Phenome-Wide Association Study (PheWAS) for Detection of Pleiotropy within the Population Architecture using Genomics and Epidemiology (PAGE) Network

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Abstract

Using a phenome-wide association study (PheWAS) approach, we comprehensively tested genetic variants for association with phenotypes available for 70,061 study participants in the Population Architecture using Genomics and Epidemiology (PAGE) network. Our aim was to better characterize the genetic architecture of complex traits and identify novel pleitropic relationships. This PheWAS drew on five population-based studies representing four major racial/ethnic groups (European Americans (EA), African Americans (AA), Hispanics/Mexican-Americans, and Asian/Pacific Islanders) in PAGE, each site with measurements for multiple traits, associated laboratory measures, and intermediate biomarkers. A total of 83 single nucleotide polymorphisms (SNPs) identified by genome-wide association studies (GWAS) were genotyped across two or more PAGE study sites. Comprehensive tests of association, stratified by race/ethnicity, were performed, encompassing 4,706 phenotypes mapped to 105 phenotype-classes, and association results were compared across study sites. A total of 111 PheWAS results had significant associations for two or more PAGE study sites with consistent direction of effect with a significance threshold of \( p < 0.01 \) for the same racial/ethnic group, SNP, and phenotype-class. Among results identified for SNPs previously associated with phenotypes such as lipid traits, type 2 diabetes, and body mass index, 52 replicated previously published genotype-phenotype associations, 26 represented phenotypes closely related to previously known genotype-phenotype associations, and 33 represented potentially novel genotype-phenotype associations with pleitropic effects. The majority of the potentially novel results were for single PheWAS phenotype-classes, for example, for \( \text{CDKN2A/B rs1333049} \) (previously associated with type 2 diabetes in EA) a PheWAS association was identified for hemoglobin levels in AA. Of note, however, \( \text{GALNT2 rs2144300} \) (previously associated with high-density lipoprotein cholesterol levels in EA) had multiple potentially novel PheWAS associations, with hypertension related phenotypes in AA and with serum calcium levels and coronary artery disease phenotypes in EA. PheWAS identifies associations for hypothesis generation and exploration of the genetic architecture of complex traits.


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Introduction

Phenomic approaches are complementary to the more prevalent paradigm of genome-wide association studies (GWAS), which have provided some information about the contribution of genetic variation to a wide range of diseases and phenotypes [1]. While a typical GWAS evaluates the association between the variation of hundreds of thousands, to over a million, genotyped single nucleotide polymorphisms (SNPs) and one or a few phenotypes, a common limitation of GWAS is the focus on a pre-defined and limited phenotypic domain. An alternate approach is that of PheWAS, which utilizes all available phenotypic information and all genetic variants in the estimation of associations between genotype and phenotype [1]. By investigating the association between SNPs and a diverse range of phenotypes, a broader picture of the relationship between genetic variation and networks of phenotypes is possible.

A challenge for PheWAS is the availability of large studies with genotypic data that are also linked to a wide array of high quality phenotypic measurements and traits for study. Biorepositories linked to electronic medical records (EMR) have been an important resource for PheWAS, but these EMR-based studies are often limited to phenotypes and traits commonly collected for clinical use and may represent sets of limited racial/ethnic diversity [2,3]. While there is no U.S. national, population-based cohort [4], several diverse, population-based studies exist with tens of thousands of samples linked to detailed survey, laboratory, and medical data. These large population-based studies have limitations [5], but collectively [6] they offer an opportunity to perform a PheWAS of unprecedented size and diversity.

To capitalize on the potential for collaborative discovery among some of the large population-based studies of the U.S., the National Human Genome Research Institute (NHGRI) funded the Population Architecture using Genomics and Epidemiology (PAGE) network. PAGE includes eight extensively characterized, large population-based epidemiologic studies where data were collected across multiple racial/ethnic groups, supported by a coordinating center [7], providing an exceptional opportunity to pursue PheWAS with a large number of SNPs, and thousands of phenotypic measurements including a wide range of common diseases, risk factors, intermediate biomarkers and quantitative traits in diverse populations. Herein, we illustrate the feasibility and utility of the PheWAS approach for large population-based studies and demonstrate that PheWAS provides information on, and exposes the complexity of, the relationship between genetic variation and interrelated and independent phenotypes. We have found PheWAS results to replicate previously identified genotype-phenotype associations with the exact phenotype in previous associations or closely related phenotypes, as well as a series of novel genotype-phenotype associations. This data exploration method exposes a more complete picture of the relationship between genetic variation and phenotypic outcome. PheWAS provides the unbiased, high throughput design achieved by GWAS in the genome and phenotype domains simultaneously. This approach changes the paradigm of phenotypic characterization and allows for exploratory research in both genomics and phenomics.

Results

Data from five PAGE study sites were available for this PheWAS: Epidemiologic Architecture for Genes Linked to Environment (EAGLE) using data from the National Health and Nutrition Examination Surveys (NHANES); the Multietnic Cohort Study (MEC); the Women's Health Initiative (WHI); and two studies of the Causal Variants Across the Life Course (CALiCo) group: the Cardiovascular Health Study (CHS) and Atherosclerosis Risk in Communities (ARIC). Text S1 provides full information on study design, phenotype measurement, and genotyping for each study. These studies collectively include four major racial/ethnic groups: European Americans (EA), African Americans (AA), Hispanics/Mexican Americans (H), and Asian/Pacific Islanders (API). All PAGE study sites included both males and females, except for WHI (which includes only women). Table 1 provides an overview of the sample sizes by PAGE study site as well as the number of SNPs and phenotypes available for this PheWAS. Sample size and the number of phenotypes varied across studies, and the sample size for various phenotypes within each study varied dependent on the number of individuals for which a given phenotype was measured. The number of phenotypes available for this PheWAS ranged within studies from 63 (MEC) to 3,363 (WHI). Study sites also had differing numbers of genotyped SNPs, and Table S1 contains the list of all SNPs available for two or more sites in this study, arranged by previously associated phenotypes. The PAGE network has focused on characterization of well-replicated variants across multiple race/
In phenome-wide association studies (PheWAS) all potential genetic variants in a dataset are systematically tested for association with all available phenotypes and traits that have been measured in study participants. By investigating the relationship between genetic variation and a diversity of phenotypes, there is the potential for uncovering novel relationships between single nucleotide polymorphisms (SNPs), phenotypes, and networks of interrelated phenotypes. PheWAS also can expose pleiotropy, provide novel mechanistic insights, and foster hypothesis generation. This approach is complementary to genome-wide association studies (GWAS) that test the association between hundreds of thousands, to over a million, single nucleotide polymorphisms and a single phenotype or limited phenotypic domain. The Population Architecture using Genomics and Epidemiology (PAGE) network has measures for a wide array of phenotypes and traits, including prevalent and incident status for clinical conditions and risk factors, as well as clinical parameters and intermediate biomarkers. We performed tests of association between a series of genome-wide association study (GWAS)--identified SNPs and a comprehensive range of phenotypes from the PAGE network in a high-throughput manner. We replicated a number of previously reported associations, validating the PheWAS approach. We also identified novel genotype-phenotype associations possibly representing pleiotropic effects.

