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Mitochondrial genetic variants associated with bipolar disorder and Schizophrenia in a Japanese population

Ryobu Tachi[1], Kazutaka Ohi[2,3*], Daisuke Nishizawa[4], Midori Soda[5], Daisuke Fujikane[2], Junko Hasegawa[4], Ayumi Kuramitsu[2], Kentaro Takai[2], Yukimasa Muto[2], Shunsuke Sugiyama[2], Kiyoyuki Kitaichi[5], Ryota Hashimoto[6], Kazutaka Ikeda[4] and Toshiki Shioiri[2]

Abstract

Background Bipolar disorder (BD) and schizophrenia (SZ) are complex psychotic disorders (PSY), with both environmental and genetic factors including possible maternal inheritance playing a role. Some studies have investigated whether genetic variants in the mitochondrial chromosome are associated with BD and SZ. However, the genetic variants identified as being associated are not identical among studies, and the participants were limited to individuals of European ancestry. Here, we investigate associations of genome-wide genetic variants in the mitochondrial chromosome with BD, SZ, and PSY in a Japanese population.

Methods After performing quality control for individuals and genetic variants, we investigated whether mitochondrial genetic variants [minor allele frequency (MAF) > 0.01, $n = 45$ variants) are associated with BD, SZ, and PSY in 420 Japanese individuals consisting of patients with BD ($n = 51$), patients with SZ ($n = 172$), and healthy controls (HCs, $n = 197$).

Results Of mitochondrial genetic variants, three (rs200478835, rs200044200 and rs28359178 on or near *NADH dehydrogenase*) and one (rs200478835) were significantly associated with BD and PSY, respectively, even after correcting for multiple comparisons (P_{GC}=0.045–4.9×10^{-3}). In particular, individuals with the minor G-allele of rs200044200, a missense variant, were only observed among patients with BD (MAF = 0.059) but not HCs (MAF = 0) (odds ratio=∞). Three patients commonly had neuropsychiatric family histories.

Conclusions We suggest that mitochondrial genetic variants in NADH dehydrogenase-related genes may contribute to the pathogenesis of BD and PSY in the Japanese population through dysfunction of energy production.

Keywords Bipolar disorder, Schizophrenia, Mitochondria, Genetic variant, Family history

*Correspondence:
Kazutaka Ohi
k_ohi@gifu-u.ac.jp
[1]School of Medicine, Gifu University, Gifu, Japan
[2]Department of Psychiatry, Gifu University Graduate School of Medicine, Gifu, Japan
[3]Department of General Internal Medicine, Kanazawa Medical University, Ishikawa, Japan
[4]Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
[5]Laboratory of Pharmaceutics, Department of Biomedical Pharmaceutics, Gifu Pharmaceutical University, Gifu, Japan
[6]Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan

Introduction

Bipolar disorder (BD) and schizophrenia (SZ) are severe and chronic psychotic disorders (PSY) with a lifetime prevalence of approximately 1% (Grande et al. 2016; Saha et al. 2005). BD and SZ have high heritability of approximately 80% (McGuffin et al. 2003; Sullivan et al. 2003). To date, the largest-scale genome-wide association studies (GWASs) have reported 64 and 287 genetic loci associated with BD and SZ, respectively (Mullins et al. 2021; Trubetskoy et al. 2022). Moreover, these PSY extensively share genetic factors with BD and SZ (Ohi et al. 2022b; Ruderfer et al. 2018; Smeland et al. 2020), though each disorder has disorder-specific genetic factors (Ruderfer et al. 2018). Most GWASs have focused on autosomal and/or sex chromosomes, and the genetic etiology for BD and SZ remains to be fully resolved.

Higher rates of PSY are observed in offspring of maternal probands compared to offspring of paternal probands with BD (McMahon et al. 1995) and SZ (Verge et al. 2011; Wolyniec et al. 1992). Therefore, several studies have investigated genetic associations with PSY comprising BD and SZ of variants in the chromosome of mitochondria, the energy-producing structures within cells, but not in autosomal and sex chromosomes (Gonçalves et al. 2018; Hagen et al. 2018; Kato et al. 2000; Mosquera-Miguel et al. 2012; Munakata et al. 2004; Ryu et al. 2018; Sequeira et al. 2012; Xu et al. 2017; Zhang et al. 2014). However, the mitochondrial genetic variants examined in these studies were selected based on a candidate gene approach, and the examined mitochondrial genetic variants were inconsistent among studies (Gonçalves et al. 2018; Hagen et al. 2018; Kato et al. 2000; Munakata et al. 2004; Ryu et al. 2018; Sequeira et al. 2012). Furthermore, results were also inconsistent among studies because of relatively small sample sizes.

