disorders, we conducted cross-sectional assessments to collect information regarding self-identified ethnicity, immigration and treatment history. Ancestry was identified using 292 markers overlapping with the HapMap project. Using a regression analysis, we tested whether a history of migration, ethnicity or genetic ancestry were predictive of treatment resistance.
Results: Our logistic regression model revealed no significant association between immigration (OR = 0.04; 95%CI = 0.35–3.07; p = 0.93) and treatment resistant schizophrenia. White Europeans did not show significant association with resistance status regardless of whether ethnicity was determined by self-report (OR = 1.89; 95%CI = 0.89–4.20; p = 0.105) or genetic analysis (OR = −0.73; 95%CI = −0.18–2.97; p = 0.667).
Conclusion: Neither ethnicity nor migrant status was significantly associated with treatment resistance in this Canadian study. However, these conclusions are limited by the small sample size of our investigation.

1. Introduction

Ten to 30% of patients with schizophrenia are treatment resistant and up to a further 30% of patients are only partially responsive to their antipsychotic treatments [1,2]. In addition, 20–30% of patients on pharmacological treatment relapse within the first two years of maintenance treatment despite compliance to medications [3,4]. Due to the prevalence of poor response to medication, treatment-resistant schizophrenia poses a long-standing problem for delivering clinical care to patients.

According to the American Psychiatric Association (APA) guidelines, treatment-resistant status is little or no symptom reduction to at least two antipsychotics at therapeutic dose range for a trial of at least six weeks [2]. There are also other criteria for resistance such as those proposed by The National Institute of Health and Care Excellence (NICE). The NICE uses poor psychosocial and community functioning as an indicator for the ineffectiveness of the antipsychotic treatment [5].

A proper antipsychotic dosage is an important factor in defining treatment-resistant schizophrenia criteria. However, previous research has suggested that different ethnic groups may respond differently to the same antipsychotic dose. For example, a review by Frackiewicz et al. [6] suggested that Asians may respond to lower doses of antipsychotics due to pharmacokinetic and pharmacodynamic differences. It has also been suggested that Hispanic patients need lower doses of neuroleptics to attain the same response than other populations [7].

However, it is unclear whether these different responses to antipsychotics imply a different rate of treatment-resistant schizophrenia. For instance, Hassan et al. [8] reported no differences in dosing between White Europeans and non-White Europeans. However, others have reported differences in antipsychotic dosages between ethnicities [9]. In particular, African-American patients were more likely to receive higher doses of antipsychotics compared to white patients [9,10]. Qualitative differences in prescriptions have also been reported, thus prescriptions may reflect heterogeneous responses among ethnicities through

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different types of medications [11]. These factors may contribute to differences in the incidence of treatment-resistant schizophrenia among ethnicities.

For example, a study on risk for treatment-resistant schizophrenia conducted by Teo et al. [12] found that White European ethnicity confers risk for treatment resistance schizophrenia. Teo et al. [12] suggested that this risk is not genetic because family history was not associated with treatment resistance. However, no study tried to confirm and extend the findings of [12] using genetic data to dissect the geographical ancestry form cultural influences.

Furthermore, national surveys of the Latino and Asian immigrants in the USA, found lower incidence of mental health problems among migrants compared with natives [13–18].

On the other hand, there is also reason to believe that the stress of migration may influence resistance to antipsychotics since stressful life events have been associated with treatment resistance [19]. A meta-analysis on the incidence rate of schizophrenia including 18 studies found that first and second generation migrants are at three times increased risk at being diagnosed with schizophrenia than non-migrants, especially if the migrant is from a developing country or a country where the majority of the population is black [20]. Although this may be due to migrants' access to healthcare, a study on ethnic diversity and pathways to healthcare in Ontario showed no significant difference between the duration of untreated illness between ethnic groups [21]. Archie et al. [21] attributed the result to the public healthcare system in Ontario which creates relatively equal opportunity for patients of different ethnicities to receive treatment. Furthermore, a recent study by [22], did not find that closer family relationship in Chinese immigrants in the US does not predict health service use [22].

However, if migration could confer risk for schizophrenia, it may also have an effect on treatment resistance.