**Author Summary**

In phenome-wide association studies (PheWAS) all potential genetic variants in a dataset are systematically tested for association with all available phenotypes and traits that have been measured in study participants. By investigating the relationship between genetic variation and a diversity of phenotypes, there is the potential for uncovering novel relationships between single nucleotide polymorphisms (SNPs), phenotypes, and networks of interrelated phenotypes. PheWAS also can expose pleiotropy, provide novel mechanistic insights, and foster hypothesis generation. This approach is complementary to genome-wide association studies (GWAS) that test the association between hundreds of thousands, to over a million, single nucleotide polymorphisms and a single phenotype or limited phenotypic domain. The Population Architecture using Genomics and Epidemiology (PAGE) network has measures for a wide array of phenotypes and traits, including prevalent and incident status for clinical conditions and risk factors, as well as clinical parameters and intermediate biomarkers. We performed tests of association between a series of genome-wide association study (GWAS)--identified SNPs and a comprehensive range of phenotypes from the PAGE network in a high-throughput manner. We replicated a number of previously reported associations, validating the PheWAS approach. We also identified novel genotype-phenotype associations possibly representing pleiotropic effects.

Table 1. Study Descriptions.

<table>
<thead>
<tr>
<th>Study</th>
<th>PMID</th>
<th>Age Range</th>
<th>Sex</th>
<th>EA</th>
<th>AA</th>
<th>H</th>
<th>API</th>
<th># SNPs</th>
<th># Phenotypes</th>
<th>Total # of Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>[36]</td>
<td>45–64</td>
<td>M/F</td>
<td>11,068</td>
<td>4,007</td>
<td>NA</td>
<td>NA</td>
<td>17</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>CHS</td>
<td>[37]</td>
<td>65–100 at baseline</td>
<td>M/F</td>
<td>4,487</td>
<td>820</td>
<td>NA</td>
<td>NA</td>
<td>151</td>
<td>116</td>
<td>NA</td>
</tr>
<tr>
<td>EAGLE</td>
<td>[38]</td>
<td>12–95</td>
<td>M/F</td>
<td>2,628</td>
<td>2,107</td>
<td>2,071</td>
<td>NA</td>
<td>7</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>MEC</td>
<td>[39]</td>
<td>45–75</td>
<td>M/F</td>
<td>3,893</td>
<td>4,749</td>
<td>6,863</td>
<td>6,810</td>
<td>33</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>WHI</td>
<td>[40]</td>
<td>50–79 at baseline</td>
<td>F</td>
<td>13,334</td>
<td>4,274</td>
<td>2,023</td>
<td>927</td>
<td>14</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: European American (EA), African American (AA), Hispanic/Mexican American (H), Asian/Pacific Islander (API).

1 Data from PAGE studies available for this PheWAS include: Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Epidemiologic Architecture for Genes Linked to Environment (EAGLE), Multiethnic Cohort (MEC), and Women’s Health Initiative (WHI). PAGE study sites and study design descriptions are in Text S1.

2 Pubmed ID of study description manuscript for each study.

3 Maximum sample size and Minimum sample size are dependent both on who was genotyped and who had a specific phenotype measured. Not all phenotypic measurements were available for all participants within each study. This is the total number of SNPs available for each study. Table S1 has the list of these SNPs for each study, genotyped across two or more studies. This includes the number of phenotypes transformed and untransformed, as well as categorical phenotypes divided into binary phenotypes, full description in Materials and Methods.

4 Total number of tests of association calculated for each study, in parenthesis is the total number of associations with p < 0.01 reflecting the variability in both the number of phenotypes available for study as well as the number of SNPs genotyped by each PAGE study site. As expected, the total number of significant tests of association (p < 0.01) represented a fraction of the total number of tests performed.

Results from these tests of association were then compared across study sites to identify overlapping significant associations, as these results most likely represent robust findings. To facilitate determining overlapping significant associations, similar phenotypes that existed across more than one study were binned into 105 distinct phenotype-classes. For some phenotypes, the specific phenotype existed across more than one PAGE study, such as for the phenotype “Hemoglobin”, where hemoglobin measurements were available for ARIC, CHS, EAGLE, and WHI. Other groups of phenotypes binned within phenotype-classes were within similar phenotypic domains but were not represented in exact same form across studies. Table S2 contains a list of the study level phenotypes, the study from which the phenotype is available, and the phenotype-class for each phenotype that overlapped with another study.

The same or similar phenotypes may or may not have been collected by each PAGE study. Thus, the number of studies that were available for comparison of results across studies varied from one phenotype-class to another phenotype-class. Table 2 presents the number of results where at least two of five independent studies had SNP-phenotype associations with p < 0.01 for single phenotype-class and single race/ethnicity group, compared to the total number of SNP-phenotype association tests performed. For example, >8,500 tests of association for the same SNP and same phenotype were available from two PAGE study sites whereas only 906 and 58 tests of association were available from four and five PAGE study sites, respectively. There were 3 results where two or more of the groups had a SNP-phenotype association p < 0.01 for a single phenotype class across 5 groups represented.

For this PAGE-wide PheWAS, tests of association were considered significant across PAGE study sites where two or more phenotypes in the same phenotype-class in the same racial/ethnic group passed a significance threshold of p < 0.01 with a consistent direction of genetic effect. Based on these criteria, a total of 111

[102x297]Study Descriptions.

[128x243]# Total

[464x460], [468x334], [471x460], [475x334], [476x692], [486x243], [488x243], [507x243], [518x387], [526x387], [545x660], [566x650], [597x608], [629x650], [639x650], [650x650], [681x650], [723x650].
PheWAS associations were identified (Table S3). Overall, among the 111 significant PheWAS associations identified, 52 PheWAS results replicated previously published genotype-phenotype associations (Table S4), 26 represented phenotype-classes closely related to previously known genotype-phenotype associations (Table 3), and 33 represented novel genotype-phenotype associations (Table 4).

