SUPPLMEMENTAL MATERIAL

Supplement Methods

Genotyping and Quality Control

Participants were excluded if sample genotype call rates were below 95% and SNPs were excluded if genotype call rates were below 90%. The genotype data were not reclustered after QC filters, but the genotype and sample call rate was recalculated after QC. Sample contamination was detected by checking gender mismatches using X chromosome genotype data and cryptic relatedness was estimated by pairwise identity-by-descent (IBD) analysis implemented using PLINK (http://pngu.mgh.harvard.edu/purcell/plink/).[1] Heterozygosity was also assessed using PLINK, by estimating the inbreeding coefficient, F. After the QC procedures, the total SNP call rate in the remaining individuals was 99.519%. Hardy-Weinberg equilibrium was assessed using with chi-square tests with one degree of freedom.

To address the issue of population substructure and admixture in our racially and ethnically diverse population, a Principal Component Analysis (PCA) was performed in all subjects on a linkage disequilibrium (LD) pruned dataset using the EIGENSTRAT method.[2] Race/ethnic groups were confirmed with PCA clustering results. If race/ethnic category disagreed strongly, patients were re-categorized to reflect the PCA result, considered to better reflect genetic ancestry. The top principal components (PCs 1-2) that provided the best separation of ancestry clusters were selected to be included as covariates for analysis.

Supplement References

1. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. Plink: A tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559-575.
2. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*. 2006;38:904-909.

Supplement Table 1

Association between baseline amino acid level (per standard deviation) and odds for developing impaired fasting glucose following treatment with atenolol

	Model 1 OR (95% CI), p value	Model 2 OR (95% CI), p value	Model 3 OR (95% CI), p value	Model 4 OR (95% CI), p value
Ile	1.91 (1.23-2.96), 0.004	1.64 (1.03-2.62), 0.037	2.28 (1.29-4.01), 0.004	2.29 (1.31-4.01), 0.0034
Leu	1.69 (1.10-2.58), 0.017	1.46 (0.93-2.28), 0.101	1.76 (1.07-2.88), 0.025	1.80 (1.10-2.96), 0.019
Val	1.68 (1.09-2.59), 0.020	1.54 (0.97-2.45), 0.068	1.76 (1.06-2.91), 0.027	1.77 (1.07-2.92), 0.025
Tyr	1.64 (1.06-2.54), 0.028	1.68 (1.05-2.71), 0.032	2.03 (1.16-3.56), 0.014	2.13 (1.20-3.78), 0.010
Phe	1.62 (1.03-2.54), 0.037	1.67 (1.03-2.71), 0.039	2.01 (1.14-3.54), 0.016	2.04 (1.16-3.59), 0.014

Model 1 = unadjusted, model 2 = model 1+ age, sex, BMI, model 3 = model 2 + baseline glucose and baseline insulin, model 4 = model 3 + HOMA IR. Each amino acid level is included in the models as a continuous variable. Values are odds ratios per standard deviation (95% confidence intervals) and p values for impaired fasting glucose from an unadjusted logistic regression model and conditional logistic regression models adjusted for baseline fasting glucose and baseline fasting insulin or baseline fasting glucose and baseline fasting insulin. Ile=isoleucine, Leu=leucine, Val=valine, Tyr=tyrosine, Phe=phenylalanine

Supplement Table 2

Association between baseline amino acid level (per standard deviation) and odds for developing impaired fasting glucose following treatment with atenolol according to gender

	Women n=68 (6 developed IFG and 62 did not develop IFG) OR (95% CI), p value	Men n=54 (18 developed IFG and 36 did not develop IFG) OR (95% CI), p value
Ile	3.67 (0.84-16.35), 0.084	2.06 (1.09-3.89), 0.025
Leu	1.90 (0.51-7.05), 0.339	1.75 (0.97-3.16), 0.063
Val	1.36 (0.52-3.58), 0.531	1.85 (0.97-3.54), 0.062
Tyr	1.18 (0.38-3.66), 0.780	2.47 (1.15-5.32), 0.020
Phe	1.36 (0.46-4.05), 0.576	2.25 (1.07-4.72), 0.032