The relationships between immigration, race, ethnicity, and mental health outcomes are complex [23]. However, there are no published studies examining whether migration is linked to treatment resistance schizophrenia.

The primary aim of the current study is to determine whether ethnicity and migration are associated with treatment-resistant schizophrenia. The secondary aim is to dissect between self-report ethnicity effect and genetically determined geographical ancestry in influencing treatment resistance.

2. Methods

2.1. Sample

We included 251 participants with schizophrenia spectrum disorder (schizophrenia or schizoaffective disorder) aged 18–70 recruited by referral from staff clinicians or in person from clinics at the Centre of Addiction and Mental Health (CAMH), a teaching hospital in Toronto (Ontario). Only patients with DSM-IV diagnosis of schizophrenia spectrum disorders were included.

The study was approved by the CAMH REB. Participants gave written informed consent for the review of their electronic medical charts. Information on demographics, past medications, number of hospitalizations, years of education, migration status, duration of illness, duration of untreated illness, and suicide attempter status were collected in a structured interview. Substance use information was also collected during the interview, including alcohol, tobacco, marijuana, and other drug use. Patients with organic psychoses were excluded. The study design was cross-sectional and retrospective.

2.2. Treatment resistance definition

Treatment-resistant status was determined retrospectively based on electronic medical records supplemented by patient self-report medication history. Treatment resistance was defined using the APA guidelines, according to which treatment resistance is little or no symptom reduction with at least two antipsychotics administered at adequate therapeutic dosages for at least six weeks [2]. In the current study, the APA guidelines were used because it is the standard in North America. Medication history in the chart was collected from the first adequate antipsychotic trial to the time of the research assessment for this study.

2.3. Predictors

The main predictors in this analysis were migration status, self-reported ethnicity and genetically determined ancestry. The migration and the self-report ethnicity were collected during the research assessment, and the geographical origin was determined using genetic markers. Migration was categorized as a binary variable collecting the information about the place where the subject was born.

Self-Report Ethnicity was determined using an ad hoc form completed during the research interview collecting the ancestry of the four grandparents (Fig. 2). Subjects with four grand-parents from White European background were classified as White European and all the other subjects from different backgrounds were classified as Non-White Europeans. The ethnic/ancestry groups considered for inclusion in the non-White European category were African, East Indian, Asian, Hispanic/Latino, Native North American and Pacific Islander (Fig. 2).

2.4. Clinical measures

The diagnosis of schizophrenia was confirmed using the SCID-I/P for DSM-IV. Clinical variables (such as current antipsychotic regimen and age at onset) were collected cross-sectionally at the time of the research assessment. The age at onset of schizophrenia was collected as part of the Psychoses Module of the SCID. High number of hospitalizations [12] was defined as having more than three hospitalizations lifetime (the median number of hospitalization in our sample).

2.5. Genetics

The genetic analysis was performed using *Structure 2.3.2* including the sample of this study (n = 251) and three HapMap Reference samples with known origins: White European (n = 60), African (n = 60), and East Asian (n = 90), making a total of 461 individuals used in the genetic analysis (Fig. 1).

Three populations were assumed in the *Structure* analysis. To determine the genetic ancestry, we used 292 SNPs present in the HapMap Phase II project with a Burn-in period of 5000, and 10,000 Markov Chain Monte Carlo repetitions.

2.6. Statistics

Logistic regressions were performed using *R 3.2.2* on the clinical variables gender, self-report ethnicity, migrant status, current or lifetime use of depot medication, current or past use of clozapine, and current use of polypharmacy. To explore whether ethnicity and place of birth can affect the likelihood of treatment resistance, regression models with ethnicity and, migrant status as predictor variables were used. In one model, ethnicity is determined using self-report, whereas the other model uses the genetically determined ethnicity. Due to the small sample size of this study, all clinical variables were analyzed in separate linear models.