Known Associations—Validating the PheWAS Approach

Almost half of the PAGE PheWAS results (52/111; 48%) replicated previously known genotype-phenotype associations. These replicated results serve as positive controls and demonstrate that the high-throughput PheWAS approach is feasible and valid. As an example, low-density lipoprotein cholesterol (LDL-C) has been previously associated with rs4420638 near APOE/APOC1/C11P1/C2/C4 in European Americans [8,9]. In the PAGE PheWAS, a significant association between the same SNP and LDL-C phenotypes of the “LDL-C” phenotype-class in European Americans as reported in the literature [8,9] was observed in two PAGE study sites, with the same direction of effect (β) as well as a third PAGE site with near significant results: ARIC (p = 1.27 x 10^{-15}, β = -5.75), WHI (p = 7.89 x 10^{-12}, β = -7.06), and WHI (p = 0.06, β = -4.15). Figure 1 shows the significant PheWAS LDL-C results, as well as other associations considered significant for rs4420638 across PAGE study sites for other phenotype-classes in a similar racial/ethnic group passed a significance threshold of p<0.01 with a consistent direction of genetic effect.

related Associations

Approximately one-fourth of the PAGE PheWAS results (26/111; 23%) represented SNP-phenotype associations in phenotype-classes closely related to previously known genotype-phenotype associations. For example, rs10757278 near CDKN2A/CDKN2B has been robustly associated with myocardial infarction (MI) [10,11]. In this PheWAS, rs10757278 was associated with the “Cardiac” phenotype-class, but also with the related phenotype-classes of “Artery Treatment” and “Angina”. Specifically, rs10757278 was associated with phenotypes in the Artery Treatment phenotype-class, such as “percutaneous transluminal coronary angioplasty” (WHI, p = 2.86 x 10^{-16}, β = -0.17, EA), and “coronary bypass surgery” (CHS, p = 9.60 x 10^{-3}, β = -0.26, EA). The SNP rs10757278 was also associated with phenotypes in the Angina phenotype-class, such as presence or absence of angina (WHI, p = 6.59 x 10^{-3}, β = -0.14, EA) and the phenotype “Ever see a doctor because of chest pain?” (ARIC, p = 4.44 x 10^{-3}, β = -0.31, EA). Replication of association of this SNP with previously known phenotypes were also found with the phenotype-class “Cardiac”, with phenotypes such as “MI (Y/N)” (WHI, p = 1.39 x 10^{-4}, β = -0.11, EA), and “MI status at baseline (Y/N)” (CHS, p = 6.35 x 10^{-3}, β = -0.18, EA). Significant PheWAS associations at p<0.01 for rs10757278 are plotted by phenotype in Figure 2, as well as additional results at p<0.05.

Another example of PheWAS associations for phenotype-classes closely related to known genotype-phenotype associations existed for rs599839 near the CELSR2/PSRC1/SORT1 gene cluster. The SNP rs599839 has been associated with serum LDL cholesterol levels [8,12–14], and coronary artery disease [13,15]. In our PheWAS, associations were found for the “LDL-C” phenotype-class, as well the coronary artery disease related “Angina” and lipid related “HDL-C” phenotype-classes, including specific phenotypes such as “angina, presence or absence of” (WHI, p = 2.10 x 10^{-4}, β = 0.25, EA), and “HDL-C” (WHI, p = 1.23 x 10^{-3}, β = -0.04, AA). As expected, a significant association was also identified for the LDL-C level related phenotype “LDL-C (mg/dl)” (ARIC, p = 5.25 x 10^{-22}, β = 6.42 EA). Significant PheWAS associations at p<0.01 for rs599839 are plotted by phenotype in Figure 3, as well as additional results at p<0.05.

Potentially Novel Associations

PheWAS results were considered novel, if the significant phenotype-class associations varied substantially from the previously reported GWAS and candidate gene studies. Approximately one-third of the PAGE PheWAS results (33/111; 30%) represented novel genotype-phenotype-class associations. Further research will be required to determine the further validity of these exploratory results.

