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Genome-wide association study of peripheral neuropathy with D-drug-containing regimens in AIDS Clinical Trials Group protocol 384

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Abstract

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Conflict of interest David W. Haas has been the principal investigator on research grants to Vanderbilt University from Boehringer Ingelheim, Merck, and Gilead Sciences and has been a consultant to Merck. Gregory K. Robbins received research support from Gilead Sciences and Schering-Plough and received royalties from Wolters Kluwer. David B. Clifford has served on Data Safety Boards for Millennium, Pfizer, Genzyme, and Amgen and has been a consultant to Biogen Idec, Millennium, Bristol Myers Squibb, Pfizer, Genzyme, Amgen, and Quintiles. For the remaining authors, none were declared.

Stavudine (d4T) was, until recently, one of the most widely prescribed antiretroviral drugs worldwide. While there has been a major shift away from d4T use in resource-limited countries, a large number of patients have previously received (or continue to receive) d4T, and many have developed peripheral neuropathy. The identification of genetic predictors of increased risk might suggest novel therapeutic targets for such patients. In AIDS Clinical Trials Group protocol 384, antiretroviral-naïve patients were randomized to d4T/didanosine (ddI)- or zidovudine/lamivudine-containing regimens. Data from d4T/ddI recipients were analyzed for genome-wide associations (approximately 1 million genetic loci) with new onset distal sensory peripheral neuropathy. Analyses involved 254 patients (49 % White, 34 % Black, 17 % Hispanic), comprising 90 peripheral neuropathy cases (32 grade 1, 35 grade 2, 23 grade 3) and 164 controls. After correcting for multiple comparisons, no polymorphism was consistently associated with neuropathy among all patients, among White, Black, and Hispanic patients analyzed separately, both in genome-wide analyses (threshold, $P < 5.0 \times 10^{-8}$) and focused on 46 neuropathy-associated genes (threshold, $P < 3.5 \times 10^{-5}$). In the latter analyses, the lowest P values were in *KIFIA* among Whites (rs10199388, $P = 8.4 \times 10^{-4}$), in *LITAF* among Blacks (rs13333308, $P = 6.0 \times 10^{-6}$), and in *NEFL* among Hispanics (rs17763685, $P = 5.6 \times 10^{-6}$). Susceptibility to d4T/ddI-associated neuropathy is not explained by a single genetic variant with a marked effect.

Keywords

Peripheral neuropathy; HIV-1; Stavudine; Didanosine; Genomics

Introduction

Antiretroviral therapy has greatly reduced human immunodeficiency virus (HIV)-1-associated morbidity and mortality. The dideoxynucleoside reverse transcriptase inhibitors didanosine (ddI) and stavudine (d4T) have been widely prescribed in multidrug antiretroviral regimens, but severe toxicities associated with these “D-drugs” have markedly curtailed their prescribing (Dalakas 2001). Such toxicities including peripheral neuropathy, hepatic steatosis, lactic acidosis, and peripheral lipoatrophy are likely the consequence of inhibition of mitochondrial DNA polymerase gamma (Lewis et al. 2001).

Until recently, d4T was one of the most widely prescribed antiretroviral drugs worldwide. Over the past several years, there has been a major shift from d4T use to tenofovir use in resource-limited countries, a change that had already occurred in most developed countries. Large numbers of patients, however, have previously received (or continue to receive) d4T for many months or years, and many have developed peripheral neuropathy. The identification of genetic predictor(s) of increased risk for peripheral neuropathy might suggest therapeutic targets for such patients.

Previous reports involving patients of European and African ancestry have suggested associations between heritable variations in mitochondrial DNA (so-called mitochondrial haplogroups) and increased risk for peripheral neuropathy with ddI/d4T-containing regimens (Canter et al. 2010; Hulgan et al. 2005). The present study examined genetic associations

between nuclear variants and risk of developing peripheral neuropathy among HIV-infected patients who initiated d4T/ddI-containing regimens in a prospective clinical trial.