To date, a limited number of studies have investigated genetic associations with BD and SZ of genome-wide genetic variants in the mitochondrial chromosome (n=220–465 variants) (Gonçalves et al. 2018; Hagen et al. 2018; Hudson et al. 2014; Sequeira et al. 2012) (summarized in Supplementary Table 1). These studies have identified several mitochondrial genetic variants associated with BD (rs28357375 and rs28357968 in 965 patients with BD and 3,938 controls (Sequeira et al. 2012) and SZ (rs527236209, rs869096886 and rs1599988 in 4,778 patients with SZ and l5,819 controls (Gonçalves et al. 2018), rs2854131, rs2853503, rs2853504, rs193302985 and rs2853506 in 2,019 patients with SZ and 15,302 controls (Hudson et al. 2014), rs193302985 and rs2853506 in 2,538 patients with SZ and 23,743 controls (Hagen et al. 2018), rs3937033 and rs2857291 in 1,137 patients with SZ and 3,938 controls (Sequeira et al. 2012). Furthermore, a study investigated associations of mitochondrial genetic variants with PSY in BD and SZ and identified some genetic variants (rs2857291, rs28357968, rs28380140, rs3088053 and rs2853497) related to PSY in 2,102 patients with PSY and 3,938 controls (Sequeira et al. 2012). However, these genetic variants are not identical among studies. Furthermore, the investigated individuals were limited to those of European ancestry. The minor allele frequencies (MAF) of most of these genetic variants are < 1% in the Asian population (Supplementary Table 1).

Mitochondria are essential intracellular organelles that harbor original haploid genomes. Mitochondria play a crucial role in oxidative phosphorylation. In humans, thirteen proteins related to oxidative phosphorylation are synthesized from an approximately 16,600 bp of the mitochondrial genome. On the other hand, mitochondria are sources of free radicals. As their DNA does not have histones or effective repair mechanisms, it is particularly susceptible to certain stress-induced damage. Mitochondrial dysfunction can cause dysfunction of the central nervous system, which demands high energy. Associations between mitochondrial dysfunctions and PSY have been investigated (Nishimura et al. 2021; Wu et al. 2019), with hypotheses that mitochondrial dysfunctions affect synaptic, energic and metabolic pathways, resulting in SZ and BD (Giménez-Palomo et al. 2021; Morris et al. 2020; Steckert et al. 2010).

Although most previous studies have targeted European populations (Gonçalves et al. 2018; Hagen et al. 2018; Hudson et al. 2014; Sequeira et al. 2012), we hypothesized that common mitochondrial genetic variants are associated with BD and SZ in both European and Asian populations but that some mitochondrial genetic variants might be associated with BD and SZ only in Asian populations. In this study, we investigated possible associations of genome-wide genetic variants (MAF > 0.01, n=45 variants) in the mitochondrial chromosome with BD, SZ, and PSY in a Japanese population. Furthermore, we investigated common characteristics among the patients who carried specific mitochondrial genetic variants.

Methods

Sample description

The subjects consisted of 51 patients with BD (23 males/28 females; mean age ± SD: 54.5 ± 16.8 years), 172 patients with SZ (77 males/95 females; 45.3 ± 14.0 years), and 197 HCs (129 males/68 females; 35.6 ± 13.8 years). The patients were recruited from both outpatient and inpatient populations at Kanazawa Medical University Hospital and related psychiatric hospitals. These participants were recruited from the Schizophrenia Non-Affected Relative Project (SNARP) (Kataoka et al. 2020; Ohi et al. 2017, 2019, 2020a, b, 2021) and the Bipolar & Schizophrenia Network on Intermediate Phenotypes

in Japan (B-SNIP-J) (Ohi et al. 2022a; Ohi et al., 2022c) All SZ patients ($n=172$) and HCs ($n=197$) who participated in a previous study (Ohi et al. 2020b, 2022b) were included in the current study. Each patient was diagnosed by at least two trained psychiatrists based on unstructured clinical interviews, medical records, and clinical conferences. The patients were diagnosed according to the criteria in the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). HCs were recruited through local advertisements and from among hospital staff at Kanazawa Medical University and were also evaluated using the nonpatient version of Structured Clinical Interview for DSM-IV (SCID) to exclude individuals who had current or past contact with psychiatric services, who had received psychiatric medication or who had a family history of any neuropsychiatric diseases among second-degree relatives. Imipramine equivalents of total antidepressants (IMI-eq), diazepam equivalents (DZ-eq), chlorpromazine equivalents of total antipsychotics (CPZ-eq), and biperiden equivalents of total antiparkinsonian drugs (BPD-eq) were calculated based on a previous study (Inada and Inagaki 2015). Current clinical symptoms were evaluated using the 17-item Hamilton Rating Scale for Depression (HAMD-17), the Young Mania Rating Scale (YMRS), and the Positive and Negative Syndrome Scale (PANSS). The premorbid IQ was evaluated using JART (Matsuoka et al. 2006), which is the Japanese version of the National Adult Reading Test (NART). The demographic variables among the three groups are summarized in Table 1. Written informed consent was obtained from all participants after the procedures had been thoroughly explained. This study was performed in accordance with the Declaration of Helsinki from the World Medical Association and was approved by the Research Ethical Committees of Gifu University and Kanazawa Medical University.