The most statistically significant of the novel phenotype-class associations identified by this PheWAS include multiple associations involving phenotype-classes for hematologic traits in African Americans (Figure 4). SNPs rs599839 (CELSR2/PSRC1), rs10923931 (NOTCH2), rs2228145 (IL6R), rs2144300 (GALNT2), rs1075728 (CDKN2A/CDKN2B), and rs7901695 (TCP7L2) were each associated with white blood cell count phenotypes among AA (significant p-values ranging 7.96 x 10^{-3} to 9.99 x 10^{-15}). IL6R rs2228145 was also associated with neutrophils and lymphocyte numbers in AA with p-values ranging from 2.44 x 10^{-4} to 4.66 x 10^{-10}. These SNPs were previously associated with LDL-C, total cholesterol levels, and coronary artery disease (rs599839).
<table>
<thead>
<tr>
<th>Nearest Gene</th>
<th>SNP ID</th>
<th>CA (CAF²)</th>
<th>Phenotypes²</th>
<th>Associated Phenotype Class²</th>
<th>Ethnicity²</th>
<th>P-Values⁶</th>
<th>Beta(SE)⁷</th>
<th>Sample Size⁶</th>
<th>Substudies⁹</th>
<th>Substudy Count¹⁰</th>
<th>Previously Associated Phenotype¹¹</th>
<th>References¹²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELSR2, PSRC1</td>
<td>RS599839 A (0.8)</td>
<td>Ever hospitalized for chest pain? (Y/N)</td>
<td>ANGINA</td>
<td>EA</td>
<td>2.57e-3</td>
<td>0.55(0.18)</td>
<td>568</td>
<td>ARIC</td>
<td>3</td>
<td>Coronary Artery Disease, LDL cholesterol, Total cholesterol</td>
<td>18262040, 18193043, 18179892, 17634449, 18193044</td>
<td></td>
</tr>
<tr>
<td>CDKN2A, CDKN2B</td>
<td>RS1333049 C (0.5)</td>
<td>Chest pain or discomfort? (Y/N)</td>
<td>ANGINA</td>
<td>EA</td>
<td>4.69e-3</td>
<td>0.08(0.03)</td>
<td>9338</td>
<td>ARIC</td>
<td>3</td>
<td>Coronary Artery Disease, Type 2 Diabetes, Hypertension</td>
<td>17554300, 17634449</td>
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</tr>
<tr>
<td>LPL</td>
<td>RS6586891 A (0.6)</td>
<td>LN1 Total triglycerides in mmol/l</td>
<td>Serum Triglycerides</td>
<td>EA</td>
<td>7.76e-7</td>
<td>-0.02(4.75e-3)</td>
<td>9326</td>
<td>ARIC</td>
<td>3</td>
<td>HDL Cholesterol</td>
<td>18193043</td>
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<tr>
<td>CDKN2A, CDKN2B</td>
<td>RS10757278 A (0.5)</td>
<td>Ever had pain/discomfort in your chest (Y/N)</td>
<td>ANGINA</td>
<td>EA</td>
<td>5.96e-3</td>
<td>-0.12(0.04)</td>
<td>4474</td>
<td>CHS</td>
<td>3</td>
<td>Myocardial infarction</td>
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<tr>
<td>LDLR</td>
<td>RS6511720 G (0.9)</td>
<td>Total cholesterol (mmol/l)</td>
<td>Serum Cholesterol</td>
<td>EA</td>
<td>6.84e-16</td>
<td>0.18(0.02)</td>
<td>10891</td>
<td>ARIC</td>
<td>2</td>
<td>LDL Cholesterol</td>
<td>18193043</td>
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Table 3. PheWAS Tests of Association: Related Associations.
<table>
<thead>
<tr>
<th>Nearest Gene</th>
<th>SNP ID</th>
<th>CA(^1), (CAF(^2))</th>
<th>Phenotypes(^3)</th>
<th>Associated Phenotype Class(^4)</th>
<th>Ethnicity(^5)</th>
<th>P-Values(^6)</th>
<th>Beta(SE)(^7)</th>
<th>Sample Size(^8)</th>
<th>Substudies(^9)</th>
<th>Substudy Count(^10)</th>
<th>Previously Associated Phenotype(^11)</th>
<th>References(^12)</th>
</tr>
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<tbody>
<tr>
<td>LN1</td>
<td>Total cholesterol (mg/dl)</td>
<td>1.87e-5</td>
<td>0.05(0.01)</td>
<td>924</td>
<td>WHI</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>PCSK9</td>
<td>Total cholesterol (mmol/l)</td>
<td>1.13e-16</td>
<td>0.46(0.06)</td>
<td>10833</td>
<td>ARIC</td>
<td>2</td>
<td>LDL Cholesterol, lipids</td>
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<tr>
<td>APOE, APOC1, APOC4, APOC2</td>
<td>Total cholesterol (mmol/l)</td>
<td>1.18e-6</td>
<td>2</td>
<td>0.22(0.04)</td>
<td>12430</td>
<td>WHI</td>
<td></td>
<td></td>
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<tr>
<td>TMEM18</td>
<td>Hip circumference cm</td>
<td>5.99e-3</td>
<td>0.62(0.22)</td>
<td>4456</td>
<td>CHS</td>
<td>2</td>
<td>Body Mass Index</td>
<td>19079261</td>
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<tr>
<td>TMEM18</td>
<td>Hip circumference cm</td>
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<td>0.59(0.02)</td>
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<td>WHI</td>
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<tr>
<td>TMEM18</td>
<td>Hip circumference cm</td>
<td>6.85e-3</td>
<td>5.84e-3</td>
<td>4456</td>
<td>CHS</td>
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<tr>
<td>TMEM18</td>
<td>Hip circumference cm</td>
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<td>5.80e-3</td>
<td>13272</td>
<td>WHI</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMEM18</td>
<td>High blood pressure ever diagnosed?</td>
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<td>Total cholesterol in mmol/l</td>
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<td>APOE, APOC1, APOC4, APOC2</td>
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<td>A (0.8)</td>
<td>LN1 dietary cholesterol (mg) (dietary consumption)</td>
<td>Cholesterol MG</td>
<td>EA</td>
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<td>LN1 hip circumference cm</td>
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Table 3. Cont.

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<th>P-Values⁶</th>
<th>Beta(SE)⁷</th>
<th>Sample Size⁸</th>
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<th>Substudy Count¹⁰</th>
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<td>Baseline glucose (mg/dl)</td>
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<td>Circulating glucose value in mg/dl</td>
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</table>

Related associations that met the criteria for PheWAS significance are given here, sorted by the number of PAGE site replications for a given phenotype class. Related associations were defined as SNPs significantly associated in this PheWAS with phenotype classes closely related to phenotypes among known associations. Significance was defined as a test of association with p ≤ 0.01 observed in two or more PAGE studies for the same SNP, phenotype class, and race/ethnicity and consistent direction of effect when relevant. For each, the nearest gene(s), the SNP rs number, coded allele (CA) and frequency (CAF), associated phenotypes, phenotype class, race/ethnicity, p-values, genetic effect/beta values (standard error; SE), sample size, substudies, number of substudies with results passing our p-value cutoff, the previously associated phenotype for that SNP, and references for the previously associated phenotypes are given.

¹Coded allele
²Coded allele frequency
³Associated phenotypes for individual results
⁴Phenotype class
⁵Race/ethnicity for association, abbreviations: African American (AA), European American (EA), Mexican American/Hispanic (H)
⁶p Values of results that passed p ≤ 0.01 threshold in order of the associated phenotypes
⁷Beta and standard error in order of the associated phenotypes
⁸Sample size in order of the associated phenotypes
⁹Studies with the significant result, in order of the associated phenotypes
¹⁰Total number of studies with at least one result passing p-value threshold for specific phenotype class and SNP
¹¹Previously reported associated phenotypes for SNP
¹²PubMed ID’s for previously associated phenotypes

doi:10.1371/journal.pgen.1003087.t003
Table 4. PheWAS Tests of Association: Novel Associations.

