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Brain Neurotransmitter Transporter/Receptor Genomics and Efavirenz Central Nervous System Adverse Events

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Abstract

Objective—We characterized associations between central nervous system (CNS) adverse events and brain neurotransmitter transporter/receptor genomics among participants randomized to efavirenz-containing regimens in AIDS Clinical Trials Group studies in the United States.

Methods—Four clinical trials randomly assigned treatment-naïve participants to efavirenz-containing regimens. Genome-wide genotype and PrediXcan were used to infer gene expression

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levels in tissues including 10 brain regions. Multivariable regression models stratified by race/ethnicity were adjusted for *CYP2B6*/*CYP2A6* genotypes that predict plasma efavirenz exposure, age and sex. Combined analyses also adjusted for genetic ancestry.

Results—Analyses included 167 cases with grade 2 or greater efavirenz-consistent CNS adverse events within 48 weeks of study entry, and 653 efavirenz-tolerant controls. *CYP2B6/CYP2A6* genotype level was independently associated with CNS adverse events (O.R.: 1.07; p = 0.044). Predicted expression of 6 genes postulated to mediate efavirenz CNS side effects (*SLC6A2*, *SLC6A3*, *PGR*, *HTR2A*, *HTR2B*, *HTR6*) were not associated with CNS adverse events after correcting for multiple testing, the lowest P-value being for *PGR* in hippocampus (p=0.012), nor were polymorphisms in these genes or *AR* and *HTR2C*, the lowest P-value being for rs12393326 in *HTR2C* ($p=6.7\times10^{-4}$). As a positive control, baseline plasma bilirubin concentration was associated with predicted liver *UGT1A1* expression level ($p = 1.9\times10^{-27}$).

Conclusions—Efavirenz-related CNS adverse events were not associated with predicted neurotransmitter transporter/receptor gene expression levels in brain or with polymorphisms in these genes. Variable susceptibility to efavirenz-related CNS adverse events may not be explained by brain neurotransmitter transporter/receptor genomics.

Keywords

HIV; efavirenz; pharmacogenomics; neurotransmitter transporter; neurotransmitter receptor

Introduction

Efavirenz is a frequently prescribed antiretroviral, with its efficacy demonstrated in multiple clinical trials [1–6]. However, central nervous system symptoms (CNS) are common with efavirenz [7–9]. Several *CYP2B6* polymorphisms predict increased plasma efavirenz exposure, including *CYP2B6* 516G→T (rs3745274) [10–15], 983T→C (rs28399499) [15–18], and 15582C→T (rs4803419) [15]. A *CYP2A6* polymorphism, -48T→G (rs28399433), also affects efavirenz pharmacokinetics [19–22] when present with *CYP2B6* slow metabolizer genotypes [19, 22]. These polymorphisms explain approximately 35% of interindividual variability in plasma efavirenz exposure [15]. A possible association with efavirenz pharmacokinetics has also been reported with *UGT2B7* genotype [21] but with small effect size [22].

Increased likelihood of efavirenz CNS symptoms has been attributed to *CYP2B6* slow metabolizer genotypes [18, 23, 24]. In an initial analysis of AIDS Clinical Trials Group (ACTG) data [18], *CYP2B6* slow metabolizer genotypes were associated with adverse events in 276 white participants (p=0.04) but not in 217 black participants (p=0.58). Similarly, among 563 patients who initiated efavirenz-containing regimens at a clinic in the Southeastern United States, slow metabolizer *CYP2B6* genotypes were associated with efavirenz discontinuation for CNS symptoms in 335 white patients (p = 0.001) but not in 198 black patients (p = 0.27) [23]. Among 1833 ACTG study participants in the United States, an association between *CYP2B6* genotype and suicidality was strongest among white participants but nearly null among black participants [24]. The reason for this apparent difference by race is not known.

Brain neurotransmitter transporters/receptors are postulated to mediate efavirenz CNS symptoms, including the norepinephrine transporter (encoded by *SLC6A2*), dopamine transporter (*SLC6A3*), progesterone PR-B (*PGR*), serotonin receptors 5-HT2A (*HTR2A)*, 5-HT2B (*HTR2B*), 5-HT2C (*HTR2C*), and 5-HT6 (*HTR6*), and androgen receptor (*AR*) (Daria Hazuda, personal communication). Lower expression levels of neurotransmitter transporter/receptor genes in brain tissue could possibly confer increased susceptibility to efavirenz side effects. This hypothesis may be addressed indirectly using, PrediXcan, a novel computational algorithm that uses genome-wide genotype data to infer RNA expression levels for individual genes in various human organs and tissues [25].

We examined whether predicted expression levels of selected neurotransmitter transporter/receptor genes in brain were associated with risk for CNS adverse events in participants randomized to receive efavirenz-containing regimens in ACTG studies. We also examined whether individual polymorphisms in these genes were associated with CNS adverse events with efavirenz.