Methods

This retrospective, case-control genome-wide association study (GWAS) utilized data and specimens that had been prospectively collected from participants in AIDS Clinical Trials Group (ACTG) protocol 384, who consented for genetic analysis under protocol A5128. Study ACTG 384 was a multicenter randomized trial designed to compare antiretroviral drug regimens (ddI/d4T or zidovudine/lamivudine given with efavirenz, nelfinavir or both) as initial treatment for HIV-1 infection (Robbins et al. 2003). Patients in the present analyses enrolled in ACTG 384 in 1998 and 1999 in the USA and received ddI/d4T-containing regimens. Cases were patients who developed clinical signs or symptoms of distal sensory neuropathy within the first 96 weeks of initiating ddI/ d4T. Controls were patients who did not develop such signs or symptoms within 96 weeks of initiating ddI/d4T. Patients with peripheral neuropathy documented prior to initiating ddI/d4T were excluded from these analyses. Peripheral neuropathy was assessed at each study visit and was categorized as grade 1 (asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social and functional activities), grade 2 (sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities), and grade 3 (sensory alteration or paresthesia causing inability to perform usual social and functional activities).

Genotyping of DNA extracted from whole blood was by Illumina Human-1M Duo Beadchip (Illumina Inc., San Diego, CA, USA) and was available from a separate HIV immunogenomics project (Pereyra et al. 2010). Population ancestry was assessed by projecting genetic assay data onto HapMap Phase III data (Pereyra et al. 2010). Analyses were limited to nuclear polymorphisms. Hereafter, we refer to non-Hispanic White, non-Hispanic Black, and Hispanic patients as White, Black, and Hispanic, respectively.

Quality control was applied to genetic assay data as follows. Variants with missingness $>2\%$ or minor allele frequencies $<5\%$ were excluded. Data from samples with exceptionally high or low heterozygosity values ($|F|>0.1$) or genotyping failure $>2\%$ were excluded. A total of 936,149 polymorphisms passed quality control. Within each race/ethnicity group, associations were assessed for genome-wide significance ($P<5.0\times 10^{-8}$) by logistic regression. To examine associations across all three race/ethnicity groups together, meta-analyses were also performed. Further analyses focused on polymorphisms in the set of neuropathy-associated genes listed in the Inherited Peripheral Neuropathies Mutation Database (Timmermen 2011) and also in *DNMT1* and *KIF1A* (list of genes provided in Supplemental On-line Table 1). For analyses involving neuropathy-associated gene, polymorphisms within 100 kb upstream and downstream of each gene were included, and the genome-wide significance threshold was $P<3.5\times 10^{-5}$. Analyses were performed separately for grade 1, grade 2, and grade 3 peripheral neuropathies. Quality control of genotype data and genetic association analyses were performed using PLINK v1.07 (Purcell et al. 2007). Additional statistical analyses were done with the R statistical package version 2.13.1.

Results

A total of 254 patients were included in these analyses, comprising 90 peripheral neuropathy cases (32 grade 1, 35 grade 2, and 23 grade 3) and 164 controls. There were 125 (49.0 %) White, 86 (34 %) Black, and 43 (17 %) Hispanic patients as assessed by principal components. In meta-analyses, involving all 254 White, Black, and Hispanic patients, that focused on the 90 grade 1 peripheral neuropathy cases, no polymorphism was genome-wide significant (Fig. 1). The lowest P value was intronic in *KRR1* (rs11540407, odds ratio (OR)= 2.6; $P=9.6\times 10^{-6}$). Separate meta-analyses limited to the 58 grade 2 peripheral neuropathy cases and limited to the 23 grade 3 peripheral neuropathy cases did not similarly show any polymorphism to be genome-wide significant. Polymorphisms with the lowest P values were not consistent between analyses nor were they consistent between populations (Table 1).