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<th>Nearest Gene</th>
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<th>Associated Phenotype Class</th>
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<th>Substudies</th>
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<td>CELSR2,PSRC1</td>
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<td>LN1 white blood count (×1000/cubic mm)</td>
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\(^3\)CA: Common Allele; CAF: Common Allele Frequency

\(^4\)Previously Associated Phenotype

\(^5\)Ethnicity

\(^6\)P-Values

\(^7\)Beta (SE)

\(^8\)Phenotypes

\(^9\)Sample Size

\(^10\)Substudies

\(^11\)Substudy Count

\(^12\)References
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**Table 4. Cont.**
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Novel associations that met the criteria for PheWAS significance are given here, sorted by the most to least number of PAGE study sites available. Related associations were defined as SNPs significantly associated in this PheWAS with phenotype-classes closely related to phenotypes among known associations. Significance was defined as a test of association with p<0.01 observed in two or more PAGE studies for the same SNP, phenotype class, and race/ethnicity and consistent direction of effect when relevant. For each, the nearest gene(s), the SNP rs number, coded allele (CA) and frequency (CAF), associated phenotypes, phenotype-class, race/ethnicity, p-values, genetic effect/beta values (standard error; SE), sample sizes, substudies, number of substudies with results passing our p-value cutoff, the previously associated phenotype for that SNP, and references for the previously associated phenotypes are given.

<sup>1</sup>Coded Allele.

<sup>2</sup>Coded allele frequency.

<sup>3</sup>Associated phenotypes.

<sup>4</sup>Phenotype-class.

<sup>5</sup>Race/ethnicity for association, abbreviations: African American (AA), European American (EA), Mexican American/Hispanic (H).

<sup>6</sup>P-Values of results that passed p<0.01 threshold in order of the associated phenotypes.

<sup>7</sup>Beta and standard error in order of the associated phenotypes.

<sup>8</sup>Samples size in order of the associated phenotypes.

<sup>9</sup>Studies with the significant result, in order of the associated phenotypes.

<sup>10</sup>Total number of studies with at least one result passing p-value threshold for specific phenotype class and SNP.

<sup>11</sup>Previously reported associated phenotypes for the SNP.

<sup>12</sup>Previous ID's for previously associated phenotypes.

doi:10.1371/journal.pgen.1003087.t004
Figure 1. PheWAS associations for rs4420638 near APOC1. SNP rs4420638 has previously been associated with LDL cholesterol levels, triglycerides, Alzheimer’s disease, coronary artery disease, and sporadic late onset Alzheimer’s. The length of the lines correspond to $-\log_{10}(p$-value), and the lines are plotted clockwise starting at top for the association with the smallest $p$-value. Lines are labeled with the study-specific phenotype, the PAGE study, racial/ethnic group, and direction of effect (+ or −). Red lines represent associations at $p<0.001$. "LNI" indicates the phenotype had 1 added to the variable, and then the variable was natural log transformed. The PheWAS phenotypes significantly associated with this SNP varied, with known associations for LDL cholesterol levels, as well as the related phenotypes “Total cholesterol (mmol/l)” and “Dietary cholesterol (mg)”, and novel phenotypes such as “Baseline glucose (mg/dl)”. doi:10.1371/journal.pgen.1003087.g001

Aside from hematologic traits, the most significant novel association identified in this PheWAS was identified for phenotypes in the phenotype-class “High blood pressure ever” (ARIC, $p = 1.61 \times 10^{-6}$), “Coronary artery bypass graft (CABG)” (WHI, $p = 2.46 \times 10^{-3}$), “Pills for hypertension ever?” (WHI, $8.27 \times 10^{-4}$), and “Artery treatment”, specifically the phenotypes “Coronary artery bypass graft (CABG)” (WHI, $p = 2.46 \times 10^{-3}$), “Aortic aneurysm repair” (WHI, $5.49 \times 10^{-3}$), “Duffy null allele” (CDKN2A/B, $p = 0.24$), and “Forced Expiratory Volume in 3 Seconds (FEV3)” (CHS, $p = 2.6 \times 10^{-5}$). Indeed, rs2144300, previously associated with HDL-C in European Americans and African Americans [13,24], has not previously been associated with lung function or asthma quantitative traits. Interestingly, rs2144300 was also associated with phenotypes in the “Hypertension” phenotype-class among African Americans in this PheWAS (specifically the phenotypes were “High blood pressure ever diagnosed?” (ARIC, $p = 1.61 \times 10^{-6}$), “Pills for hypertension ever?” (WHI, $8.27 \times 10^{-4}$), and “Artery treatment”, specifically the phenotypes “Duffy null allele” (CDKN2A/B, $p = 0.24$).
The PheWAS results herein present the result of tests of association between a large number of SNPs and an extensive range of phenotypes and traits available within five studies of the PAGE network. For this first PAGE PheWAS analysis we have emphasized associations that replicated across two or more independent PAGE studies for the same phenotype class and same race/ethnicity. Most of the robust findings reported here represent previously known genotype-phenotype relationships, but a tantalizing few also represent potentially novel pleiotropic relationships.

The 33 novel results presented here are intriguing, but it is important to emphasize that these first-pass analyses are considered hypothesis-generating, exploratory, and require additional scrutiny before the findings are further considered for follow-up, unlike the directed a priori hypothesis-testing analyses within PAGE that involve SNPs hypothesized to be associated with specific phenotypes. Further analysis of PheWAS results will be on an individual result basis and will include careful phenotype harmonization for traits and outcomes that cross two or more PAGE studies, as well as considerable investigation of the possible effect of covariates such as age, sex, and environmental exposure(s) on the association between genetic variation and phenotypic outcome.

One of the many challenges for the interpretation of PheWAS results is dissecting the genetic effect observed among correlated phenotypes. In some cases, the relationship is likely attributable to a common biological process with known genetic contribution (e.g., body mass index and waist circumference). In other cases, the networks that exist between intermediary and/or outcome related phenotypes add complexity to interpreting association results. For instance, genetic variation may impact the variation of a single range of phenotypes and traits available within five studies of the PAGE network. For this first PAGE PheWAS analysis we have emphasized associations that replicated across two or more independent PAGE studies for the same phenotype class and same race/ethnicity. Most of the robust findings reported here represent previously known genotype-phenotype relationships, but a tantalizing few also represent potentially novel pleiotropic relationships.

The 33 novel results presented here are intriguing, but it is important to emphasize that these first-pass analyses are considered hypothesis-generating, exploratory, and require additional scrutiny before the findings are further considered for follow-up, unlike the directed a priori hypothesis-testing analyses within PAGE that involve SNPs hypothesized to be associated with specific phenotypes. Further analysis of PheWAS results will be on an individual result basis and will include careful phenotype harmonization for traits and outcomes that cross two or more PAGE studies, as well as considerable investigation of the possible effect of covariates such as age, sex, and environmental exposure(s) on the association between genetic variation and phenotypic outcome.