Methods

Study Design and Participants

Data were pooled from antiretroviral-naïve individuals who had been randomly assigned to initiate efavirenz-containing regimens in four studies: ACTG 384 (ClinicalTrials.gov: NCT00000919) [26, 27], A5095 (ClinicalTrials.gov: NCT00013520) [2, 28], A5142 (NCT00050895) [3], and A5202 (NCT00118898) [6]. Drug class components of the regimens were randomly assigned (efavirenz-based regimen vs. comparator regimen) except for nucleoside analogue choice in A5142. Genetic association testing was limited to participants who consented to genetic testing under ACTG protocol A5128 [29]. Participants self-reported race/ethnicity.

Each protocol required reporting of signs, symptoms, or diagnoses at each visit, severe and life-threatening graded signs or symptoms [30], and signs or symptoms that led to change in study regimen. Diagnoses were not graded. Further, study A5142 required report of all moderate signs or symptoms, study ACTG 384 required entry of all signs and symptoms grade 3 or greater, all signs and symptoms which resulted in dose modification regardless of grade, and all grade 2 or greater CNS symptoms, and A5095 and A5202 required report of moderate CNS symptoms. Site institutional review boards approved each study, and participants provided written informed consent.

Outcomes

The outcome of interest was new onset grade 2 or greater CNS signs or symptoms that were consistent with possible efavirenz effect. These included agitation, behavior changes, abnormal cognition, confusion, depression, difficulty concentrating, dizziness, abnormal dreams, excessive anger, hyperactivity, inappropriate behavior, insomnia, lethargy, change in level of consciousness, lightheadedness, memory loss, psychiatric mental status change, rage, or sleeping problems. Adverse event data were based on self-report, and did not

involve questionnaires specifically targeting CNS events. Death by suicide was also considered a possible efavirenz effect.

Cases were participants with grade 2 or greater efavirenz-consistent CNS signs or symptoms, or with death due to *suicide*, documented within 48 weeks after study entry while still being prescribed efavirenz, or within 2 weeks after efavirenz was discontinued. Controls were participants with no documented efavirenz-consistent CNS signs or symptoms regardless of any grade after study entry while being prescribed efavirenz for at least 96 weeks. Cases and controls were excluded for any neuropsychological signs or symptoms of any grade documented at study entry.

Covariates

Baseline covariates included in multivariable models included age, sex and *CYP2B6*/*CYP2A6* genotype. The first two principal components generated from genome-wide genotype data were also included to minimize confounding by unrecognized population stratification. Analyses performed separately among self-identified white, black, and Hispanic participants also adjusted for age, sex and *CYP2B6*/*CYP2A6* genotype, but not principal components.

Genetic assays and data

Genotypes for *CYP2B6* 516G→T, 983T→C, 15582C→T and *CYP2A6* -48T→G were largely available from a MassARRAY® iPLEX Gold (Sequenom, Inc.) assay, generated by Vanderbilt Technologies for Advanced Genomics (VANTAGE) [15]. Genome-wide genotype data largely available from a previous immunogenomics project [31] were generated by Illumina HumanHap 650Y array for A5095 and by Illumina 1M duo array for A5142 and A5202. Quality control and imputation of genome-wide data was performed as described elsewhere [32]. The PLINK program and R statistical programming language were used for QC procedures [33, 34]. Polymorphisms were censored for call rates <99%. We excluded 18 samples where genetically inferred sex differed from clinical data, or missing sex status that could not be inferred, 105 samples with overall genotyping call rates <99%, and 17 samples with cryptic relatedness based on identity by descent (IBD) estimates >0.3 from approximately 100,000 pruned SNPs.

Post QC data were imputed to 1000 Genomes [35] after converting to genome build 37 using liftOver [36] and stratifying by chromosome to parallelize imputation processing. ShapeIt2 [37] was used to check strand alignment and to phase data. The IMPUTE2 algorithm [38] was used to impute additional genotypes that were available in the 1000 Genomes reference panel, but not directly genotyped. Each chromosome was segmented into 6 MB regions with at least 3500 reference variants in each region. Imputed genotypes were included if posterior probabilities exceeded 0.9.

Quality of imputed data was assessed following the Electronic Medical Records and Genomics (eMERGE) protocol [39]. Each chromosome from each phase was checked for 100% concordance with genotyped data. We dropped imputed SNPs with imputation scores <0.7, genotyping call rates <99% and minor allele frequencies (MAF) <0.01.