Genotyping and quality control

A detailed description of the genotyping and quality control (QC) applied in the study has been reported previously (Ohi et al. 2020a, b, 2021). Briefly, venous blood was collected from the participants, and genomic DNA was extracted from whole-blood samples. Genotyping was performed using Infinium OmniExpressExome-8 v1.4 or v1.6 BeadChips (Illumina, San Diego, CA, USA). After QC for removing subjects with high missing genotype rates (>95%) and sex chromosome anomalies and genetic variants deviating from Hardy-Weinberg equilibrium (HWE) ($p<1.0\times10^{-5}$) or having a low MAF<0.01 (Ohi et al. 2020b, 2022b), only genetic variants in the mitochondrial chromosome were extracted from the whole-genome genotyping data using PLINK v1.90 beta. As the sample sizes for each diagnostic group were different, the different sample size, especially smaller sample size, would affect the SNP QC including lower MAF (e.g., 0.001–0.05) and excess SNPs might be excluded for combined diagnostic comparison group (PSY vs. HCs). Thus, we also performed SNP QC procedure for each diagnostic comparison group (BD vs. HCs, and SZ vs. HCs). For mitochondrial genetic variants ($n=80$), those that deviated from HWE ($p<1.0\times10^{-5}$), had a low MAF<0.01, or had a poor genotype call rate (<0.95) were excluded from each diagnostic comparison group (BD vs. HCs, and SZ

Table 1 Demographic characteristics of patients with BD, patients with SZ, and HCs.

	HCs	BD	SZ		
Variables	($n=197$)	($n=51$)	($n=172$)	*P* values (*F* or χ^2)	*post hoc*
Age (years)	35.6 ± 13.8	54.5 ± 16.8	45.3 ± 14.0	**6.79×10^{-18}(43.5)**	HCs < SZ < BD
Sex (male/female)	129/68	23/28	77/95	**1.25×10^{-4}(18.0)**	-
Education (years)	16.2 ± 2.4	13.5 ± 3.0	12.5 ± 2.2	**7.60×10^{-41}(116.2)**	HCs > BD > SZ
Estimated premorbid IQ	108.9 ± 7.4	100.8 ± 11.3	98.2 ± 11.0	**7.29×10^{-22}(55.3)**	HCs > BD,SZ
IMI-eq (mg/day)	-	45.9 ± 99.2	4.9 ± 27.0	**2.06×10^{-6}(23.8)**	-
DZ-eq (mg/day)	-	6.1 ± 10.4	6.2 ± 11.3	0.96 (< 0.1)	-
CPZ-eq (mg/day)	-	152.9 ± 213.3	523.3 ± 511.4	**9.80×10^{-7}(27.7)**	-
BPD-eq (mg/day)	-	0.1 ± 0.6	0.8 ± 2.3	**0.045 (4.1)**	-
Age at onset (years)	-	37.0 ± 16.2	27.0 ± 11.0	**9.19×10^{-7}(25.5)**	-
DOI (years)	-	17.5 ± 14.1	18.1 ± 12.7	0.76 (0.1)	-
HAMD-17	-	8.5 ± 5.9	-	-	-
YMRS	-	1.7 ± 4.5	-	-	-
PANSS positive symptoms	-	-	16.5 ± 6.2	-	-
PANSS negative symptoms	-	-	19.4 ± 7.0	-	-

HCs, healthy controls; BD, bipolar disorder; SZ, schizophrenia; IQ, intelligence quotient; IMI-eq, imipramine equivalents of total antidepressants; DZ-eq, diazepam equivalents; CPZ-eq, total antipsychotic dosage in chlorpromazine equivalents; BPD-eq, biperiden equivalents of total antiparkinsonian drugs; DOI, duration of illness; HAMD-17, 17-item Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale; PANSS, Positive and Negative Syndrome Scale. Complete demographic information was not obtained for all subjects (number of participants for which the estimated premorbid IQ was available: HCs, $n=177$; BD, $n=46$; SZ, $n=168$; number of participants for which the HAMD-17 was available: BD, $n=47$). Means ± SDs are shown. *P* values < 0.05 are shown in boldface, and *post hoc* analysis was performed

vs. HCs) as well as a combined diagnostic comparison group (PSY vs. HCs).

Statistical analyses

Statistical analyses for demographic variables were performed using IBM SPSS Statistics 28.0 software (IBM Japan, Tokyo, Japan). Differences in continuous variables, such as age and years of education, among diagnostic groups were analyzed using analysis of variance (ANOVA). Differences in categorical variables, such as sex, were analyzed using Pearson's χ^2 test. Genetic analyses were performed in PLINK. Differences in allele frequency between PSY and HCs, BD and HCs, and SZ and HCs were analyzed using the χ^2 test. To test for the existence of genetic structure in the data, we have performed a principal component analysis (PCA), and the first 10 principal components (PCs) were calculated using PLINK [see Supplementary Figure S1 in our previous study (Ohi et al. 2020b)]. We have confirmed that there was no population stratification using PCs from the SNP array in our Japanese participants, and the PCs extracted from our participants were completely located on those extracted from the JPT (Japanese in Tokyo, Japan) population (Ohi et al. 2020b). Thus, we did not use the PCs to control for possible population stratification in this study. The marginal significance level for all statistical tests was set at P_{uncorr}<0.05. To control for type I error due to multiple testing, we calculated the P_{GC} value corrected by genomic control (GC). GC is a method used to control for multiple comparisons in genetic association study testing multiple genetic variants (Devlin et al. 2001). The GC method utilizes the distribution of test statistics across all genetic variants to estimate the genomic inflation factor (λ), which reflects the extent of inflation in the test statistics due to population structure or other confounding factors. To implement GC, the test statistics from the individual SNP association tests are divided by the estimated λ. This adjustment effectively counteracts the inflation caused by population structure or other sources of systematic bias. By applying GC, more accurate P values that appropriately account for multiple comparisons can be obtained. The significance level in this study was set at P_{GC}<0.05.