Using whole genome data, separate analyses were performed in White, Black, and Hispanic patients and separately for grade 1, grade 2, and grade 3 peripheral neuropathies (i.e., nine separate analyses) (Supplemental on-line Table 2). Polymorphisms with the lowest P values are as follows. In White patients with grade 3 peripheral neuropathy, the polymorphism with the lowest P value was intronic in *IL2RA* (rs12722486, OR=38.2; 95 % confidence interval (CI)=6.6–219.6; $P=1.5\times 10^{-9}$). In Black patients with grade 3 peripheral neuropathy, the polymorphism with the lowest P value was intronic in *ZNF648* (rs7554128, OR=48.5; 95 % CI= 5.7–414; $P=5.7\times 10^{-8}$). In Hispanic patients with grade 2 peripheral neuropathy, the polymorphism with the lowest P value was within 100 kb of *RSP04* (rs502716, OR=28; 95 % CI=6.8–114.7; $P=3.2\times 10^{-8}$)

Further analyses were limited to 46 neuropathy-associated genes and comprised 1,395 polymorphisms. In a meta-analysis, involving White, Black, and Hispanic patients, that focused on all 90 grade 1 peripheral neuropathy cases, no polymorphism was genome-wide significant at $P<3.5\times 10^{-5}$. The polymorphism with the lowest P value was intronic in *FGD4* (rs1909509, OR=2.1; $P=9.6\times 10^{-4}$). Separate meta-analyses limited to grade 2 as well as grade 3 peripheral neuropathy cases did not show any polymorphism to be genome-wide significant.

Considering only the 46 neuropathy-associated genes, separate analyses were conducted in White, Black, or Hispanic patients and for grade 1, grade 2, and grade 3 peripheral neuropathies (Supplemental on-line Table 3). Polymorphisms with the lowest P values were as follows. In White patients with grade 3 peripheral neuropathy, the lowest P value was within 100 kb of *KIF1A* (rs10199388, OR=5.3; 95 % CI= 1.8–15.3; $P=8.4\times 10^{-4}$). In Black patients with grade 2 peripheral neuropathy, the polymorphism with the lowest P value was within 100 kb of *LITAF* (rs13333308, OR=17.1; 95 % CI=2.1–138.9; $P=4.6\times 10^{-4}$). This polymorphism also had the lowest P value in an analysis limited to 23 grade 3 peripheral neuropathy cases (rs13333308, OR=32.3; 95 % CI=3.7–284.9; $P=6.0\times 10^{-6}$). In Hispanic patients with grade 2 peripheral neuropathy, the polymorphism with the lowest P value was within 100 kb of *NEFL* (rs6557786, OR=23.2; 95 % CI=4.3–125.6; $P=4.7\times 10^{-6}$).

Discussion

Among patients exposed to ddI/d4T-containing regimens in ACTG 384, who were evaluable for genetic associations with new onset sensory peripheral neuropathy within the first 96 weeks of treatment, no polymorphism was consistently genome-wide significant. This was so in analyses of polymorphisms across the entire nuclear genome, and in analyses focused on polymorphisms in neuropathy-associated genes. This was also so in analyses that included all grade 1 peripheral neuropathy cases and in analyses limited to grade 2 and grade 3 peripheral neuropathy cases. Furthermore, polymorphisms with the lowest *P* values were not consistent across analyses limited to grade 1, grade 2, and grade 3 peripheral neuropathies. The fact that associations did not reproduce across populations nor across grades of neuropathy suggests that such associations may not also reproduce in other cohorts.

In White patients with grade 3 peripheral neuropathy, the polymorphism with the lowest *P* value was in *IL2RA*. The interleukin-2 receptor alpha (*IL2RA*) gene encodes a regulator of immune responses (Maier et al. 2009) but has no clear relevance to neuronal physiology. In Black patients with grade 3 peripheral neuropathy, the polymorphism with the lowest *P* value was in *ZNF648*, which may be involved in transcriptional regulation. In Hispanic patients with grade 2 peripheral neuropathy, the polymorphism with the lowest *P* value was near *RSPO4* (which encodes R-spondin 4, possibly involved in Wnt/beta-catenin signaling pathways) (Blaydon et al. 2006) and *ANGPT4* (which encodes angiopoietin 4, involved in vascular development and angiogenesis) (Olsen et al. 2006), genes with no specific relevance to neuronal physiology.