Twelve composite *CYP2B6*/*CYP2A6* genotype levels that predict progressively greater plasma efavirenz exposure were defined by combinations of three *CYP2B6* and one *CYP2A6* polymorphisms [15, 22] as described elsewhere [22]. Each *CYP2B6*/*CYP2A6* polymorphism (rs3745274, rs28399499, rs4803419, and rs28399433) was in Hardy-Weinberg equilibrium in white, black, and Hispanic participants analyzed separately except rs4803419 in white participants (multiple testing-corrected P = 0.045). Consent for genetic analysis was obtained under ACTG protocol A5128 [29], and the ACTG approved this use of DNA.

PrediXcan

PrediXcan was used to infer, from genome-wide genotype data, the heritable component of RNA expression levels in 43 available reference tissues [25], using the 2015 PrediXcan models. PrediXcan was able to infer expression of approximately 10,000 genes in each tissue. The 10 reference brain tissues analyzed included anterior cingulate cortex, caudate, cerebellar hemisphere, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens, and putamen. The additional 33 reference tissues included adipose subcutaneous, adrenal gland, aorta, coronary artery, tibial artery, breast, EBV-transformed lymphocytes, transformed fibroblasts, sigmoid colon, transverse colon, gastroesophageal junction, esophagus mucosa, esophagus muscularis, heart atrial appendage, heart left ventricle, liver, lung, skeletal muscle, tibial nerve, ovary, pancreas, pituitary gland, skin suprapubic not sun exposed, skin lower leg sun exposed, terminal ileum, terminal ileum (Elastic Net), spleen, stomach, testis, thyroid, whole blood unscaled, whole blood, and cross tissue.

Statistical analysis

We characterized associations between predicted expression of six autosomal brain neurotransmitter transporter/receptor genes (*SLC6A2*, *SLC6A3*, *PGR*, *HTR2A*, *HTR2B*, *HTR6*) and efavirenz CNS adverse events. We also characterized associations between polymorphisms in these six genes as well as *AR* and *HTR2C* and efavirenz CNS adverse events. Because *AR* and *HTR2C* are on the X chromosome, PrediXcan cannot infer their expression. Analyses controlled for *CYP2B6*/*CYP2A6* genotype level as a linear covariate, age, and sex. The first two principal components, calculated using EIGENSOFT [40] were used to adjust for global ancestry in analyses that pooled all race/ethnicity groups. Associations with CNS adverse events were evaluated using logistic regression models, stratified by race/ethnicity. As a positive control, associations between baseline total plasma bilirubin concentration and hepatic *UGT1A1* expression were similarly evaluated, controlling for *CYP2B6*/*CYP2A6* genotype level, age, sex, and the first two principal components. The Bonferroni method was used to adjust for multiple testing.

Results

Study participants

Of 4,742 participants from ACTG studies ACTG 384, A5095, A5142, and A5202, a total of 2,171 who had been randomly assigned to initiate efavirenz-containing regimens consented to genetic testing at research sites in the United States. Of these participants, 1,425 were

successfully genotyped for *CYP2B6*/*CYP2A6* and had imputed genome-wide genotype and principal component data. Of these participants, 820 met definitions as either cases with documented grade 2 or greater efavirenz-consistent CNS adverse events by week 48 (n = 167) or efavirenz-tolerant controls that continued efavirenz for at least 96 weeks without documented CNS adverse events (n = 653). Participant disposition is presented in Figure 1. Baseline characteristics of study participants are shown in Table 1. Females were underrepresented among cases versus controls.

CYP2B6/CYP2A6 genotype and CNS adverse events

In logistical regression analyses, among the 820 participants who were evaluable as either cases who developed grade 2 or greater CNS adverse events by week 48 (n = 167), or efavirenz-tolerant controls (n = 653), and controlling for age, sex, and the first 2 principal components, *CYP2B6/CYP2A6* genotype level was associated with grade 2 or greater CNS adverse events within 48 weeks (O.R.: 1.07; 95% C.I.: 1.00 to 1.15; p = 0.044). In analyses performed separately among 335 white, 264 black, and 184 Hispanic participants, and adjusted for age and sex but not principal components, odds ratios for association between *CYP2B6/CYP2A6* genotype level and grade 2 or greater CNS event by week 48 were similar to the total group (1.10 for white, 1.07 for black, and 1.08 for Hispanic participants), but none were statically significant (P>0.10 for each). In the above multivariable models, female sex was associated with fewer grade 2 or greater CNS adverse events within 48 weeks among all participants (O.R.: 0.33; 95% C.I.: 0.17 to 0.63; p = 0.001), and among white participants (O.R.: 0.14; 95% C.I.: 0.18 to 1.04; p = 0.055) and black participants (O.R.: 0.43; 95% C.I.: 0.19 to 0.96; p = 0.040) analyzed separately.