Results

Associations between mitochondrial genetic variants and schizophrenia, bipolar disorder, and psychotic disorders

In total, 42, 42, and 38 genetic variants in the mitochondrial chromosome remained after each QC in the PSY vs. HC, BD vs. HC, and SZ vs. HC cohorts, respectively. The mitochondrial allelic frequencies of all 45 genetic variants among patients with BD, patients with SZ, and HCs are summarized in Table 2. As shown in Table 2, all genetic variants that survived only in one of the comparisons (PSY vs. HC, BD vs. HC, or SZ vs. HC) were variants with lower MAF (e.g., 0.001–0.05) in patients or in HCs. LD relationships between mitochondrial genetic variants in each diagnostic group are provided in Supplementary Fig. 1. Overall, linkage disequilibrium (LD) patterns were similar among the three groups.

We first investigated genetic associations between mitochondrial genetic variants and PSY consisting of BD and SZ. Of 42 genetic variants, the allelic frequencies of six genetic variants (rs199713564, rs200999343, rs200478835, rs28359178, rs200786872, and rs201250154) differed between patients with PSY and HCs (Table 2; Fig. 1, χ^2=4.5–7.8, P_{uncorr}=0.033–5.17×10^{-3}). After correcting for multiple comparisons, only the association with rs200478835 was significant (P_{GC}=0.045), with other associations being not significant (P_{GC}>0.05). The MAF of the genetic variant (rs200478835) was higher in patients with PSY than in HCs.

We next investigated genetic associations of mitochondrial genetic variants with BD and SZ separately. Of 42 genetic variants, the allelic frequencies of five (rs111033179, rs200165736, rs200478835, rs200044200, and rs28359178) differed between patients with BD and HCs (Table 2; Fig. 1, χ^2=4.0–11.7, P_{uncorr}=0.047–6.15×10^{-4}). Even after correcting for multiple comparisons, three genetic variants (rs200478835, rs200044200 and rs28359178) were significantly associated with BD (P_{GC}=0.034–4.9×10^{-3}), with no significant associations with the other two genetic variants (P_{GC}>0.05). The MAFs of those genetic variants (rs200478835, rs200044200 and rs28359178) were higher in patients with BD than in HCs. Of the 38 genetic variants, the allelic frequencies of three (rs199713564, rs200478835, and rs201250154) differed between patients with SZ and HCs (Table 2; Fig. 1, χ^2=4.4–6.4, P_{uncorr}=0.035–0.011). However, there were no significant genetic variants associated with SZ after correcting for multiple comparisons (P_{GC}>0.05).

Case reports of BD patients who carry the minor G-allele of rs200044200

Individuals with the minor G-allele of *NADH dehydrogenase 5* (*ND5*) rs200044200 were found only among patients with BD (MAF=0.059) and not in HCs (MAF=0) [odds ratio (OR)=∞]. The detailed medical information of the three patients with BD is shown in Table 3.

The three patients commonly had neuropsychiatric family histories, though the neuropsychiatric diagnoses differed: patient 1, SZ (aunt); patient 2, unspecified psychiatric disorder (brother); and patient 3, autism spectrum disorder/attention-deficit hyperactivity disorder (son) and dementia (father). There were no other

Table 2 Differences in mitochondrial allelic frequencies among patients with BD, patients with SZ, and HCs