In analyses limited to neuropathy-associated genes, a meta-analysis considering all grades of peripheral neuropathy showed the lowest *P* value for a polymorphism in *FGD4*. This gene encodes frabin which is involved in peripheral nerve myelination, and *FGD4* mutations have been associated with autosomal recessive Charcot-Marie-Tooth Type 4H (Charcot-Marie-Tooth disease comprises of a clinically and genetically diverse group of inherited disorders of peripheral nerves) (Delague et al. 2007). Meta-analysis of grade 3 peripheral neuropathy showed the lowest *P* value for a polymorphism near *KIF1B*. In White patients, the polymorphism with the lowest *P* value for association with all grades of peripheral neuropathy and with grade 3 peripheral neuropathy was in *KIF1A*, while in Black patients, the lowest *P* values were for polymorphisms in *LITAF*. *KIF1A* encodes a protein involved in anterograde transport of organelles along axonal microtubules, and *KIF1A* mutations have been associated with spastic paraplegia and hereditary sensory neuropathy (Klebe et al. 2012; Riviere et al. 2011), while *KIF1B* encodes for a protein involved in apoptosis and axonal transport of membranous organelles. Mutations to KIF family genes have been associated with Charcot-Marie-Tooth disease type 2A, while *LITAF* mutations have been associated with Charcot-Marie-Tooth disease type 1C (CMT1C) (Street et al. 2003). In Hispanic patients, the polymorphism with the lowest *P* value for association with all grades of peripheral neuropathy was in *NEFL*, which encodes the neurofilament light polypeptide. Mutations in *NEFL* have been associated with Charcot-Marie-Tooth disease types 2E and 1F (Jordanova et al. 2003; Shin et al. 2008)

There were limitations to this study. The sample size was modest, so only polymorphisms with marked effects could have achieved genome-wide significance. In addition, peripheral neuropathy in ACTG 384 was based on signs and symptoms, rather than formal neurologic evaluation assessments.

In summary, among patients exposed to ddI/d4T-containing regimens in the ACTG 384, no genetic polymorphism was consistently associated with new onset distal sensory peripheral neuropathy at genome-wide significance. Polymorphisms identified herein (e.g., in *KIF1A*, *LITAF*, and *NEFL*) warrant replication in other cohorts of HIV-infected patients who have developed D-drug-associated peripheral neuropathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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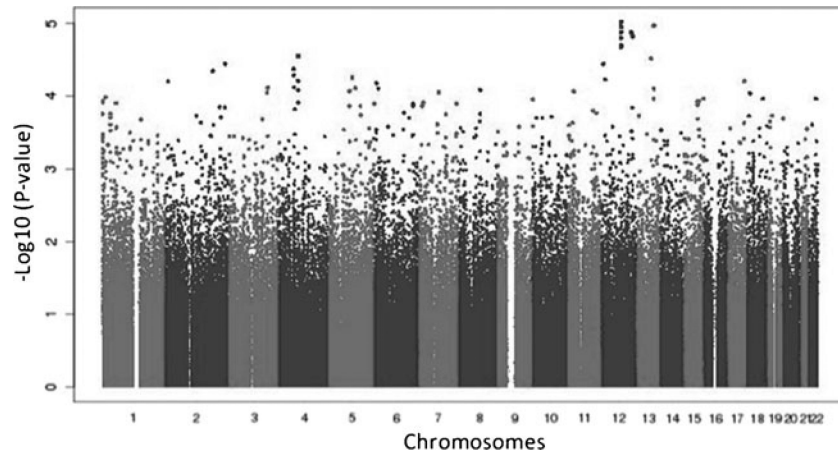