Predicted expression levels of neurotransmitter transporter/receptor genes and CNS adverse events

For each participant, genome-wide genotype data was used to predict the heritable component of gene expression for 43 tissues, including multiple reference regions of the brain. Primary analyses characterized associations between 6 neurotransmitter transporter/receptor genes postulated to mediate efavirenz effects in brain (*SLC6A2*, *SLC6A3*, *PGR*, *HTR2A*, *HTR2B*, *HTR6*), and grade 2 or greater CNS adverse events within 48 weeks. Among all subjects, and controlling for *CYP2B6*/*CYP2A6* genotype level, age, sex, and 2 principal components, the lowest nominal P-value was for *PGR* in hippocampus (p=0.012). The two lowest nominal P-value results for each gene and associated brain regions are presented in Table 2. None were significant after correcting for multiple testing. In analyses performed separately among white, black, and Hispanic participants, and adjusted for age and sex but not principal components, there were no significant associations. The lowest P-value in white participants was for *HTR2A* in cerebellar hemisphere (p=0.12), in black participants was for *SLC6A2 in* caudate (p=0.17), and in Hispanics participants was for *HTR2A* in cortex (p=0.082). The two lowest nominal P-value results for each gene within race /ethnicity group, and associated brain regions are presented in Supplemental Table 1, supplemental Digital Content 1, http://links.lww.com/NMC/A133.

Following the approach of Li et al [41], we were able to assess correlations between predicted and observed gene expression in reference datasets in brain tissue for *SLC6A3*,

HTR2B, and *HTR6*. Among Caucasians, the strongest correlations were with *SLC6A3* (r^2 = 0.038) and *HTR2B* in hypothalamus (r^2 = 0.028). Among Africans the strongest correlations were with *SLC6A3* in hypothalamus (r^2 = 0.040) and *HTR6* in cortex (r^2 = 0.029). These would not be considered well-predicted genes.

Predicted expression levels for all evaluable genes in brain and CNS adverse events

In secondary analyses we explored associations with expression across all evaluable autosomal genes in the brain. Among all subjects, and controlling for *CYP2B6*/*CYP2A6* genotype level, age, sex, and 2 principal components, the lowest nominal p-value was for *RCE1* (a metalloproteinase) in cerebellar hemisphere ($p = 5.3\times10^{-8}$). The two lowest nominal P-value results for each brain region are presented in Table 3. In analyses performed separately among white, black, and Hispanic participants, and adjusted for age and sex but not principal components, there were no significant associations after adjusting for multiple comparisons. The lowest P-value in white participants was for *ACSF3* in anterior cingulate cortex ($p=9.5\times10^{-6}$), in black participants was for *TRPC3* in cerebellar hemisphere ($p=1.9\times10^{-5}$), and in Hispanics participants was for *KLK5* in cerebellar hemisphere ($p=3.0\times10^{-5}$). The two lowest nominal P-value genes for each brain region each gene within race /ethnicity group are in Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/NMC/A133.

Predicted UGT1A1 expression in all tissues and baseline plasma bilirubin concentration

As a positive control we considered total plasma bilirubin concentration at baseline, which should correlate inversely with *UGT1A1* expression, especially in liver. By linear regression analysis involving 1354 participants evaluable for baseline plasma bilirubin, and controlling for *CYP2B6*/*CYP2A6* genotype, age, sex, and 2 principal components, hepatic *UGT1A1* expression was associated with bilirubin concentration ($p = 3.4\times10^{-27}$). This association was also present among white participants ($p = 4.3\times10^{-15}$), black participants ($p = 4.2\times10^{-12}$), and Hispanic participants ($p = 1.5\times10^{-6}$) analyzed separately without adjusting for principal components (Table 4). In contrast, for 17 non-liver tissues for which PrediXcan could predict *UGT1A1* expression levels, only three had nominal p-values less than 0.05 for association of *UGT1A1* expression with baseline total bilirubin - skeletal muscle (p = 0.002), non-sun-exposed skin (p = 0.005), and putamen (p = 0.046). P-values exceeded 0.10 for the other 14 tissues. This established that PrediXcan could identify a true gene expression-phenotype association in our dataset, and could do so in a tissue-specific manner.

Neurotransmitter transporter/receptor gene polymorphisms and CNS adverse events

Primary analyses characterized associations between polymorphisms in the eight neurotransmitter transporter/receptor genes (± 100 kB) noted above (*SLC6A2*, *SLC6A3*, *NR3C3*, *HTR2A*, *HTR2B*, *HTR2C*, *HTR6*, *NR3C4*) and grade 2 or greater CNS adverse events within 48 weeks. Analysis among all participants, and controlling for *CYP2B6*/*CYP2A6* genotype level, age, sex, and 2 principal components, the lowest nominal P-value was for rs12393326 in *HTR2C* ($p=6.7\times10^{-4}$). The two lowest nominal P-value polymorphisms among all participants and among white, black, and Hispanic participants analyzed separately are presented in Table 5. None were significant after correcting for multiple testing.