			MAF (A1)				PSYs			BD			SZ		
Rs number	**BP**	**A1/A2**	**PSYs**	**BD**	**SZ**	**HCs**	**OR**	P_{uncorr} (χ^2)	P_{GC}	**OR**	P_{uncorr} (χ^2)	P_{GC}	**OR**	P_{uncorr} (χ^2)	P_{GC}
rs28625645	489	A/G	0.32	0.33	0.31	0.37	0.79	0.26 (1.3)	0.42	0.85	0.62 (0.2)	0.69	0.78	0.25 (1.3)	0.47
rs3901846	499	A/G	0.022	0.039	0.017	0.051	0.43	0.12 (2.4)	0.26	0.76	0.73 (0.1)	0.78	0.33	0.083 (3.0)	0.27
rs3888511	961	G/A	0.050	0.020	0.058	0.051	0.97	0.95 (< 0.1)	0.97	0.38	0.35 (0.9)	0.44	1.15	0.75 (0.1)	0.84
rs111033179	1005	G/A	-	0.039	-	0.005	-	-	-	8.00	**0.047 (4.0)**	0.10	-	-	-
rs2000974	1048	A/G	0.018	-	0.023	0.005	3.56	0.23 (1.5)	0.39	-	-	-	4.64	0.13 (2.3)	0.34
rs111033358	1382	C/A	0.081	0.059	0.087	0.10	0.78	0.46 (0.6)	0.59	0.55	0.35 (0.9)	0.44	0.85	0.64 (0.2)	0.77
rs28358573	1442	A/G	0.022	0.020	0.023	0.025	0.88	0.84 (< 0.1)	0.89	0.77	0.81 (0.1)	0.84	0.91	0.90 (< 0.1)	0.93
rs200251800	1709	A/G	0.009	0	0.012	0.025	0.35	0.19 (1.7)	0.35	0	0.25 (1.3)	0.35	0.45	0.33 (0.9)	0.54
rs28358580	2416	G/A	-	0.020	-	0.010	-	-	-	1.95	0.58 (0.3)	0.65	-	-	-
rs200221487	2772	A/G	0.090	0.020	0.11	0.066	1.39	0.37 (0.8)	0.52	0.28	0.20 (1.6)	0.29	1.76	0.13 (2.3)	0.33
rs199713564	2831	A/G	0.014	0.020	0.012	0.051	0.26	**0.029 (4.8)**	0.12	0.38	0.34 (0.9)	0.44	0.22	**0.035 (4.4)**	0.18
rs3928306	3010	A/G	0.39	0.37	0.40	0.32	1.36	0.14 (2.2)	0.29	1.23	0.52 (0.4)	0.60	1.39	0.13 (2.3)	0.33
rs200999343	3206	A/G	0.11	0.12	0.10	0.051	2.26	**0.033 (4.5)**	0.13	2.49	0.083 (3.0)	0.15	2.19	0.051 (3.8)	0.21
rs2853516	3316	A/G	0.014	0.020	0.012	0.010	1.34	0.75 (0.1)	0.82	1.95	0.58 (0.3)	0.65	1.15	0.89 (< 0.1)	0.93
rs41460449	3394	G/A	0.023	0.039	0.018	0.021	1.10	0.88 (< 0.1)	0.92	1.92	0.45 (0.6)	0.54	0.86	0.84 (< 0.1)	0.90
rs201212638	3398	G/A	0.018	-	-	0	-	0.058 (3.6)	0.17	-	-	-	-	-	-
rs200319905	3497	A/G	0.046	0.040	0.047	0.041	1.13	0.80 (0.1)	0.86	0.98	0.98 (< 0.1)	0.99	1.17	0.75 (0.1)	0.84
rs3021088	5460	A/G	0.045	0.059	0.041	0.071	0.62	0.25 (1.3)	0.41	0.82	0.76 (0.1)	0.80	0.56	0.21 (1.5)	0.43
rs200165736	6253	G/A	0.022	0.039	0.017	0.005	4.50	0.13 (2.2)	0.28	8.00	**0.047 (4.0)**	0.10	3.48	0.25 (1.3)	0.47
rs28358884	8414	A/G	0.39	0.37	0.40	0.32	1.36	0.13 (2.3)	0.28	1.26	0.48 (0.5)	0.56	1.39	0.13 (2.3)	0.33
rs201336180	8684	A/G	0.009	0.020	-	0.010	0.88	0.90 (< 0.1)	0.93	1.95	0.58 (0.3)	0.65	-	-	-
rs2000975	8701	A/G	0.34	0.37	0.33	0.40	0.76	0.18 (1.8)	0.34	0.89	0.71 (0.1)	0.76	0.73	0.14 (2.1)	0.35
rs199646902	9053	A/G	0.009	0	0.012	0.015	0.59	0.56 (0.3)	0.68	0	0.38 (0.8)	0.47	0.77	0.78 (0.1)	0.86
rs201397417	10,345	G/A	0.036	0.059	0.029	0.061	0.57	0.23 (1.4)	0.39	0.96	0.96 (< 0.1)	0.96	0.46	0.15 (2.1)	0.35
rs2853826	10,398	A/G	0.29	0.30	0.29	0.32	0.90	0.61 (0.3)	0.71	0.92	0.81 (0.1)	0.84	0.89	0.61 (0.3)	0.74
rs200478835	10,410	G/A	0.099	0.12	0.093	0.030	3.48	**5.17×10−3(7.8)**	**0.045**	4.24	**9.70×10−3(6.7)**	**0.034**	3.27	**0.011 (6.4)**	0.11
rs200487531	10,609	G/A	0.040	0.039	0.041	0.051	0.79	0.61 (0.3)	0.71	0.76	0.73 (0.1)	0.78	0.79	0.65 (0.2)	0.77
rs200873900	11,696	A/G	0.013	0	0.017	0.025	0.52	0.37 (0.8)	0.52	0	0.25 (1.3)	0.35	0.68	0.60 (0.3)	0.74
rs28359169	11,969	A/G	0.013	-	-	0.005	2.67	0.38 (0.8)	0.53	-	-	-	-	-	-
rs2853501	13,105	G/A	0.014	0.020	0.012	0.036	0.37	0.14 (2.2)	0.29	0.54	0.56 (0.3)	0.63	0.32	0.14 (2.2)	0.34
rs200044200	13,135	A/G	-	0.059	-	0	-	-	-	-	**6.15×10−4(11.7)**	**4.9×10−3**	-	-	-
rs28359178	13,708	A/G	0.036	0.078	0.023	0.005	7.29	**0.030 (4.7)**	0.12	16.68	**8.94×10−4(11.0)**	**6.4×10−3**	4.67	0.13 (2.3)	0.34
rs200657506	13,942	G/A	0.013	0.039	0.006	0.015	0.88	0.88 (< 0.1)	0.91	2.64	0.28 (1.2)	0.37	0.38	0.38 (0.8)	0.58
rs28357671	14,178	G/A	0.004	0	0.006	0.020	0.22	0.14 (2.2)	0.28	0	0.30 (1.1)	0.40	0.28	0.23 (1.4)	0.44
rs201551481	14,927	G/A	0.018	0.020	0.017	0.015	1.18	0.83 (< 0.1)	0.88	1.29	0.82 (< 0.1)	0.86	1.15	0.87 (< 0.1)	0.91
rs200786872	14,979	G/A	0.11	0.12	0.10	0.051	2.26	**0.033 (4.5)**	0.13	2.49	0.083 (3.0)	0.15	2.19	0.051 (3.8)	0.21
rs2853506	15,218	G/A	0.014	0	0.018	0.016	0.87	0.87 (< 0.1)	0.90	0	0.37 (0.8)	0.47	1.13	0.88 (< 0.1)	0.92
rs201250154	15,236	G/A	0.013	0.020	0.012	0.051	0.25	**0.027 (4.9)**	0.11	0.37	0.33 (0.9)	0.43	0.22	**0.034 (4.5)**	0.18