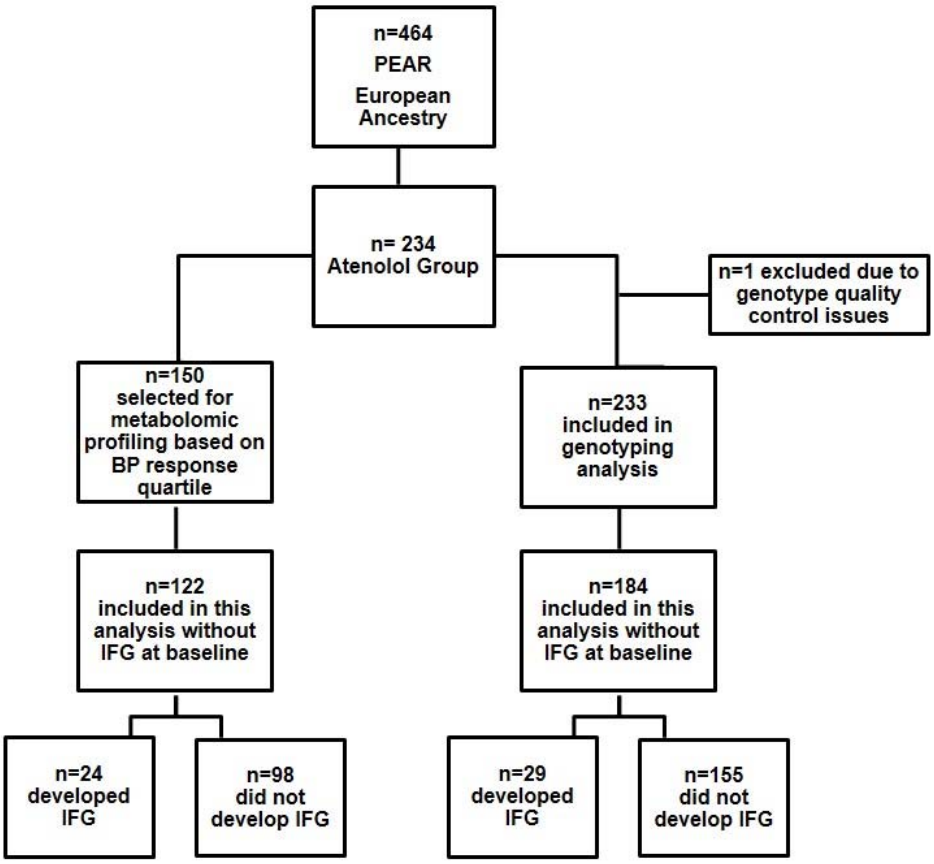
Values are odds ratios (OR) per standard deviation (95% confidence intervals [CI]) and p values for impaired fasting glucose from logistic regression models adjusted for age, body mass index, baseline fasting glucose, baseline fasting insulin and HOMA IR. Each amino acid level is included in the models as a continuous variable. Ile=isoleucine, Leu=leucine, Val=valine, Tyr=tyrosine, Phe=phenylalanine

SUPPLEMENT FIGURE LEGENDS

Figure 1. Flow diagram of participants included in the analyses.

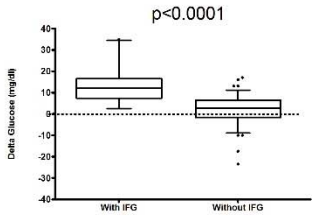
Figure 2. In the 122 participants with metabolomics data and without impaired fasting glucose at baseline, **A**. Change in glucose following treatment with atenolol according to those who did and did not develop IFG, **B.** Baseline amino acid levels according to those who did and did not develop IFG for Isoleucine, Leucine, Valine, Tyrosine and Phenylalanine. The data in B are presented as ion counts (measurement unit). Horizontal bars are median and 25th and 75% percentile. Whiskers are 5th and 95th percentile.

Supplement Figure 1



Supplement Figure 2

A



B