Genome-wide polymorphisms and CNS adverse events

To complement the above analyses focused on eight neurotransmitter transporter/receptor gene polymorphisms, secondary analyses explored polymorphism associations genome-wide. Analysis among all participants, and controlling for *CYP2B6*/*CYP2A6* genotype level, age, sex, and 2 principal components, the lowest nominal P-value was for rs7143465 in *SLC8A3*, which encodes solute carrier family 8 member A3 ($p=2.2\times10^{-9}$). The two lowest nominal P-value polymorphisms among all participants and among white, black, and Hispanic participants analyzed separately are presented in Table 6.

For the four genes in Table 6, we attempted to examine whether predicted expression in brain was associated with CNS events. Of these, *CFAP36* was not represented in PrediXcan. Among white participants, but not among black or Hispanic participants, predicted *ACSF3* expression in brain tissues tended to be associated with grade 2 or greater CNS adverse events within 48 weeks, including in anterior cingulate cortex ($P = 9.46\times10^{-6}$), frontal cortex $P = 1.08\times10^{-5}$), cortex (1.24×10^{-5}), and caudate ($P = 8.53\times10^{-5}$). Of note, *ACSF3* rs144103499 (Table 6) is not a known expression quantitative trait locus (eQTL) for *ACSF3* in any tissue [42]. There were not associations with *BBS12* or *SLC8A3*. The lowest P-value for *BBS12* was in cerebellum among black participants (P = 0.092), and for *SLC8A3* was in hypothalamus among all participants (P = 0.014).

Discussion

Among individuals who were randomly assigned to initial treatment with efavirenz-containing regimens in four ACTG studies, and with correction for multiple comparisons, we found no significant association between predicted expression of 6 neurotransmitter transporter and receptor genes postulated to mediate efavirenz effects in brain (*SLC6A2*, *SLC6A3*, *PGR*, *HTR2A*, *HTR2B*, *HTR6*) and grade 2 or greater CNS adverse events, both among all participants, and in analyses performed separately among white, black, and Hispanic participants. The lowest nominal P-value among all participants was for *PGR* in hippocampus (p=0.012). Similarly, after correction for multiple comparisons we found no significant association between individuals SNPs in these genes or *AR* and *HTR2C* and grade 2 or greater CNS adverse events, both among all participants, and in analyses performed separately among white, black, and Hispanic participants. The lowest nominal P-value was for rs12393326 in *HTR2C* ($p=6.7\times10^{-4}$).

Analyses were controlled for *CYP2B6*/*CYP2A6* genotype, age, and sex, and in analyses that pooled all race/ethnicity groups, also the first 2 principal components. We demonstrated significant, though weak, associations between *CYP2B6*/*CYP2A6* genotype level and grade 2 or greater CNS adverse events, which is generally consistent with several previous reports [18, 23, 24]. It was therefore important that we adjust for *CYP2B6*/*CYP2A6* genotype level in analyses for associations with predicted neurotransmitter transporter/receptor gene expression and polymorphisms. In addition, controlling for principal components in analyses involving all participants reduced the likelihood for false associations due to unrecognized population stratification.

PrediXcan is a relatively new computational algorithm that allows the heritable component of RNA expression levels for individual genes in different tissues to be inferred from genome-wide genotype data [25]. It was developed to exploit genotype-tissue expression (GTEx) data, and evaluates aggregate effects of cis-regulatory variants (within 1MB upstream or downstream) on gene expression by an elastic net regression method, and generates potential eQTLs and their weights for each gene in each GTEx tissue type. By considering genes rather than individual polymorphisms, PrediXcan should have a greatly reduced multiple testing burden versus single-variant-single-trait association tests. PrediXcan may therefore identify loci with modest to weak effect sizes that are not significant in genome-wide association studies. To assess the performance of PrediXcan we tested for associations with baseline plasma total bilirubin concentration. It is reassuring that we found significant associations between predicted *UGT1A1* expression in liver and bilirubin concentrations among all participants, and separately among white, black, and Hispanic participants. Thus PrediXcan detected a known association in a tissue-specific manner in our dataset.

By analyzing all participants pooled, as well as racial/ethnic groups of white, black, and Hispanic participants separately, we had the potential to identify consistent genetic associations across groups. While true genetic associations need not be present in all populations, finding the same association in all participants and in each race/ethnicity group increases the likelihood that the association is not by chance. For example, associations between *CYP2B6* genotype level and plasma efavirenz concentrations were previously demonstrated in pooled analyses and among white, black, and Hispanic participants analyzed separately [15]. In the present analyses, neither predicted gene expression levels or polymorphisms with the lowest P-values were consistent across populations.

We cannot explain the apparent association between female sex and fewer grade 2 or greater CNS adverse events among all participants, and among white participants and black participants analyzed separately. Previous reports have been inconsistent in this regard, with studies showing no difference by sex [43, 44], increased efavirenz CNS adverse events in males [45], and increased CNS adverse events in females [46].