Table 2 (continued)

			MAF (A1)				PSYs			BD			SZ		
Rs number	BP	A1/A2	PSYs	BD	SZ	HCs	OR	P_{uncorr} (χ^2)	P_{GC}	OR	P_{uncorr} (χ^2)	P_{GC}	OR	P_{uncorr} (χ^2)	P_{GC}
rs527236176	15,314	A/G	0.022	0.039	-	0.010	2.24	0.33 (1)	0.48	3.98	0.14 (2.2)	0.23	-	-	-
rs527236177	15,323	A/G	0.036	0.039	0.035	0.046	0.78	0.61 (0.3)	0.71	0.85	0.84 (< 0.1)	0.87	0.76	0.60 (0.3)	0.74
rs199951903	15,497	A/G	0.041	0.039	0.041	0.046	0.88	0.79 (0.1)	0.85	0.85	0.84 (< 0.1)	0.87	0.89	0.82 (0.1)	0.88
rs527236193	15,758	G/A	0.009	0	0.012	0.015	0.59	0.56 (0.3)	0.67	0	0.38 (0.8)	0.47	0.76	0.77 (0.1)	0.85
rs201023973	15,860	G/A	0.036	0.039	0.035	0.041	0.88	0.8 (0.1)	0.86	0.96	0.96 (< 0.1)	0.97	0.85	0.77 (0.1)	0.85
rs193303003	15,941	G/A	0.018	0.020	0.017	0.020	0.88	0.86 (< 0.1)	0.90	0.97	0.97 (< 0.1)	0.98	0.86	0.84 (< 0.1)	0.90
rs41378955	16,390	A/G	0.040	0.059	0.035	0.015	2.72	0.12 (2.4)	0.27	4.04	0.071 (3.3)	0.14	2.34	0.22 (1.5)	0.44

MAF, minor allele frequency; BP, biological position; OR, odds ratio; PSY, psychotic disorder; BD, bipolar disorder; SZ, schizophrenia

The reference genome sequence is GRCh38/hg38. P_{uncorr} values < 0.05 are shown in boldface. P_{GC} values < 0.05 are shown in boldface and underlined

common characteristics, such as types of BD, developmental disorders or premorbid IQ, among these patients.

Discussion

This is the first study to investigate associations of genome-wide genetic variants in the mitochondrial chromosome with BD, SZ and PSY in a Japanese population. Of mitochondrial genetic variants, five, three, and six were associated with BD, SZ and PSY, respectively. Of these variants, three (rs200478835, rs200044200 and rs28359178) and one (rs200478835) were significantly associated with BD and PSY, respectively, even after correcting for multiple comparisons. The minor alleles of rs200478835, rs200044200 and rs28359178 were commonly associated with risks of BD and PSY. Interestingly, the minor G-allele of rs200044200 was observed only in three patients with BD but not in HCs. The common feature of the three patients with BD was a neuropsychiatric family history. Our findings suggest that mitochondrial genetic variants may be associated with BD and PSY in both European and Japanese populations.

