Pharmacogenetic Effect of the Stromelysin (MMP3) Polymorphism on Stroke Risk in Relation to Antihypertensive Treatment

The Genetics of Hypertension Associated Treatment Study

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Background and Purpose—Atherothrombotic diseases including stroke share a common etiology of atherosclerosis, and susceptibility to atherosclerosis has a genetic component. Stromelysin-1 (matrix metalloproteinase-3 [MMP3]) regulates arterial matrix composition and is a candidate gene for atherothrombosis. A common polymorphism of MMP3 alters expression levels and affects atherosclerotic progression and plaque stability. As part of the Genetics of Hypertension Associated Treatment study, ancillary to the Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial, we evaluated the 5A/6A polymorphism in MMP3 to determine its association with stroke and determine whether it modifies clinical outcome response to blood pressure–lowering drugs.

Methods—The effect of the MMP3 5A/6A polymorphism on stroke rates was examined by using multivariate-adjusted Cox regression models, including a test for interactions between genotype and antihypertensive drug class.

Results—Compared with participants treated with chlorthalidone with the 6A/6A genotype, individuals with the 6A/6A genotype randomized to lisinopril had higher stroke rates (hazard ratio = 1.32; 95% CI, 1.08 to 1.61; \( P = 0.007 \)) and 5A/6A individuals taking lisinopril had lower stroke rates (hazard ratio \( interaction \) = 0.74; 95% CI, 0.53 to 1.04; \( P_{interaction} = 0.08 \)), whereas 5A/5A individuals taking lisinopril had the lowest stroke rate (hazard ratio \( interaction \) = 0.51; 95% CI, 0.31 to 0.85; \( P_{interaction} = 0.009 \)). There were no pharmacogenetic differences in stroke rate by genotype in patients taking amlodipine or doxazosin vs chlorthalidone.

Conclusions—The MMP3 6A/6A genotype is associated with an increased risk of stroke in hypertensive subjects taking lisinopril compared with patients treated with chlorthalidone, whereas a protective effect was found for 5A/5A individuals treated with lisinopril. Genetic screening for the MMP3 5A/6A genotype might be a useful tool to select optimal antihypertensive therapy if this finding is replicated.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00563901.

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Key Words: stroke ■ pharmacogenetics ■ matrix metalloproteinase-3 ■ antihypertensive agents

Stroke is the third leading cause of death in the United States and the leading cause of long-term disability. There are \( \approx \) 700,000 stroke cases per year, and estimates of the annual burden placed on healthcare costs by stroke range between $30 and $50 billion.\(^1\)

In addition to numerous lifestyle risk factors, atherosclerosis\(^2\)–\(^4\) and hypertension\(^5\)–\(^6\) are central to the pathogenesis of stroke. Changes in the composition of the arterial matrix are among the primary mechanisms underlying this progression. As atherosclerosis and hypertension persist, there is a reduction in the ratio of elastin to collagen in the arterial matrix, reducing arterial compliance and increasing blood pressure (BP).\(^7\)

Stromelysin-1 (matrix metalloproteinase-3 [MMP3]) is an important enzymatic regulator of extracellular matrix remodeling secreted predominantly by connective-tissue cells.\(^8\) MMP3 cleaves several types of collagen at various sites in the helical domain and degrades other constituents of the extracellular matrix, including proteoglycan, fibronectin, and laminin.\(^9\) Because hypertension is a major cause of atherosclerotic remodeling of the large arteries and is also the most important stroke risk factor, we chose stroke as the outcome through which to test for an antihypertension pharmacogenetic effect of MMP3.
A common polymorphism, MMP3 5A/6A, consisting of either 5 or 6 adenosine residues, respectively, is located in the interleukin-1 response element of the MMP3 promoter region. The 6A allele is associated with decreased MMP3 expression and more rapid progression of atherosclerosis presumably due to collagen buildup in the arterial matrix. Other studies have directly linked increased MMP3 expression and 5A alleles to plaque instability and myocardial infarction (MI), and heterozygotes are thought to have the optimal balance of matrix accumulation and degradation. Although 6A alleles have been shown to predispose individuals to carotid artery stenosis, a known stroke risk factor, no studies have directly linked either allele to stroke risk.