This study had limitations. Because providers may not have referred patients perceived to be at increased risk for CNS adverse events to studies of efavirenz, risk may be underestimated. Analyses largely involved white, black, and Hispanic participants in the United States, so findings may not translate to other countries or race/ethnicity groups. The open-label design of 3 of the 4 studies might have biased investigators into reporting CNS adverse events in patients randomized to efavirenz. While PrediXcan readily identified an association between predicted *UGT1A1* expression in liver and bilirubin concentrations, this does not prove that we could detect associations of efavirenz CNS adverse events with predicted gene expression levels in brain. To our knowledge, there is no brain gene-phenotype pair in our dataset that could serve as a positive control. A larger sample size would increase power to identify associations. The present study was not designed to address rare polymorphisms, epigenetics, inducibility of gene expression, and trans regulatory elements. In addition, factors not evaluated in this study such as nicotine and alcohol use may affect expression of *CYP2B6*, *CYP2A6*, and other genes, and could conceivably differ by ancestry.

In summary, it is important to identify genetic factors that affect susceptibility to antiretroviral toxicities. The present study suggests that interindividual differences in brain neurotransmitter transporter/receptor genomics may not explain variable susceptibility to efavirenz CNS adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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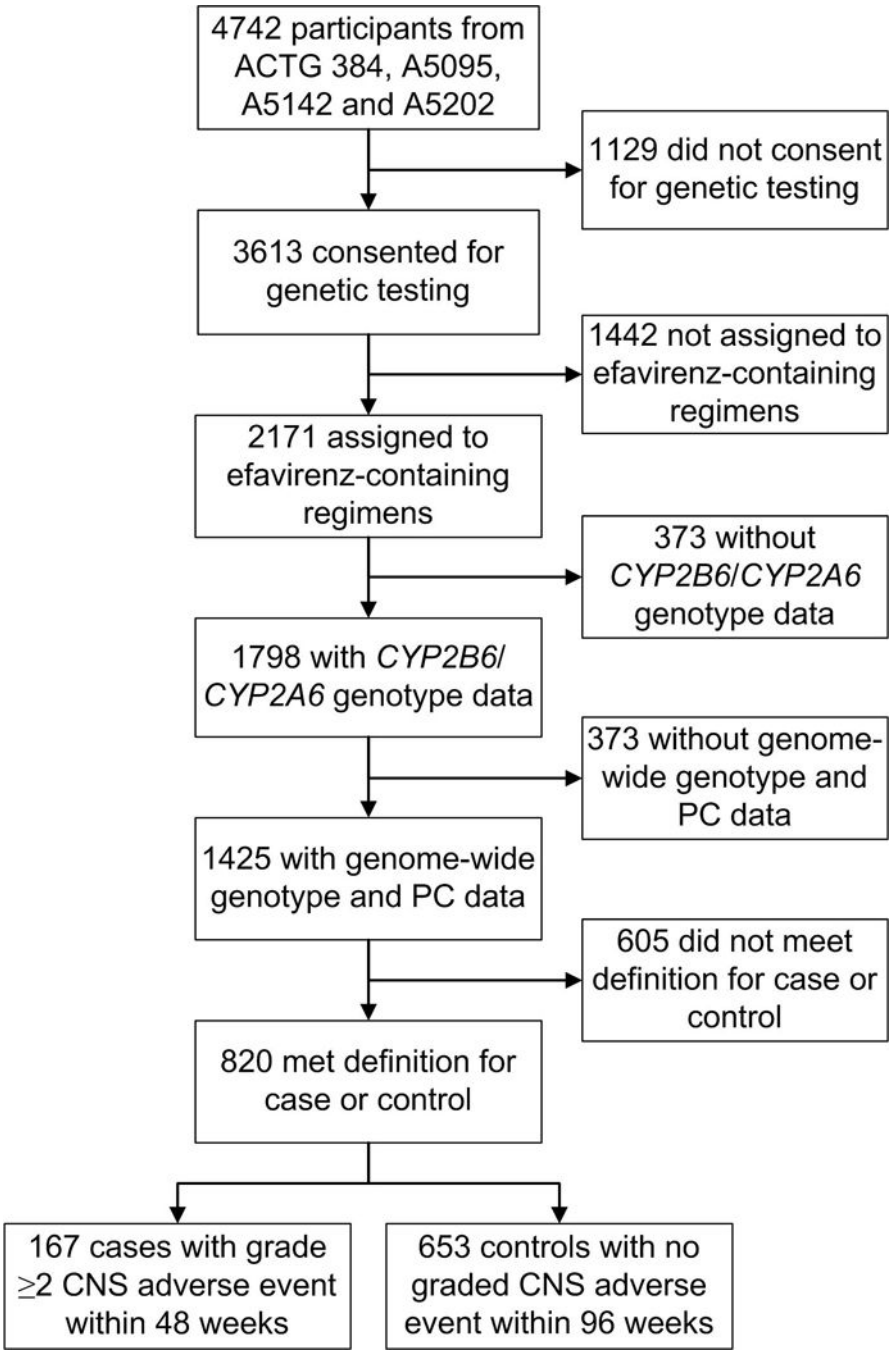