We found rs200478835, rs200044200 and rs28359178 to be associated with BD and rs200478835 with PSY in a Japanese population. In contrast, previous studies have not investigated associations of these genetic variants with BD or PSY in European populations (Gonçalves et al. 2018; Hagen et al. 2018; Hudson et al. 2014; Sequeira et al. 2012). MAFs of rs200478835, rs200044200 and rs28359178 in European populations are 0.0049, 0.0041, and 0.11, respectively (https://www.ncbi.nlm.nih.gov/snp/). Due to low MAFs, these studies might not have investigated associations in European populations. rs200478835 of the arginine-tRNA (*TRNR*) gene (protein noncoding) is located approximately 500 bp downstream of the *NADH dehydrogenase 3* (*ND3*) gene (protein coding) and approximately 2 kb upstream of the *NADH dehydrogenase 4* (*ND4*) gene (protein coding). rs200044200 and rs28359178 are both missense variants, A (Ala)>T (Thr) and A (Ala)>T (Thr), respectively, of the *ND5* gene.

NADH dehydrogenase is a membrane-associated protein localizing to mitochondrial membranes and is also known as complex I. NADH dehydrogenase is the enzyme that catalyzes the first reaction of the electron transfer system, which is vital for energy production. Previous studies have suggested that NADH dehydrogenase expression and activity in cells are decreased in patients with BD and SZ (Andreazza et al. 2010; Das et al. 2022; Holper et al. 2019). Furthermore, mutations in the *ND4* and *ND5* genes of the mitochondrial genome are associated with BD and SZ (Bamne et al. 2008; Frye et al. 2017; Torrell et al. 2013). These findings suggest that mitochondrial genetic variants in genes related to NADH

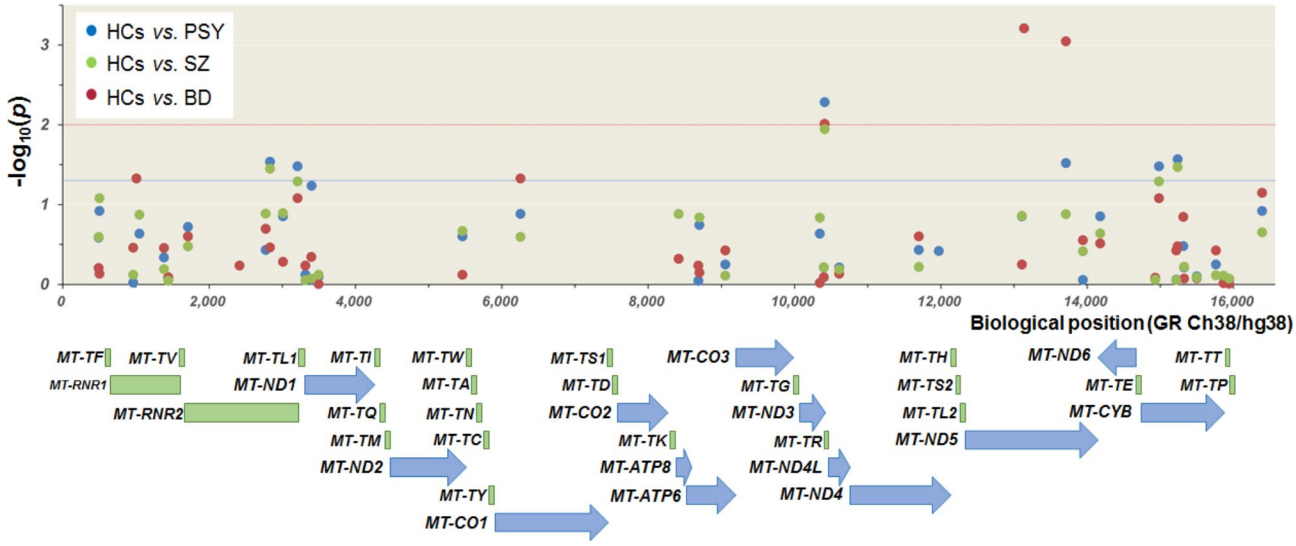

Fig. 1 Associations of mitochondrial genetic variants with bipolar disorder, schizophrenia, and psychotic disorders. The red line indicates a *P* value of 0.01; the blue line indicates a *P* value of 0.05. Genes (blue arrow) and RNAs (green) in the mitochondrial chromosome are indicated. HCs, healthy controls; PSY, psychotic disorders; BD, bipolar disorder; SZ, schizophrenia

Table 3 Case series of three BD patients with the minor G-allele of rs200044200

	BD patient 1	BD patient 2	BD patient 3
Age (years)	48	58	44
Sex	female	male	male
Age at onset (years)	25	44	35
Duration of illness (years)	23	14	9
Family history	SZ (aunt)	Unspecified psychiatric disorder (brother)	ASD/ADHD (son), Dementia (father)
Types of BD	I	II	II
Developmental disorders	-	-	-
Years of education	14	12	16
Premorbid IQ	92	110	104
Present IQ	80	n.a.	n.a.
Present occupation	Support for continuous employment type A	Unemployed	Unemployed
Former occupation	Children's nurse	Bus driver	Clerical work
Primary symptom	Mania	Depression	Depression
Psychotic episode	+	-	-
Rapid cycler	+	-	+
Present prescription (mg/day)	Aripiprazole 12 mg, Zotepine 25 mg, Biperiden 2 mg, Clonazepam 2 mg, Loflazepic acid 2 mg, Flunitrazepam 4 mg, Triazolam 0.25 mg, Valproic acid 800 mg	Flunitrazepam 2 mg, Lithium 400 mg	Quetiapine 100 mg, Flunitrazepam 2 mg, Zopiclone 7.5 mg, Lithium 900 mg

BD, bipolar disorder; ASD, autism spectrum disorder; ADHD, attention-deficit hyperactivity disorder

dehydrogenase may contribute to the pathogenesis of BD and SZ via dysfunction of energy production.