Materials and Methods

Study Design

The Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial (ALLHAT) is a practice-based, double-blind, active-controlled, randomized, clinical trial with 42,418 high-risk hypertensives randomized in 623 clinical centers. Participants are 55 years of age or older, with systolic or diastolic hypertension and 1 or more risk factors for cardiovascular disease. BP eligibility for ALLHAT was based on current antihypertensive medication use and/or the average of 2 seated measurements during 2 prerandomization visits. For patients currently taking BP–lowering drugs, the systolic (SBP) and diastolic (DBP) BP could not exceed 160/100 mm Hg at the first visit or 180/110 mm Hg at the second visit. Patients were eligible if they met any of the inclusion criteria (in addition to a diagnosis of hypertension). Inclusion criteria were ST–T–wave ECG changes indicative of ischemia, a history of coronary revascularization, angina pectoris, other documented atherosclerotic disease, type 2 diabetes, HDL cholesterol <35 mg/dL (any 2 determinations in the past 5 years), current smoking, and a combined ECG wall thickness of 0.25 mm measured in the past 2 years, and ECG evidence of left ventricular hypertrophy in the past 2 years. Exclusion criteria were symptomatic MI, stroke, or angina pectoris within the past 6 months; symptomatic heart failure or ejection fraction <35%; nonhypertensive indications for an aversion to the drugs being tested in ALLHAT; requirement for >2 medications to control BP; sensitivity/contraindications to any of the first-line study medications; serum creatinine ≥2 mg/dL; low likelihood of compliance with the study protocol; serious illness likely to lead to noncardiac death during the trial; or current participation in another clinical trial.

Participants were randomized to 1 of 4 treatment arms, chlorthalidone, lisinopril, amiodipine, and doxazosin, in a ratio of 1:7:1:1:1, respectively. They were initially started on the lowest possible dose of each agent, and dosages were increased until BP control was achieved (SBP <140 and DBP <90 mm Hg). If BP control was not achieved at the maximum dose of the study medication, a second-line, open-label agent (reserpine, clonidine, or atenolol) and/or a third-line, open-label agent (hydralazine) was added.

After BP goals were met and medication regimens stabilized, clinic visits were scheduled at 3-month intervals during the first year and at 4-month intervals thereafter. BP was measured at each visit. Laboratory measurements, including potassium, glucose, creatinine, total cholesterol, HDL cholesterol, triglycerides, and alanine aminotransferase, were measured after an 8-hour fast at years 1, 2, 4, and 6. The primary outcome for ALLHAT was a composite measure including coronary heart disease death and nonfatal MI. Major secondary outcomes included all-cause mortality; fatal and nonfatal stroke; combined coronary heart disease, defined by coronary revascularization or hospitalized angina; combined cardiovascular disease defined by combined coronary heart disease, stroke, other treated angina, heart failure, or peripheral arterial disease; and end-stage renal disease defined by dialysis, renal transplantation, or death from kidney disease. For this analysis, we focused on 1 secondary outcome, fatal and nonfatal stroke, which included ischemic and hemorrhagic strokes. Outcomes were ascertained at clinic visits and through national databases and death certificates, and hospitalization records were used to support clinician-assigned outcomes.

In the Genetics of Hypertension Associated Treatment (GenHAT) study, variants in candidate genes were typed in ALLHAT participants in an attempt to determine whether these genes interact with antihypertensive medications to modify the risks of developing adverse cardiovascular end points. Of the original ALLHAT sample, 39,114 had DNA available and were included in GenHAT. This research was approved by local institutional review boards, and informed consent was collected from all participants in ALLHAT.

Genotyping

DNA was isolated and immobilized on FTA paper (Fitzco Inc, Maple Plain, MN). Polymerase chain reaction amplification was done on 96-well plates by robotic workstations and multichannel pipettes with positive and negative controls. The MMP3 polymorphism was genotyped in the context of a larger panel of cardiovascular disease candidate gene variants, so each sample was amplified in a multiplex polymerase chain reaction and then hybridized to an array of immobilized, sequence-specific oligonucleotide probes (Roche Molecular Systems, Pleasanton, CA) according to the methods described by Cheng et al.