Figure 1. Derivation of the study sample

Derivation cases who developed grade 2 or greater efavirenz-consistent CNS adverse events by week 48, and efavirenz-tolerant controls who continued efavirenz for at least 96 weeks without efavirenz-consistent CNS adverse events, during participation in ACTG 384, A5095, A5142 or A5202 is shown. Abbreviation: *PC*, principal components.

Table 1

Baseline characteristics of participants included in analyses of grade 2 or greater CNS adverse events after being randomly assigned to efavirenz-containing regimens.

		Cases (n=167)	Controls (n=653)	Total (N=820)
Parent study, n (%)	ACTG384	28 (13.9)	173 (86.1)	201
	A5095	63 (34.4)	120 (65.6)	183
	A5142	15 (10.1)	133 (89.9)	148
	A5202	61 (21.2)	227 (78.8)	288
Sex, n (%)	Male	156 (16.4)	539 (77.6)	695
	Female	11 (8.8)	114 (91.2)	125
Race or ethnic group, n (%)	White Non-Hispanic	81 (22.8)	274 (77.2)	355
	Black Non-Hispanic	53 (20.1)	211 (79.9)	264
	Hispanic	26 (14.1)	158 (85.9)	184
	Asian	2 (25.0)	6 (75.0)	8
	Native American	3 (42.9)	4 (57.1)	7
	Multiracial	1 (100)	0 (0)	1
	Unknown	1 (100)	0 (0)	1
Age, Median (IQR)		38 (31, 45)	37 (31, 45)	37 (31, 45)

Table 2

Associations between predicted expression levels of six autosomal neurotransmitter receptor/transporter genes and grade 2 or greater CNS adverse events within 48 weeks of starting efavirenz-containing regimens.

Gene	Chromosome	Brain Region	Beta	P value
HTR2A	13	Cerebellar hemisphere	−0.61	0.086
		Frontal cortex	−1.24	0.677
HTR2B	2	Frontal cortex	−0.77	0.331
		Hippocampus	−0.31	0.601
HTR6	1	Nucleus accumbens	0.45	0.258
		Caudate	0.53	0.587
PGR	11	Hippocampus	−0.91	0.012
		Cortex	−1.00	0.204
SLC6A2	16	Cortex	1.85	0.405
		Caudate	0.69	0.454
SLC6A3	5	Nucleus accumbens	1.59	0.116
		Hypothalamus	0.65	0.192

Logistic regression analysis involved 820 total participants, which included 167 grade 2 or greater CNS event cases and 653 efavirenz-tolerant controls. The analysis controlled for *CYP2B6*/*CYP2A6* genotype level, age, sex, and the first 2 principal components. The analyses included all evaluable participants without stratification for race/ancestry. The two lowest P-value results are shown for six genes postulated to mediate efavirenz CNS side effects. The positive or negative beta indicates directionality of the relationship.

Table 3

Associations between predicted expression levels of all genes in brain and grade 2 or greater CNS adverse events within 48 weeks of starting efavirenz-containing regimens.

Brain region	*Gene*	Chromosome	Beta	P value
Anterior cingulate cortex	*PAXBP1*	21	−6.73	1.7×10^{-6}
	SEMA3G	3	2.80	2.8×10^{-6}
Caudate	*EMC10*	19	2.79	1.0×10^{-5}
	SIRPB1	20	1.52	1.9×10^{-5}
Cerebellar hemisphere	*RCE1*	11	−2.64	5.3×10^{-8}
	RABEPK	9	−1.21	4.6×10^{-6}
Cerebellum	*CDK10*	16	−0.73	1.8×10^{-5}
	C4orf48	4	−4.90	4.9×10^{-5}
Cortex	*TFAP2D*	6	−6.61	1.2×10^{-6}
	EHMT1	9	−1.44	1.1×10^{-4}
Frontal cortex	*ZNF76*	6	−59.49	2.2×10^{-6}
	HLA-G	6	0.59	1.5×10^{-4}
Hippocampus	*C11orf68*	11	−2.45	5.3×10^{-8}
	ZNF555	19	42.89	7.6×10^{-6}
Hypothalamus	*IKBKE*	1	0.10	2.7×10^{-7}
	ADRBK1	11	4.63	2.4×10^{-6}
Nucleus accumbens	*SHANK3*	22	4.80	2.9×10^{-7}
	MSX2	5	−4.92	1.2×10^{-4}
Putamen	*UBL4B*	1	5.62	1.0×10^{-5}
	SMIM6	17	−1.49	1.0×10^{-5}

Logistic regression analysis involved 820 total participants, which included 167 grade 2 or greater CNS event cases and 653 efavirenz-tolerant controls. The analysis controlled for *CYP2B6*/*CYP2A6* genotype level, age, sex, and the first 2 principal components. The analyses included all evaluable participants without stratification for race/ancestry. The two lowest P-value results are shown for each brain region.