Fig. 1. Manhattan plot of associations between genetic polymorphisms and grade 1 sensory peripheral neuropathy by meta-analysis. The $-\log_{10}$ of P values are shown. The genome-wide significance threshold is $P=5.0 \times 10^{-8}$

Table 1

Polymorphisms with the lowest *P* values for association with sensory peripheral neuropathy

| | Case/control | Entire genome ^a | | | | Neuropathy-associated genes ^{a,b} | | | |
|---------|--------------|-----------------------------|--------------|------------|----------------------|--|--------------|------------|----------------------|
| | | Gene | Polymorphism | Odds ratio | <i>P</i> value | Gene | Polymorphism | Odds ratio | <i>P</i> value |
| Grade 1 | 90/164 | <i>KRR1</i> | rs11540407 | 2.6 | 9.6×10^{-6} | <i>FGD4</i> | rs1909509 | 2.1 | 9.6×10^{-4} |
| | | Intergenic | rs9518599 | 2.5 | 1.1×10^{-5} | <i>FGD4</i> | rs7298165 | 1.9 | 1.8×10^{-3} |
| | | <i>KRR1</i> | rs1552039 | 2.6 | 1.1×10^{-5} | <i>FGD4</i> | rs6488066 | 1.9 | 2.2×10^{-3} |
| | | <i>ACE2</i> | rs1514280 | 3.6 | 1.2×10^{-5} | <i>RAD52</i> | rs1051669 | 1.8 | 3.4×10^{-3} |
| | | <i>KRR1</i> | rs2070162 | 2.6 | 1.3×10^{-5} | <i>NDRG1</i> | rs2930004 | 1.7 | 4.3×10^{-3} |
| Grade 2 | 58/164 | <i>SASH1</i> | rs8641 | 3.1 | 5.8×10^{-6} | <i>FAM134B</i> ^c | rs149511 | 0.4 | 4.7×10^{-3} |
| | | <i>SASH1</i> ^c | rs208740 | 2.9 | 9.0×10^{-6} | <i>FGD4</i> | rs1909509 | 2.1 | 5.4×10^{-3} |
| | | <i>ST8SIA2</i> ^c | rs12913269 | 3.4 | 1.3×10^{-5} | <i>WISPI</i> | rs2929965 | 0.5 | 5.6×10^{-3} |
| | | <i>ST8SIA2</i> ^c | rs2129797 | 3.4 | 1.4×10^{-5} | <i>LITAF</i> ^c | rs12595973 | 0.5 | 7.7×10^{-3} |
| | | <i>NTF3</i> | rs6332 | 2.7 | 1.7×10^{-5} | <i>KIF1A</i> ^c | rs4234121 | 0.4 | 9.2×10^{-3} |
| Grade 3 | 23/164 | <i>ST8SIA2</i> ^c | rs12913269 | 6.5 | 3.2×10^{-7} | <i>KIF1B</i> ^c | rs11587309 | 2.7 | 5.1×10^{-3} |
| | | <i>ST8SIA2</i> ^c | rs2129797 | 6.4 | 3.5×10^{-7} | <i>KIF1A</i> | rs10198394 | 2.4 | 7.3×10^{-3} |
| | | Intergenic | rs4397851 | 5.3 | 1.5×10^{-6} | <i>NDRG1</i> | rs10505606 | 2.4 | 7.7×10^{-3} |
| | | <i>ADAMTS2</i> | rs6873892 | 6.1 | 2.1×10^{-6} | <i>NDRG1</i> | rs2233326 | 2.4 | 1.1×10^{-2} |
| | | <i>ST8SIA2</i> ^c | rs12910290 | 5.1 | 2.8×10^{-6} | <i>KIF1B</i> | rs10492970 | 7.1 | 1.1×10^{-2} |

^aMeta-analyses were performed to combine results from White, Black, and Hispanic groups

^bThe neuropathy-associated genes from the Inherited Peripheral Neuropathies Mutation Database plus *DNMT1* and *KIF1A* are listed in Supplemental On-line Table 1

^cThese polymorphisms are within 100 kb of the named gene