One of the many challenges for the interpretation of PheWAS results is dissecting the genetic effect observed among correlated phenotypes. In some cases, the relationship is likely attributable to a common biological process with known genetic contribution (e.g., body mass index and waist circumference). In other cases, the networks that exist between intermediary and/or outcome related phenotypes add complexity to interpreting association results. For instance, genetic variation may impact the variation of a single
phenotype, but variation in that phenotype could then result in changes in other downstream phenotypes indirectly. Examples of added complexity include obesity leading to impaired immune function [28], and metabolic syndrome where there is a spectrum of risk factors that are all associated with increased risk of cardiovascular disease and type 2 diabetes [25]. As a result, significant associations between a genetic variant and many phenotypes could represent a network or cascade of events. This is a potential interpretation of results found for SNP rs10923931 (\textit{NOTCH2}) in AA, where type 2 diabetes was the previously reported association for this SNP and the novel result was found for hypertension, and type 2 diabetes and hypertension are often a co-occurrence. Further analysis of individual PheWAS results is necessary to conclusively establish the impact of the relationship between phenotypes on significant SNP-phenotype associations.

For our first PAGE PheWAS analysis, we chose to seek replication of results across studies and required the same direction of effect as one approach to reduce the false discovery rate. Significant results can still be found by chance across more than one study. Multiple challenges arise when attempting to get a metric of the type 1 error rate across multiple studies. First, as with individual studies, correlations between phenotypes and previous associations for the SNPs are still present. Also, there are varying type 1 error rates depending on the number of studies available for seeking replication. Quantification of how many results were found with a p-value cutoff, and without a p-value cutoff, depending on the number of studies where replication could be sought (2, 3, 4, or 5) provides some information about the number of significant results we found, in Table 2. Table 1 has the total number of results with and without p-value cutoff for individual studies. It is important to note that in cases where replication could be sought in more than two studies, there were cases where the result replicated in 3 or more studies, further increasing our confidence in the result.

A potential limitation of this study is the granularity of phenotypes within our phenotype classes. The phenotypes within some phenotype classes are the same or extremely similar, such as white blood cell count measurements across studies. However, the phenotype class “Artery Treatment” is broad in terms of the types

![Figure 3. PheWAS associations for rs599839 near CELSR2/PSRC1. This SNP has previously published associations with serum LDL cholesterol levels, total cholesterol, and coronary artery disease. Genotype-phenotype associations are plotted clockwise starting at top for the association with the smallest p-value. The length of the line corresponds to \(-\log_{10}(p\text{-value})\), the longer the line the more significant the result. The study race/ethnicity and phenotype for each tests of association are listed. Red lines represent associations at p < 0.01, and results with p < 0.05 are also plotted in grey to show trends for additional phenotypes. "LN1" indicates the phenotype had 1 added to the variable, and then the variable was natural log transformed. The PheWAS phenotypes significantly associated with this SNP varied, from LDL cholesterol levels (previously published), to lipid level-related phenotypes such as "High cholesterol requiring pills ever". In the case of coronary artery disease, phenotypes with significant results that were related to coronary artery disease included "Ever had pain/discomfort in your chest", and "Hospitalized for chest pain". doi:10.1371/journal.pgen.1003087.g003]
PheWAS for Detection of Pleiotropy in PAGE

PheWAS Hematologic Trait Results

-log10(p value)

beta

CAF

Sample Size

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of phenotypes included, such as presence/absence aortic aneurysm repair and presence/absence of angioplasty of the coronary arteries. For some classes, the replicated results encompass more variation in the phenotypes captured, compared to other results. As a result, significant associations between a genetic variant and all phenotypes in a network may be present. PheWAS is an exploratory and hypothesis generating exercise, thus the choice was made to have a broader match for some groups of phenotypes in order to allow for those phenotypes to be part of the exploration of the data. In addition, misclassification of phenotypes when matching is possible, and thus can limit identification of significant associations across studies. Other potential limitations include sample size/power, study heterogeneity, and the SNPs selected for study. As shown in Table 1, there is much variability across independent PAGE studies. While each PAGE study is sizeable, individual tests of association may be underpowered depending on the availability of the genetic variant, phenotype class, and race/ethnicity. Tests of association that failed to reach statistical significance may represent underpowered genotype-phenotype relationships and will require larger epidemiologic or clinic-based samples to identify. In regards to the potential impact of heterogeneity, we have some cases where replication existed in only two or three studies out of those where replication could be sought. In some instances this may be due to power, but this also may reflect the heterogeneity between studies, such as how various phenotypes are measured in individual studies and variation in mean age across the different studies. Finally, SNPs were originally selected for this study to replicate known genotype-phenotype associations and to generalize them to diverse populations. A comprehensive set of genome-wide “agnostic” SNPs may uncover additional pleiotropic or novel genotype-phenotype relationships not tested here.

Despite the limitations present for this PheWAS, there are multiple strengths within our study. We have had the opportunity to perform a PheWAS of substantial size with an unprecedented diversity of high quality phenotypic measurements and traits, across multiple races/ethnicities. In addition, because of this PheWAS was conducted across multiple independent studies, we were able to identify the most robust genotype-phenotype relationships across studies.

**GALNT2, rs2144300, Coded Allele C**

Figure 4. PheWAS results for blood cell counts and hemoglobin levels. Eleven novel genotype-phenotype-class associations were identified for white blood cell counts and hemoglobin levels collectively. The top track indicates the chromosomal location of each SNP, below that track is a SNP/phenotype identification track containing the SNP ID, as well as the phenotype, phenotype transformation if present (LN1 = ln(1+variable)), and the race/ethnicity for the test population (AA or EA). The next track is a “presence/absence” track, box presence indicates if the SNP was present for ARIC (blue), CHS (red), WHI (orange), or EAGLE (purple). The next tracks are as follows: –log10(p-value), where the each p-value is plotted, the direction of the triangle indicates the direction of effect (triangle pointed up is positive, triangle pointed down is negative), base of the triangle corresponds to the location of the p-value, solid red line is positioned at p-value = 0.01; The next track is magnitude of effect (beta) dotted grey line is positioned at the null; Next are coded allele frequencies (CAF) for each study; Final track is sample size for each test of association.