3. Results

Our sample included 251 patients (169 males and 82 females; age: 40.1±. There were 194 White Europeans in the sample. Most of the non-white Europeans were from mixed backgrounds (n = 33) but there were 11 Asians and 23 from African background. There were 62

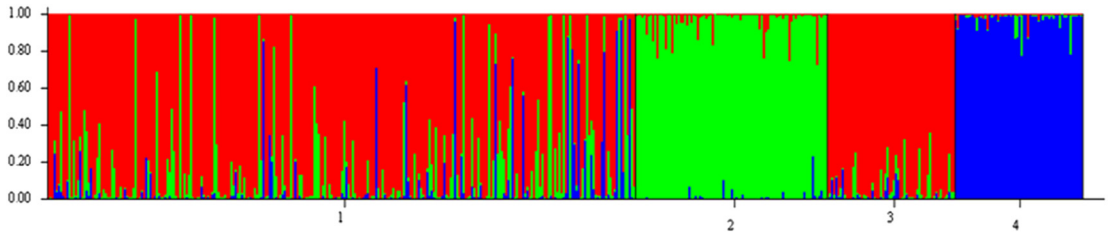

Fig. 1. STRUCTURE analysis. Geographical ancestry of study participants and reference populations from HapMap. 1 = Study participants (n = 251); 2 (green) = Japanese and Han Chinese Asians (JPT + CHB), reference population (n = 90); 3 (red) = North/western Europeans from Utah (CEU), reference population (n = 60); 4 (blue) = Yorubans from Nigeria (YRI), reference population (n = 60).

migrants that were born mainly in Europe (n = 21) but some were from Asia (n = 19), few were born in Central America (n = 8), North America (n = 2), South America (n = 5), and Oceania (n = 1). Clinical and demographics effect on treatment resistance were summarized in Table 1. All patients were treated with antipsychotics at the time of the assessment but none was treated with ECT.

3.1. Clinical factor analysis

Duration of illness was associated with treatment resistance (OR = 1.857, 95% CI = [1.103, 3.112]) and current prescription of clozapine was a significant predictor of treatment resistance (OR = 6.37, 95% CI = [3.386, 12.442]). Also, current regimen of clozapine and polypharmacy was associated with history of resistance (OR = 5.284, 95% CI [1.188, 36.59]).

3.2. Ethnicity analysis

The binary logistic regression model revealed no significant association between White European ethnicity and treatment resistance schizophrenia when ethnicity was determined by self-report (OR:1.89; 95%CI = 0.89–4.20; p = 0.105).

Furthermore, migration to Canada was not associated with treatment-resistant status (OR: 0.04; 95%CI = 0.35–3.07; p = 0.93).

3.3. STRUCTURE analysis

Based on our analysis of 292 SNPs, the overall proportion of geographical ancestry of our sample for the three populations was 0.578 White European, 0.257 African, and 0.165 Asian. European ancestry determined using the genetic markers was not associated with treatment resistance (OR: 0.735; 95%CI = −0.181–2.978; p = 0.667) (Fig. 1 and Table 2). On the other hand, genetically determined African ancestry protected against resistance (p = 0.024) and genetically determined Asian ancestry were associated with resistance status (p = 0.029) (Table 2).

4. Discussion

Neither self-report European ethnicity nor European genetic ancestry was significantly associated with treatment resistance. However, we found that the African ancestry is protecting against treatment-resistant schizophrenia, despite the fact that very few subjects in our sample were from African background.

Migrant status was not significantly associated with treatment resistance. Nevertheless, myriad of factors such as type of migration experience, cultural, social, and economic diversity within racial/ethnic groups may influence the access to healthcare, therefore these factors could have important implications for health policy makers [24,25].

Ethnic Status: (Where did the subject's family come from?) Adopted? ☐

	Maternal Grandmother	Maternal Grandfather	Paternal Grandmother	Paternal Grandfather
European/Caucasian	☐	☐	☐	☐
African Descent/ African American	☐	☐	☐	☐
East Indian Caucasian (e.g. Pakistani, Indian)	☐	☐	☐	☐
Asian (e.g. Chinese, Japanese)	☐	☐	☐	☐
Hispanic/Latino	☐	☐	☐	☐
Native N. American	☐	☐	☐	☐
Pacific Islander	☐	☐	☐	☐
Other:_____	☐	☐	☐	☐

Your Religion: _____ Your Place of Birth:

Mother's: _____
_____

Father's: _____ Primary language:
_____

Fig. 2. Research questionnaire used to identify the geographical ancestry of the participant's maternal and paternal grandparents.