As stated above, several previous studies have identified significant genetic associations between several mitochondrial genetic variants (rs28357375, rs28357968, rs527236209, rs869096886, rs1599988, rs2854131, rs2853503, rs2853504, rs193302985, rs2853506, rs3937033, rs2857291, rs28380140, rs3088053, and rs2853497) and BD, SZ or PSY in European populations (Gonçalves et al. 2018; Hagen et al. 2018; Hudson et al. 2014; Sequeira et al. 2012). Of these genetic variants associated with BD, SZ or PSY in European populations, the

current study examined associations only for rs2853506 related to the risk of SZ in European populations with BD, SZ or PSY in a Japanese population after applying our QC. However, the minor G-allele of rs2853506 was not significantly associated with SZ in the Japanese population, even though the direction of the association was consistent between the present (OR=1.13) and previous (OR≈1.30) studies (Hagen et al. 2018). This finding suggests that some mitochondrial genetic variants might be commonly associated with risk of BD and SZ in different populations.

We found individuals with the minor G-allele of rs200044200 only among three patients with BD (MAF=0.059) but not in HCs (MAF=0) (OR=∞). Moreover, all the BD patients with the minor G-allele of rs200044200 (100%, 3/3) had several neuropsychiatric family histories, such as SZ, neurodevelopmental disorders, dementia, and unspecified psychiatric disorder. Of our all patients with BD, 33.3% (17/51) had neuropsychiatric family histories; 29.2% of patients with BD who did not have the minor G-allele of rs200044200 had neuropsychiatric family histories. The minor G-allele of rs200044200 was significantly associated with neuropsychiatric family histories in patients with BD (P=0.033). Compared with that of rs200044200 in European populations (MAF=0.0041), the MAF was higher in East Asian populations (MAF=0.019). However, it has been reported that rs200044200 is benign for Leigh syndrome (https://www.ncbi.nlm.nih.gov/clinvar/RCV000854899/), which is a progressive neurodegenerative disorder caused by abnormalities in mitochondrial energy generation (Thorburn et al. 1993), even though the SNP is a missense variant. In contrast, it is unknown whether rs200044200 affects mitochondrial function in PSY, including BD. While the rs200044200 mitochondrial missense variant may be associated with an increased risk of BD in some populations, further research is needed to fully understand its role in the development of this condition and to determine how it may interact with other genetic and environmental factors.

Limitations

There are some limitations to the interpretations of our findings. The sample size of our study was small compared to previous studies, potentially resulting in false-positive and -negative findings. Due to QC based on MAFs in our small sample size, we might have excluded some SNPs investigated in previous studies. Because our participants were recruited at a single institute, sample selection bias might have occurred. Further study with a larger sample size at multiple institutes in a Japanese population is needed. Although we investigated mitochondrial genetic variants in genomic DNA extracted from whole-blood samples, there might be not whole-blood-specific but brain-specific mitochondrial genetic variants in genomic DNA extracted from brain samples in patients with BD, SZ or PSYs.

Conclusions

We investigated associations of BD, SZ and PSY with genome-wide genetic variants in the mitochondrial chromosome in a Japanese population. Of 45 genetic variants, three (rs200478835, rs200044200 and rs28359178) and one (rs200478835) were significantly associated with BD and PSY, respectively. Interestingly, the minor G-allele of rs200044200 was detected only in three patients with BD but not in HCs. The common feature of these patients with BD was neuropsychiatric family histories. Our findings suggest that mitochondrial genetic variants may be associated with BD and PSY in European populations as well as in the Japanese population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40345-023-00307-6.

Supplementary Material 1

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Author contributions

KO supervised the entire project; collected the data; wrote the manuscript; and was critically involved in the design, analysis and interpretation of the data. RT, and K.O. were responsible for performing the literature review and data analyses and drafting the manuscript. DN, MS, JH, KK, RH and KI were involved in the genotyping. KO, DF, AK, KT, YM, SS, and TS were heavily involved in the collection of the majority of the data and intellectually contributed to data interpretation. All authors contributed to and approved the final manuscript.

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Data Availability

Our data are not publicly available because they contain information that could compromise the research participants' privacy/consent.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants after the procedures had been thoroughly explained. This study was performed in accordance with the Declaration of Helsinki from the World Medical Association and was approved by the Research Ethical Committees of Gifu University and Kanazawa Medical University.

Consent for publication

Not applicable.

Competing interests
All authors have no conflict of interest to report.

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