doi:10.1371/journal.pgen.1003087.g004

Figure 5. PheWAS associations for rs2144300 within GALNT2. The previously published associations for this SNP were with triglyceride and HDL cholesterol levels. Genotype-phenotype associations are plotted clockwise starting at top for the association with the smallest p-value. The length of the line corresponds to –log10(p-value), the longer the line the more significant the result. The study race/ethnicity/and phenotype for each tests of association are listed. Red lines represent associations at p < 0.01, and results with p < 0.05 are also plotted in grey to show trends for additional phenotypes. The novel PheWAS phenotypes significantly associated with this SNP varied, including white blood cell counts, forced vital capacity at three seconds (FEV3), and serum calcium levels.

doi:10.1371/journal.pgen.1003087.g005
Conclusion

This initial PheWAS within PAGE has presented challenges in terms of generating high-throughput tests of association across large epidemiologic studies as well as the synthesis of the resulting data and its eventual interpretation. Even with these limitations, this PheWAS demonstrates the utility of investigating the relationship between genetic variation and an extensive range of phenotypes by validating known genotype-phenotype associations as well as identifying novel genotype-phenotype associations, revealing complex phenotypic relationships and perhaps actual pleiotropy. The utility of this hypothesis-generating approach will continue to improve over time as more samples, variants, and phenotypes/traits across diverse populations are available for study in PAGE and other genomic resources. Larger, richer datasets coupled with methods development promise to more fully reveal the complex nature of genetic variation and its relationship with human diseases and traits.

Methods

Study Populations

All studies were approved by Institutional Review Boards at their respective sites (details are given in Text S1). The Population Architecture using Genomics and Epidemiology (PAGE) study includes the following epidemiologic collections: Atherosclerosis Risk in Communities (ARIC), Coronary Artery Risk in Young Adults (CARIDA), Cardiovascular Health Study (CHS), the Multiethnic Cohort (MEC), the National Health and Nutrition Examination Surveys (NHANES), Strong Heart Study (SHS), and Women’s Health Initiative (WHI). For this PheWAS, data were available from ARIC, CHS, MEC, EAGLE, and WHI (Table 1). The PAGE study design is described in Matise et al [26] and the PAGE PheWAS study design is described in Pendergrass et al [1].
SNP Selection and Genotyping

All SNPs considered for genotyping in PAGE were candidate gene or GWAS-identified variants for phenotypes and traits available in the epidemiologic collections accessed by PAGE study sites. Cohorts and surveys were genotyped using either commercially available genotyping arrays (Affymetrix 6.0, Illumina 370CNV BeadChip), and/or custom mid- and low-throughput assays (TaqMan, Sequenom, Illumina GoldenGate or BeadXpress). Quality control was implemented at each PAGE study site independently. Study specific genotyping details are described in Text S1.

In this PheWAS, data were available for SNPs previously associated with HDL-C, LDL-C, and triglycerides [27], body mass index, obesity [28], type 2 diabetes, glucose, insulin [29], and measures of inflammation (C-reactive protein), among other diseases/traits. A total of 83 SNPs overlapped across at least PAGE study sites: ten were specifically selected for body mass index traits replication, three for C-reactive protein, six for coronary/cardiac traits, three for gout/kidney, 41 for lipids, and 20 for type 2 diabetes. Table S1 lists these SNPs, along with references reporting phenotypic associations from the NHGRI GWAS catalog [30] and the open access database of GWAS results of Johnson et al. 2009 [31]. The NHGRI GWAS catalog was most recently accessed in October, 2011. If no references were available from either of those two sources, a PubMed search was performed to retrieve relevant citations.

Statistical Methods

All tests of association were performed independently by each PAGE study site using the following analysis protocol: Linear or logistic regressions were performed for continuous or categorical dependent variables, respectively, assuming an additive genetic model (0, 1, or 2 copies of the coded allele). For variables with multiple categories, binning was used to create new variables of the form “A versus not A” for each category, and logistic regression was used to model the new binary variable. Linear regressions were repeated following a y to log (y + 1) transformation of the response variable with +1 added to all continuous measurements before transformation to prevent variables recorded as zero from being omitted from analysis. All analyses were stratified by race-ethnicity.

Test of association were calculated for the number of SNPs and phenotypes listed in Table 1. The software used to calculate the associations for each study was as follows: ARIC (StatSoftware), CHS (R [32]), MEC (SAS), MEC (SAS v9.2), WHI (R), EAGLE (SAS v9.2 using the Analytic Data Research by Email (ANDRE) portal of the CDC Research Data Center in Hyattsville, MD).

All association results from the tests of association were reported in standardized templates designed by the PAGE coordinating center to facilitate data sharing. All results were then imported into a relational database (MySQL). The database was also used to match previously reported GWAS data with the SNPs analyzed in this study.

Plotting Significant Results

The software PheWAS-View was developed for data visualization of the PheWAS results as well as for plotting “Sun Plots” [33]. Synthesis-View [34,35] was also used to present results within this manuscript. Both software packages are freely available software for academic users: http://ritchielab.psu.edu/ritchielab/software.

Table 5. Example phenotype-classes and binned subphenotypes within phenotype-classes.

<table>
<thead>
<tr>
<th>Phenotype Class</th>
<th>Study</th>
<th>Sub-phenotype binned within the phenotype-class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>ARIC</td>
<td>Asthma ever diagnosed?</td>
</tr>
<tr>
<td>Asthma</td>
<td>ARIC</td>
<td>Chest wheeze, whistle alot?</td>
</tr>
<tr>
<td>Asthma</td>
<td>ARIC</td>
<td>Chest wheeze, whistle, otherwise?</td>
</tr>
<tr>
<td>Asthma</td>
<td>ARIC</td>
<td>Age at 1st wheezing attack</td>
</tr>
<tr>
<td>Asthma</td>
<td>ARIC</td>
<td>Age asthma started</td>
</tr>
<tr>
<td>Asthma</td>
<td>ARIC</td>
<td>Age asthma stopped</td>
</tr>
<tr>
<td>Asthma</td>
<td>ARIC</td>
<td>Short of breath wheezing attack?</td>
</tr>
<tr>
<td>Asthma</td>
<td>CHS</td>
<td>Inhaled steroids for asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td>CHS</td>
<td>Asthma confirmed by doctor</td>
</tr>
<tr>
<td>Asthma</td>
<td>CHS</td>
<td>Current asthma diagnosis by doctor</td>
</tr>
<tr>
<td>Asthma</td>
<td>EAGLE</td>
<td>Doctor ever told you had: asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td>MEC</td>
<td>Asthma: History of Asthma, Hayfever, Skin Allergy, Food Allergy or Any Other Allergy from Baseline Questionnaire</td>
</tr>
<tr>
<td>CRP</td>
<td>CHS</td>
<td>C-reactive protein, adjusted original values (mg/l)</td>
</tr>
<tr>
<td>CRP</td>
<td>CHS</td>
<td>C-reactive protein, original values (mg/l)</td>
</tr>
<tr>
<td>CRP</td>
<td>EAGLE</td>
<td>Serum C-reactive protein (mg/dL)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>ARIC</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>CHS</td>
<td>hemoglobin (g/dl)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>EAGLE</td>
<td>Hemoglobin (g/dl)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>WHI</td>
<td>Hemoglobin (gm/dl)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>EAGLE</td>
<td>Mean cell hemoglobin concentration</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>EAGLE</td>
<td>Mean cell hemoglobin: SI (pg)</td>
</tr>
</tbody>
</table>