Statistical Analysis

Hardy-Weinberg equilibrium tests were performed by χ² tests. The MMP3 5A/6A polymorphism was analyzed in multivariate Cox regression models with stroke as the outcome. The polymorphism was initially tested as a 3-level categorical predictor (representing 2 homoygous and 1 heterozygous genotype). In addition, we compared 6A/6A individuals versus those with 6A/5A or 5A/5A, and also 5A/5A individuals versus those with 6A/5A or 6A/6A. Finally, as there is previous evidence suggesting that individuals who are heterozygous for the MMP3 5A/6A polymorphism may have the lowest cardiovascular risk profile, we tested a model comparing heterozygotes with homozygotes for the polymorphism. For the fully adjusted, model potential covariates including age, sex, race, smoking and diabetes status, BP (SBP and DBP), total cholesterol, body mass index, aspirin use, and antihypertensive treatment group were added. These covariates were chosen on the basis of previous evidence suggesting that they might influence stroke risk. Those found significant (P<0.05) were retained in the final model. We also tested for interactions between the MMP3 gene and age, sex, race, diabetes status, and smoking, as these were prespecified subgroups within ALLHAT, and also for interactions between treatment group and the 5A/6A polymorphism. The complete results for each genotypic model and interaction test are shown in Table I in the online-only Data Supplement, available at http://stroke.ahajournals.org.

In total, 78 variants were typed in the GenHAT study, which would normally require probability values on the order of 0.001 to meet Bonferroni-adjusted significance thresholds. Because only the MMP3 variant was analyzed in the current study, less conservative adjustment methods such as computing false-discovery rates were not feasible. We therefore used the Bonferroni-adjusted significance threshold as a general guideline, knowing that it is likely overly conservative.

Because the focus of this analysis was primary stroke prevention, we excluded 9076 participants with a history of stroke or MI at baseline. This also allowed us to use a cumulative incidence analysis approach and minimized potential bias due to changes in lifestyle and risk factor profiles after 1 of these events. Because the doxazosin arm of the trial was halted early, those data are not directly comparable with those of the other 3 arms, and we therefore excluded participants randomized to doxazosin. We tested for pharmacogenetic effects of the MMP3 variant on that drug, however, in a subset of the data that only contained information collected...
The results of the ALLHAT trial with regard to stroke have been previously published. In brief, rates of stroke were presented do not include data from the doxazosin group. All other results before the time that the doxazosin arm was halted. All other results including the doxazosin group.

### Results

The results of the ALLHAT trial with regard to stroke have been previously published. In brief, rates of stroke were higher in patients randomized to lisinopril than chlorthalidone (6.3% vs 5.6%; relative risk = 1.15; 95% CI, 1.02 to 1.30). This finding was primarily observed in black participants and was probably mediated, at least in part, by higher a BP in black subjects assigned to lisinopril. The number of individuals with complete genotype and phenotype information, after excluding 9076 individuals with a history of stroke or MI prior to baseline and those randomized to doxazosin, was 21,309. The average follow-up time was 4.6 years. Individuals with the 5A/6A genotype had the lowest unadjusted stroke rates (6.8 per 1000 person-years [PYs]), followed by 5A/5A individuals (7.5 per 1000 PYs). Individuals with the 6A/6A genotype had the highest stroke rates (11.1 per 1000 PYs). Table 1 shows the means and standard deviations of baseline levels of continuous traits and percentages for categorical variables by MMP3 5A/6A genotype. The means and percentages for potential confounding factors were highly similar across genotypic classes. Age, sex, black race, SBP, DBP, total cholesterol, current smoking, and diabetes status were significant stroke predictors (P<0.05) and were retained as covariates in final models.

MMP3 allele frequencies differed significantly by race, with 5A alleles much more common in European Americans (EAs). Table 2 shows the 5A/6A genotype frequencies by race. The overall stroke rate was 8.2 per 1000 PYs in the whole sample and 8.0 per 1000 PYs in people with no previous stroke or MI. There was no significant association between any MMP3 genotype and stroke rate after multivariate adjustment. Also, black participants showed a small but significantly greater response (2.2-mm Hg change in SBP between baseline and 6 months, P<0.0001) to treatment compared with a reduction in SBP in other race groups after adjustment for multiple factors including baseline SBP. The MMP3 polymorphism was not in Hardy-Weinberg equilibrium in blacks (P=0.008) or EAs (P=0.0004).

In light of the difference in allele frequency between EAs and blacks and the apparent interaction between treatment and genotype, we wanted to determine whether race could act as a surrogate for genotype information to inform first-line treatment options. To do so, we compared the fit between a model containing genotype×treatment interaction terms and a model containing a genotype×treatment term and a genotype×race term, but the model fit was not significantly improved. Also, the race×treatment interaction term was highly significant, with blacks taking lisinopril showing increased stroke risk (hazard ratio [HR]=1.81; 95% CI, 1.33 to 2.45; P=0.0002). These analyses indicate that race may be a valid surrogate for MMP genotype for informing treatment choice. We also tested for the genotype×treatment interaction in the black and EA groups separately. The interaction results were neither significant nor distinguishable from the combined race results (as determined by the overlap of the 95% CIs from the HRs). These results are shown in Table 1.

There was a nominally significant interaction between MMP3 genotype and antihypertensive treatment group in predicting stroke rates, although the associated probability values did not meet a Bonferroni-adjusted significance threshold. The Figure shows a plot of stroke HR by treatment group and genotype, illustrating the observed interaction. Each combination of genotype and drug treatment was compared with a common reference group, 6A/6A individuals randomized to chlorthalidone. In a multivariate-adjusted model, the interaction term between 5A/6A genotype and lisinopril treatment was not significant (HR=0.74; 95% CI, 0.53 to 1.04; P=0.08), but the interaction term for 5A/5A individuals taking lisinopril was nominally significant (HR=0.51; 95% CI, 0.31 to 0.85; P=0.009). There were no pharmacogenetic differences in stroke rate by genotype in patients taking amlodipine versus chlorthalidone, nor doxazosin versus chlorthalidone. Also, there were no main effects of MMP3 genotype on stroke rate in any of the subgroups, nor were there any significant genotype×subgroup interactions after correcting for multiple tests.

The HRs for stroke and probability values associated with the MMP3-lisinopril versus chlorthalidone interaction terms were similar whether or not we adjusted for the change in BP.
blacks.

ethnic groups. The greater proportion of heterozygotes in EA
5A alleles being much more common in EAs than in the other
ethnic groups, with
sample showed marked differences in several other factors
across ethnic groups. The most striking was the difference in
rates, consistent with previous studies of the variant's effect
found that the 5A/6A heterozygotes had the lowest stroke
mediated by MMP3 genotype. Although there was no signif-
icant association between MMP3 genotype and stroke, we
compared with chlorthalidone. This effect may be partially
mediated by MMP3 genotype, 5.8% of the chlorthalidone
group were also taking a calcium channel blocker and 9.3%,
an angiotensin-converting enzyme inhibitor in addition to the
randomized drug at 5 years. In the lisinopril group, 15.7%
were taking an angiotensin-converting enzyme inhibitor in addition to the
lisinopril and chlorthalidone, 5.8% of the chlorthalidone
addition, at both 1 and 5 years, more participants assigned to
chlorthalidone and amloidipine continued the study medica-
tion than did participants who were assigned to lisinopril. In
addition, at both 1 and 5 years, more participants assigned to
lisinopril received open-label medication (32.6% at year 1
and 43.0% at year 5) than did those assigned to chlorthalidone
(26.7% at year 1 and 40.7% at year 5) or amloidipine (25.9%
at year 1 and 39.5% at year 5). In the ALLHAT cohort,
among the 2 treatment groups of interest for this analysis,
lisinopril and chlorthalidone, 5.8% of the chlorthalidone
group were also taking a calcium channel blocker and 9.3%,
an angiotensin-converting enzyme inhibitor in addition to the
randomized drug at 5 years. In the lisinopril group, 15.7%
were taking an angiotensin-converting enzyme inhibitor with
a diuretic at 5 years.13 The most common second-line agent
for all race and treatment subgroups was atenolol (21% to
29%), followed by hydralazine (8% to 22%). In the chlortha-
lideone group, 25% of black and 35% of nonblack participants
were prescribed atenolol. Among blacks, 25% of the lisino-
pril group received open-label medication (32.6% at year 1
and 43.0% at year 5) or amlodipine (25.9% at year 1 and 39.5% at year 5). In the ALLHAT cohort,
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lisinopril and chlorthalidone, 5.8% of the chlorthalidone
group were also taking a calcium channel blocker and 9.3%,
an angiotensin-converting enzyme inhibitor in addition to the
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for all race and treatment subgroups was atenolol (21% to
29%), followed by hydralazine (8% to 22%). In the chlortha-
lideone group, 25% of black and 35% of nonblack participants
were prescribed atenolol. Among blacks, 25% of the lisino-
pril group received a diuretic and 17%, a calcium channel
blocker. Among nonblacks, a diuretic was prescribed for 21%
of lisinopril participants.25

Discussion

We found a novel pharmacogenetic effect of the MMP3
genotype for stroke outcomes, and our findings suggest that
angiotensin-converting enzyme inhibition is a more effective
treatment than chlorthalidone for hypertensives homozygous
for the MMP3 5A allele, whereas chlorthalidone is more
efficacious than lisinopril for hypertensives heterozygous for
the 6A allele. The mechanism for this pharmacogenetic effect
is not entirely clear. Previous data indicate that 6A alleles
are located under expression levels, greater matrix depo-
sition, and more rapid progression of atherosclerosis, whereas
homozygosity for the 5A allele leads to overexpression and
plaque instability. Although not replicated in this subset of
the data, ALLHAT results indicated that in the lisinopril
group, there was a significantly increased risk of stroke
compared with chlorthalidone. This effect may be partially
mediated by MMP3 genotype. Although there was no signif-
icant association between MMP3 genotype and stroke, we
found that the 5A/6A heterozygotes had the lowest stroke
rates, consistent with previous studies of the variant’s effect
on various cardiovascular traits.10,12–22

In addition to the expected difference in stroke rates
between black and EA participants, this large, multiethnic
sample showed marked differences in several other factors
across ethnic groups. The most striking was the difference in
MMP3 5A/6A allele frequencies across ethnic groups, with
5A alleles being much more common in EAs than in the other
ethnic groups. The greater proportion of heterozygotes in EA
participants may explain part of the increased stroke rates in
blacks.

Table 3. Compliance With Randomized Study Drug and Use of
Second-Line Agents at 1 and 5 Years of Follow-Up

<table>
<thead>
<tr>
<th>Drug</th>
<th>Compliant at Year 1</th>
<th>Compliant at Year 5</th>
<th>Additional Drugs at Year 1</th>
<th>Additional Drugs at Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>84%</td>
<td>72%</td>
<td>27%</td>
<td>41%</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>78%</td>
<td>62%</td>
<td>33%</td>
<td>43%</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>79%</td>
<td>27%</td>
<td>31%</td>
<td>46%</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>84%</td>
<td>73%</td>
<td>26%</td>
<td>40%</td>
</tr>
</tbody>
</table>

There were differences in compliance rates between some
of the study drugs and also in the number of participants
requiring a second, open-label treatment. Doxazosin and
lisinopril had lower compliance rates than did the other drugs,
as well as higher rates of additional medications required.

Strengths and Limitations

These analyses represent the largest sample to date used to
test the MMP3 5A/6A promoter polymorphism for associa-
tion with stroke and for interaction with antihypertensive
treatment. Because this was a randomized, prospective study,
we avoided the limitations of case-control designs while
retaining sufficient power to detect genetic associations and
interactions with treatment and lifestyle factors.

Despite these strengths, some limitations exist. First, no
differentiation was made between stroke subtypes, and het-
erogeneity within the combined stroke phenotype could have
limited our power to detect an association. However, because
all stroke subtypes are caused in part by atherosclerosis, the
pathway through which MMP3 acts, any power loss would
likely be minimal. Second, although previous evidence shows
that MMP3 genotype changes expression level, we had no expression data to validate this in the GenHAT sample.