Table 4

Associations between baseline plasma total bilirubin concentration and predicted gene expression levels in liver.

Race/ethnicity	Gene	Chromosome	Participants	Beta	P value
All	*UGT1A1*	14	1354	0.30	3.4×10^{-27}
	GGACT	2	1354	−0.88	7.2×10^{-6}
White	*UGT1A1*	2	645	0.32	4.28×10^{-15}
	CSN1S1	4	645	−0.37	8.72×10^{-5}
Black	*UGT1A1*	2	458	0.30	4.2×10^{-12}
	PGBD2	1	458	−1.96	3.57×10^{-5}
Hispanic	*CLDN12*	7	282	−4.17	3.69×10^{-7}
	UGT1A1	2	282	0.33	1.45×10^{-6}

Linear regression analysis involved numbers of participants shown, for baseline plasma total bilirubin concentration. Analysis among all participants controlled for *CYP2B6*/*CYP2A6* genotype level, age, and sex. Analysis among white, black, and Hispanic participants controlled for the same covariates but did not control for principal components. The two lowest P-value results are shown for each population group.

Table 5

Associations between polymorphisms in eight neurotransmitter/transporter genes and grade 2 or greater CNS adverse events within 48 weeks of starting efavirenz.

Race/ethnicity	Polymorphism	Gene	Chromosome	MAF	Cases	Controls	Beta	SE	P value
All	rs12393326	*HTR2C*	X	G:0.07	164	815	0.53	0.16	6.7×10^{-4}
	rs5988149	*HTR2C*	X	A:0.12	165	816	0.38	0.13	3.6×10^{-3}
White	rs660541	*PGR*	11	A:0.51	83	281	0.41	0.18	2.2×10^{-2}
	rs511484	*PGR*	11	C:0.49	83	281	−0.36	0.16	2.3×10^{-2}
Black	rs2497509	*HTR2C*	X	C:0.43	49	211	0.59	0.18	8.8×10^{-4}
	rs2497510	*HTR2C*	X	A:0.43	49	211	0.59	0.18	8.8×10^{-4}
Hispanic	rs3785152	*SLC6A2*	16	T:0.08	26	158	1.09	0.46	1.8×10^{-2}
	rs2016711	*HTR2A*	13	G:0.03	26	158	1.34	0.61	2.8×10^{-2}

Logistic regression analysis involved the indicated numbers of grade 2 or greater CNS event cases and efavirenz-tolerant controls. We considered polymorphisms in *SLC6A2*, *SLC6A3*, *NR3C3*, *HTR2A*, *HTR2B*, *HTR2C*, *HTR6*, and *NR3C4* ± 100 kB. The analysis controlled for *CYP2B6*/*CYP2A6* genotype level, age, sex, and, for the analysis involving all participants, the first 2 principal components. The two lowest P-value results are shown for each race/ancestry group.

Table 6

Associations between genome-wide polymorphisms and grade 2 or greater CNS adverse events within 48 weeks of starting efavirenz.

Race/ethnicity	Polymorphism	Gene	Chromosome	MAF	Cases	Controls	Beta	SE	P value
All	rs7143465	*SLC8A3*	14	C:0.45	167	653	−0.69	0.12	2.2×10^{-9}
	rs1045920	*CFAP36*	2	T:0.45	166	653	−0.74	0.13	2.6×10^{-9}
Black	rs2292493	*BBS12*	4	T:0.13	52	211	1.60	0.31	2.9×10^{-7}
	rs72671080	*BBS12*	4	A:0.13	52	211	1.60	0.31	3.0×10^{-7}
Hispanic	rs62520409	*LOC105375706*	8	A:0.04	26	158	3.34	0.68	9.8×10^{-7}
	rs1305010	Intergenic	2	C:0.06	26	157	2.31	0.54	1.9×10^{-5}
White	rs10823547	Intergenic	10	G:0.50	82	281	−0.88	0.18	1.2×10^{-6}
	rs144103499	*ACSF3*	16	CCT:0.21	83	280	1.04	0.22	1.3×10^{-6}

Logistic regression analysis involved the indicated numbers of grade 2 or greater CNS event cases and efavirenz-tolerant controls. The analysis controlled for *CYP2B6*/*CYP2A6* genotype level, age, sex, and, for the analysis involving all participants, the first 2 principal components. The two lowest P-value results are shown for each race/ancestry group.