Presented below are examples of phenotypes binned into three phenotype classes, “Asthma”, “BMI”, and “CRP”. Table S2 contains the complete list of matched phenotypes across studies within phenotype-classes, for all phenotype-classes used within this study.

doi:10.1371/journal.pgen.1003087.t005
and can be used with a web interface at: http://visualization.ritchielab.psu.edu/.

Matching Phenotypes

A total of 105 phenotype-classes were developed to manually match related phenotypes across studies. To bin related phenotypes into classes the following steps were used as visualized in Figure 6: First, using a MySQL database, the data from EAGLE, MEC, CHS, ARIC, and WHI were independently filtered for any tests of association results at \( p < 0.01 \), and then lists of the unique phenotypes for each individual PAGE study were generated. The number of phenotypes that passed this significance threshold for each of the four groups was 604 (ARIC), 331 (CHS), 63 (MEC), 324 (EAGLE), 1,312 (WHI). Resulting phenotypes were then manually matched up between ARIC, CHS, MEC, EAGLE, and WHI using knowledge about the phenotypes and the known focus of specific PAGE study survey questions (such as bone fracture questions used primarily for collecting information about osteoporosis). For some phenotypes, the specific phenotype existed clearly across more than one PAGE study, such as for the phenotype “Hemoglobin”, where hemoglobin measurements were present for ARIC, CHS, EAGLE, and WHI. Other groups of phenotypes that fell within similar phenotypic domains but were not represented in the same form across studies were also collected into phenotype classes. One example is the phenotypes grouped together for the phenotype class of “Allergy”. EAGLE collected specific quantitative data from allergy skin testing and had survey questions about the presence of allergies in participants. ARIC and MEC did not have skin allergy testing, but did have survey questions about the presence of allergies. Thus these allergy phenotypes were grouped together. Finally, phenotypes from all studies, regardless of significance from genotype-phenotype tests of association, were matched to the already-defined phenotype classes using the criteria described above. A phenotype that matched a phenotype class but was not associated with a SNP at the significance threshold of \( p < 0.01 \) for a single study would still be included in the phenotype-class list. Using these criteria, a second curator reviewed the resultant phenotypes and phenotype classes for consistency and accuracy. To provide examples of the phenotype-classes, and which subphenotypes were matched with phenotype-classes, we show three phenotype-class examples in Table 5, and Table S2 contains the matched phenotypes across studies within the phenotype-classes for all phenotype-classes used within this study.

It is important to note resources that can be used for further investigation of the phenotypes listed in Table S2, as well as in the results presented in this paper. The following study websites contain additional information about all collected study information, including how those phenotypes were collected:

- ARIC http://www.cscceehcum.edu/aric/
- WHI https://cleo.whi.org/data/Pages/home.aspx
- EAGLE http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm/
- MEC http://www.crch.org/multiethniccohort/mec_questionnaires.htm

References


Criteria for Significance of Association

After creating phenotype-classes, significant PheWAS tests of association for single genotype-phenotype associations across PAGE studies were identified using a database query. Our criteria for considering a PheWAS test of association significant included a threshold of \( p < 0.01 \) observed in two or more PAGE studies for the same SNP, phenotype class, and race/ethnicity and consistent direction of effect.

A total of 111 PheWAS tests of association met our criteria for significance (Table S5). Significant results were then binned based on class of association: known, related, and novel. In this PheWAS, Known Associations are positive controls and represent previously reported genotype-phenotype associations. Related Associations are SNPs significantly associated in this PheWAS with phenotypes judged to be closely related to phenotypes among Known Associations found here and the literature. Novel Associations are significant PheWAS results where 1) the association does not match a known association and 2) the phenotype for the PheWAS association is not within a similar phenotypic domain as the phenotype of known association.

Ethics Statement

All participating studies were approved by their respective IRBs, and all study participants signed informed consent forms.

Supporting Information

Table S1 The list of all SNPs available for two or more sites in this study, arranged by previously associated phenotypes. (XLSX)

Table S2 A list of the study level phenotypes, the study from which the phenotype is available, and the phenotype-class for each phenotype that overlapped with another study. (XLSX)

Table S3 The expanded results for the 111 PheWAS associations identified in this study. (XLSX)

Table S4 The 52 PheWAS results that replicated previously published genotype-phenotype associations. (XLSX)

Text S1 Information on study design, phenotype measurement, and genotyping for each study. (DOCX)

Acknowledgments

The PAGE consortium thanks the staff and participants of all PAGE studies for their important contributions.

Author Contributions

Conceived and designed the experiments: SAP CK SB DCC MDR JLA CLA ED MDF CAH LAH C-NH RDJ LLL KRM LM AR. Performed the experiments: SAP KB-G SD AF EST RG SB YL SLP. Analyzed the data: SAP KB-G SD AF EST RG SB YL SLP. Contributed reagents/materials/analysis tools: SAP SD AF EST RG SB GH CK LRB YL PB SLP. Wrote the paper: SAP JLA CLA SB PB ED MDF CAH GH LAH C-NH RDJ CK LLM YL SLP. Contributed significantly to early work: RW LRW DCC MDR JLA CLA ED MDF CAH LAH C-NH RDJ LLM TCM KRM LM AR. Contributed reagents/materials/analysis tools: SAP SD AF EST RG SB GH CK LRB YL PB SLP. Wrote the paper: SAP JLA CLA SB PB ED MDF CAH GH LAH C-NH RDJ CK LLM YL SLP. Contributed significantly to early work: RW LRW DCC MDR JLA CLA ED MDF CAH LAH C-NH RDJ LLM TCM KRM LM AR. All participating studies were approved by their respective IRBs, and all study participants signed informed consent forms.

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