Table 1
Clinical and demographics effect in conferring risk for TR schizophrenia.

Total (N = 251)	OR	LCI	UCI	p-Val
Sex (male/female)	1.236	0.712	2.145	0.452
Age (X, SD)	1.012	0.991	1.034	0.268
Age of onset (X, SD)	0.956	0.920	0.994	0.023
Duration of illness (years) (X, SD)	1.032	1.008	1.056	0.024
Migration status (migrant)	0.04	0.35	3.07	0.930
Comorbid drug abuse (%)	0.712	0.397	1.252	0.245
Self-reported ethnicity (White European)	1.89	0.89	4.2	0.105
Polypharmacy	1.165	0.562	2.360	0.674
Clozapine	6.37	3.386	12.442	<0.0001
Clozapine + polypharmacy	5.284	1.188	36.59	0.0442
Lifetime long-acting antipsychotics	1.472	0.801	2.689	0.208
Current long-acting antipsychotics	0.871	0.357	2.002	0.752
Long-acting antipsychotics polypharmacy	2.148	0.554	8.877	0.263

TR = treatment resistant; NTR = non-resistant.

Furthermore, previous research reported differences in the response to antipsychotics among the different ethnicities [6,7,9]. Therefore, White Europeans may require higher therapeutic dosages of antipsychotics than Asian and Hispanic patients.

It may be of interest to examine how non-white ethnic groups differ from each other using a larger sample as the non-white group considered in this study is genetically and culturally heterogeneous. However, more granular analyses by ethnic sub-groups were not feasible in the non-white European group because of the small sample size.

Effect sizes of the clinical factor associated with resistance status are small, suggesting that many complex factors contribute to treatment resistance. On the other hand, we found a strong association between treatment resistance and current clozapine use, this is probably due to the fact that APA Criteria for prescribing Clozapine matches those for treatment resistance. However, clozapine is used also when patients are intolerant to other antipsychotics due to extrapyramidal side effects and the clinical factor analysis is limited because it is retrospective in nature and we could not establish the temporal relationship between certain clinical variables and treatment resistance status. Furthermore, in our logistic regression, we incorporated the age at onset that was assessed retrospectively and we could not incorporate the duration of untreated psychoses (DUP) that prior research [26] indicated as a risk factor for non-response.

On the other hand, the duration of illness was longer in the resistant group mainly because the probability of exposure to different trials is higher when the duration of illness is longer.

5. Limitations

The main limitations in the interpretation of the results in the current study are the small sample size, the majority of the patients from White European background and the ethnicity reported by the patient rather than ascertained by other sources.

Another limitation is our analysis about migration, in fact, we could not consider the length of stay in Canada, second-generation immigrants in the native group, immigration status (permanent residents vs temporary permits) and different nationality of the immigrants.

Furthermore, treatment resistance can be influenced by non-pharmacological and psychosocial intervention [27–30] and we did not take in account these confounding factors. Also, we were unable to control for different level of care provided to the subjects in this study such as assertive community treatment or case management that can favor the response to treatment, hiding the resistance status.

Table 2
Effect of Ethnicity and genetically determined geographical ancestry.

Total (N = 251)	OR	LCI	UCI	p-Val
European ancestry (%)	0.735	0.181	2.978	0.667
African ancestry (%)	0.203	0.051	0.812	**0.024**
Asian ancestry (%)	3.109	1.122	8.615	**0.029**

The geographical ancestry was calculated using STRUCTURE incorporating genetic markers in the analysis. In bold the significant p-values. LCI and UCI: 95%CI.

6. Conclusion

In conclusion, this study found no evidence that migration and non-white European ethnicity are associated with resistant schizophrenia. However, the conclusion that we could not find an association between ethnicity and resistance, should be read carefully since there are several studies that have shown that ethnic minorities are more likely diagnosed with schizophrenia [31].

Therefore, the methodology used in this study should promote more research with larger studies with longitudinal measures controlled for DUP that would allow us to better understand the relationship between ethnicity and treatment-resistant schizophrenia or poor response to antipsychotics.

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