70 years [28], whereas all our prevalent cases (ARIC and FBPP) of diabetes were individuals who developed the disease between 30 and 45 years. Therefore, we may expect stronger genetic effects for early onset disease. To further examine this possibility, we derived measures of insulin resistance (HOMA-IR) and insulin sensitivity (HOMA-beta) in non-diabetic whites and African-Americans of the FBPP and ARIC samples. We hypothesized that since we did not detect significant associations between white ARIC participants and type 2 diabetes, we might detect significant associations between these persons for impaired insulin sensitivity and/or resistance and *CHEK2* variants. Interestingly, significant associations were detected in the white ARIC samples only (Supplement Table 2), supporting our hypothesis.

We also addressed the contribution of the identified SNP to the original linkage signal using a maximum likelihood linkage approach that modeled affection status by a liability threshold model as implemented in *SOLAR*. Adjusting for *CHEK2* rs4035540 as an additional covariate in the linkage analysis, the resulting LOD score was unchanged. While inclusion of the SNPs in the polygenic model did not account for the previously identified linkage peak, we were unable to genotype 38 participants from the linkage paper sample. Thus, our inability to account for the linkage signal may reflect a reduced power due to the exclusion of the aforementioned 38 individuals.

To further confirm our results, we evaluated the *P*-values from the association between SNP genotypes and type 2 diabetes for SNPs in LD with *CHEK2* rs4035540 among approximately 2,600 participants of the Diabetes Genetic Initiative (DGI) study (formerly available at http://www.broad.mit.edu/diabetes/). Evidence for association was observed for *CHEK2* SNP rs695388 ($P = 0.014$), rs9613617 ($P = 0.037$), rs5752764 ($P = 0.023$), and rs5762763 ($P = 0.035$) (Supplement Table 3). These results provide confirmatory evidence of our findings of association between *CHEK2* variants and type 2 diabetes susceptibility.

Our findings suggest a role for the *CHEK2* gene in susceptibility to type 2 diabetes. Our choice of the gene was driven by its location under the 1 LOD unit drop support interval of the linkage signal for type 2 diabetes and by the strong biological plausibility of a role of pancreatic β-cell apoptosis in type 2 diabetes in humans [9]. Apoptosis leads to decreased β-cell mass and therefore may contribute to exocrine pancreas dysfunction and the decreased insulin secretion observed in individuals with type 2 diabetes [9]. ER stress can lead to DNA damage, activating regulatory pathways that cause cell-cycle arrest and providing time for DNA repair. *CHEK2* protein is a tumor suppressor, and the link between ataxia telangiectasia mutated (ATM) and ataxia telangiectasia RAD3-related (ATR) kinases and checkpoint effectors in DNA repair pathway [16]. The protein structure has several evolutionary conserved elements, with high homology among eukaryotes [16]. Mutations in *CHEK2* have been associated with sporadic and hereditary human cancers [29]. In preliminary studies, Chung et al. showed that the *CHEK2* gene null mice were transitorily glucose intolerant, due to an inability to produce and secrete adequate amounts of insulin to maintain normal glucose homeostasis (personal report). The effect of *CHEK2* variants in the pathogenesis of type 2 diabetes has not been previously investigated.

In summary, we may have identified a promising type 2 diabetes candidate gene, *CHEK2*, an important mediator of diverse cellular responses to DNA damage. Variants in *CHEK2* may be causally linked to pancreatic β-cells apoptosis and the development of type 2 diabetes. One *CHEK2* variant in particular, rs4035540, was associated with increased risk of type 2 diabetes in HyperGEN participants and in two replication samples. Results from the meta-analysis affirm the results for rs4035540, particularly for African-American participants. Lastly, results from DGI provide confirmatory evidence of our findings of association between *CHEK2* variants and type 2 diabetes susceptibility. Further studies should replicate our findings and extend these findings to closely related traits such as pre-diabetes phenotypes, for example fasting glucose and insulin resistance so that the underlying mechanisms of this association may be further explored.

Supplement materials description

The supplement materials include a figure of the pattern of linkage disequilibrium (LD) across the *CHEK2* gene on chromosome 22 using data from the CEU population of HapMapII (MAF $> 5\%$; $r^2 > 0.8$), a table of the genotypic frequencies for four SNPs in the *CHEK2* gene in HapMap European and African-populations and in the FBPP populations and ARIC Cohort, a table of parameter estimates (std error) and P-values for SNP rs4035530 for insulin resistance (HOMA-IR) and insulin sensitivity (HOMA-beta) in non-diabetic whites and African-Americans of the FBPP and ARIC samples, and a table of association results for diabetes and SNPs in linkage disequilibrium with *CHEK2* rs4035540 Diabetes Genetics Initiative genome scan.

Acknowledgments The following investigators are associated with the Family Blood Pressure Program: *GenNet Network*: Alan B. Weder (Network Director), Lillian Gleiberman (Network Coordinator), Anne E. Kwitek, Aravinda Chakravarti, Richard S. Cooper, Carolina Delgado, Howard J. Jacob, and Nicholas J. Schork. *GENOA Network*: Eric Boerwinkle (Network Director), Tom Mosley, Alanna Morrison,