Although we tested for stroke risk associated with a single genetic polymorphism with well-documented effects on gene expression and multiple cardiovascular disease, we tested several genetic models and for interactions with several risk factors, and therefore, multiple comparisons become an issue. Given that 4 modes of inheritance (3 with 1 df and 1 with 2 df) were tested, with the addition of a categorical (2 df) genetic model for interactions with 5 variables, we conducted 15 tests in the initial analysis. A simple Bonferroni correction for the tests conducted here would require a probability value of 0.003 for significance, which was not met by any of the tests. To adjust for all 78 tests conducted in the larger GenHAT study would require a threshold of 0.0006. This threshold is likely conservative, as the different genetic models are not independent tests. Also, most of the variants tested in GenHAT have established effects on protein function or expression levels. We therefore assumed more prior evidence for true-positive associations than for the nonfunctional tag single-nucleotide polymorphisms that make up the bulk of markers tested in many genome-wide association studies. Still, the likelihood that these findings are false-positives is not negligible, and independent replication is necessary.

Confounding due to population stratification is also a potential problem. Although analyses were adjusted for black race, there may be additional population strata within race groups. A recent simulation study showed that the magnitude of this bias is small unless extreme differences exist in genotype frequency, and the magnitude of bias decreases as the number of admixed ethnicities increases. In addition, bias due to population stratification may be small when baseline risk differences are small within major categories of admixed ethnicity. Finally, the MMP3 polymorphism was not in Hardy–Weinberg equilibrium in the sample, which could indicate a systematic genotyping error.

Summary
In summary, these data from the GenHAT study show that the MMP3 5A/6A genotype may be a useful genetic marker for determining who should avoid lisinopril in favor of chlorthalidone as first-line treatment for hypertension in terms of stroke prevention. Specifically, our results suggest that lisinopril rather than chlorthalidone may not be as efficacious a hypertension treatment option in patients with the MMP3 6A/6A genotype but is more efficacious in hypertensives with the MMP3 5A/5A genotype. In heterozygotes, lisinopril treatment appears identical to chlorthalidone for stroke prevention, and there was no statistical difference between stroke rates between these drugs among MMP3 5A homozygotes. The observed effects are quite small, however, and would have to be replicated in an independent sample before any changes in treatment are warranted. Our results also indicate that race may be a potential surrogate for MMP3 genotype in informing treatment choice.

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Disclosures
None.

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stratification in case-control association studies of admixed populations.
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Supplementary Data

Pharmacogenetic effect of the stromelysin (MMP3) polymorphism on stroke risk in relation to antihypertensive treatment: The GenHAT Study

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Table S1. Complete results for all genotypic, interaction, and race-stratified models. All models were adjusted for age, gender, AA race, total cholesterol, current smoking, SBP, DBP, and diabetes status except for the race-stratified models which were not adjusted for AA race.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>SE</th>
<th>Chi-Square</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypic Models</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A any vs. none</td>
<td>-0.13</td>
<td>0.08</td>
<td>2.43</td>
<td>0.88</td>
<td>0.12</td>
</tr>
<tr>
<td>6A any vs. none</td>
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<td>0.10</td>
<td>0.00</td>
<td>0.99</td>
<td>0.95</td>
</tr>
<tr>
<td>5A/6A vs. other</td>
<td>-0.15</td>
<td>0.08</td>
<td>3.38</td>
<td>0.87</td>
<td>0.07</td>
</tr>
<tr>
<td>Interaction Tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A/5A x age</td>
<td>0.03</td>
<td>0.01</td>
<td>5.87</td>
<td>1.03</td>
<td>0.02</td>
</tr>
<tr>
<td>5A/6A x age</td>
<td>0.00</td>
<td>0.01</td>
<td>0.20</td>
<td>1.01</td>
<td>0.65</td>
</tr>
<tr>
<td>5A/5A x sex</td>
<td>0.11</td>
<td>0.22</td>
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