1.a. **Full Title:** Sex-hormone binding globulin allele score and risk of type 2 diabetes

b. **Abbreviated Title (Length 26 characters):** SHBG allele score and T2D

2. **Writing Group:**

   Writing group members: Jim Pankow, Linda Kao

This is a consortium analysis involving selected studies, including ARIC, participating in the DIAGRAM (Diabetes Genetics Replication And Meta-analysis Consortium). Jim Pankow is responsible for overseeing analysis in ARIC and will handle communications with the ARIC Publications and Steering Committees. The final composition of ARIC authors is still under negotiation, and the final list of all participating studies is not yet available.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __JP__ [please confirm with your initials electronically or in writing]

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3. **Timeline:**  
   Analysis to begin June 2012  
   Draft paper August 2012

4. **Rationale:**

   Sex hormone binding globulin (SHBG) is a glycated plasma transport protein primarily produced by the liver that binds sex steroids such as testosterone and dihydrotestosterone. Several prospective cohort studies have reported a significant, independent, and inverse association between SHBG levels and risk of type 2 diabetes (Ding, 2009). One explanation is that SHBG is a biomarker of elevated insulin or glucose levels; alternatively, SHBG may contribute to risk through modulation of sex hormone bioavailability or intracellular signaling pathways (Ne, 2012). Genetic studies have found that a SHBG-raising allele (rs1799941) from the SHBG gene is associated with lower risk of type 2 diabetes in both men and women (Perry, 2010), providing support for the hypothesis that the SHBG protein plays a causal role in the disease.

5. **Main Hypothesis/Study Questions:**

   A genetic risk score for sex hormone binding globulin is associated with risk of diabetes.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

   Analysis will follow a standard plan developed for the project; summary estimates will be submitted for meta-analysis at the University of Exeter. Results from ARIC will be based on a cross-sectional analysis of prevalent diabetes cases and non-cases identified at the baseline exam, and restricted to Caucasians.

**Exclusion criteria:**

- In CASES exclude:
- Individuals aged at diagnosis before 35
- If age at diagnosis was not known, those aged <45 years at the time of study

• In CONTROLS exclude:
  - HbA1c > 6.4% and/or fasting glucose > 7mmol/l

We will construct 2 allele score models – one including all 10 SNPs (allele_score_10SNPs) and one including only the 5 SNPs that occur near the SHBG encoding gene on chromosome 17 (allele_score_cis). Allele_score_10SNPs will provide most power, whilst allele_score_cis will provide a more specific test of SHBG levels to avoid possible pleiotropic effects of the “trans” SNPs.

The weighted allele score will be created in the following way:

\[ s_j = \sum_{i=1}^{4} w_i g_{ij} \]

where \( s_j \) is the score for individual \( j \), \( g_{ij} \) is the number of risk alleles (0, 1, 2 or dosage of the risk allele) for SNP \( i \) carried by individuals \( j \) and \( w_i \) is the effect size for SNP \( i \) (See Table below for values of \( w_i \); i.e. \( w_i = \) for SNP).

<table>
<thead>
<tr>
<th>SNP</th>
<th>Effect allele</th>
<th>weight</th>
<th>“cis”?</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs12150660</td>
<td>G</td>
<td>-0.082*</td>
<td>cis</td>
</tr>
<tr>
<td>rs1625895</td>
<td>T</td>
<td>-0.06*</td>
<td>cis</td>
</tr>
<tr>
<td>rs1641537</td>
<td>T</td>
<td>-0.064*</td>
<td>cis</td>
</tr>
<tr>
<td>rs6258</td>
<td>T</td>
<td>-0.272*</td>
<td>cis</td>
</tr>
<tr>
<td>rs6259</td>
<td>G</td>
<td>-0.026*</td>
<td>cis</td>
</tr>
<tr>
<td>rs17496332</td>
<td>A</td>
<td>-0.028</td>
<td></td>
</tr>
<tr>
<td>rs2411984</td>
<td>G</td>
<td>-0.033</td>
<td></td>
</tr>
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<td>rs440837</td>
<td>A</td>
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</tr>
<tr>
<td>rs7910927</td>
<td>T</td>
<td>-0.048</td>
<td></td>
</tr>
<tr>
<td>rs8023580</td>
<td>T</td>
<td>-0.03</td>
<td></td>
</tr>
</tbody>
</table>

* Weights have been calculated from meta-analysis of 5 cis SNPs in a multi-variable model.

Create allele score in 2 models using different SNPs:
- allele_score_10SNPs: use all 10 SNPs.
- allele_score_cis: use all 5 cis SNPs: rs12150660, rs1625895, rs1641537, rs6258, rs6259

Only SNPs with imputation quality >= 0.3 (imputed to hapmap) will be included in the analysis.

Logistic regression will be used to relate diabetes to allele score. Covariates will include age, sex, and center.

Analyses will include sex-combined and sex-specific models:
1- diabetes_status ~ allele_score_x * age, sex (in men and women combined)
2- diabetes_status ~ allele_score_x * age (in women only)
3- diabetes_status ~ allele_score_x * age (in men only)

7.a. Will the data be used for non-CVD analysis in this manuscript?  ___ Yes ___ No
   
   b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ___ Yes ___ No
   (This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  ___ Yes ___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ___ Yes ___ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscu.unc.edu/ARIC/search.php  ___ Yes ___ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

   1470 (Li): Genome-wide association study of prevalent type 2 diabetes in the Atherosclerosis Risk in Communities Study

   Primary results from the GWAS of type 2 diabetes in ARIC are included in a DIAGRAM consortium paper recently accepted by Nature Genetics (Morris et al.). Although the outcome (prevalent type 2 diabetes at visit 1) is the same, this analysis will be distinct from the GWAS because of its focus on a small number of SNPs summarized in an allele score.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ___ Yes ___ No
11.b. If yes, is the proposal
   _x_  A. primarily the result of an ancillary study (list number*__________)
   ___  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*__________  __________ __________)

2006.3 (Stamped and Geneva genotype funding in Caucasians)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

References:

