

**ARIC Manuscript Proposal # 1083**

**PC Reviewed:** 05/13/05

**Status:** A

**Priority:** 2

**SC Reviewed:** 05/13/05

**Status:** A

**Priority:** 2

**1.a. Full Title:** Natural history of HFE-related hereditary hemochromatosis

**b. Abbreviated Title (Length 26 characters):** HFE genotypes and disease risk

**2. Writing Group:**

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**3. Timeline:** Genotyping is completed  
Abstract by 6/21/05 (deadline for 2005 ASHG meeting)  
Manuscript by 10/1/05

**4. Rationale:** In 1996, Feder and colleagues identified the gene responsible for hereditary hemochromatosis, called it the *HFE* gene, and found that two mutations, C282Y (exon 4, nucleotide 845G->A) and H63D (exon 2, nucleotide 187C->G) were found in essentially all of their patients who presented with clinical iron overload (Feder et al., 1996). Other studies quickly confirmed that most of the patients who present with symptoms of clinical iron overload are

homozygous for the C282Y mutation, though a small number of cases, from zero to 20% in various studies, were compound heterozygotes for the C282Y and H63D mutations, with very rare cases being H63D homozygotes. From the time of the *HFE* gene's discovery in 1996 until the about two years ago, the general consensus was that most homozygotes for the C282Y mutation, perhaps as many as half of females and three quarters of males, would eventually develop significant iron overload-related morbidity and premature mortality (Cogswell et al., 1998; McDonnell et al., 1998; Adams et al., 2000).

The prevalence of C282Y homozygosity in North American Caucasians has been reported to be between 1:150 and 1:400 in various studies. Despite the reasonably high prevalence of homozygosity for the C282Y (0.3 to 0.7% in North Americans) in the general population, most practicing clinicians consider HH to be a fairly rare disease. It is unclear whether actual clinical morbidity and premature mortality caused by the iron overloading of various tissues (i.e., heart, pancreas, liver, joints, and pituitary) are truly rare, or whether a large percentage of C282Y homozygotes who develop disorders from iron overload are simply missed clinically because the signs and symptoms associated with iron overload so closely mimic those of very common diseases of the elderly, including heart disease, diabetes, arthritis and arthralgia. This question is now under intense scientific scrutiny and debate. As recently as a few years ago, almost nobody would have suggested the penetrance of clinical disease in C282Y homozygotes was below 20%, there are now several very credible studies that suggest the penetrance may be as low as a few percent (Beutler et al. 2002; Asberg A et al., 2001; Andersen RV, et al. 2003). Thus, it is of critical importance to get a more accurate estimate of clinical penetrance in C282Y homozygotes if rational healthcare screening policies are to be developed.

We believe that the 15,792 subjects in the ARIC population, who were 45 to 64 at study entry, are an ideal group to examine the natural history of hereditary hemochromatosis. The ARIC subjects were enrolled during middle age, when clinical symptoms are believed to first begin to develop, and they will have been carefully followed for nearly 20-years for disease-related morbidity and mortality over this time. Furthermore, ARIC subjects were selected using well-defined population-based sampling.

**5. Main Hypothesis/Study Questions:** We have tested all ARIC subjects who have given unrestricted permission to use their stored DNA for genetic testing for the C282Y and H63D mutations of the *HFE* gene. We will use this new genetic information to compare the all-cause mortality, disease-specific mortality, and disease-specific morbidity of C282Y homozygotes to that of subjects without either of the C282Y or H63D mutations. We have the following hypotheses:

Caucasian subjects who are C282Y homozygotes will have a higher all-cause mortality compared with Caucasian subjects without either the C282Y or H63D mutations.

Caucasian subjects who are C282Y homozygotes will have higher heart disease-, liver disease-, and diabetes-related mortality and morbidity compared with Caucasian subjects without either the C282Y or H63D mutations.

Caucasian subjects who are C282Y/H63D compound heterozygotes, H63D homozygotes, C282Y heterozygotes, or H63D heterozygotes will have no increased all-cause mortality or disease-specific mortality or morbidity compared with Caucasian subjects without either the C282Y or H63D mutations.

**6. Data (variables, time window, source, inclusions/exclusions):**

HFE genotypes from DNA lab, prevalent and incident CHD, prevalent and incident stroke, all-cause mortality, prevalent and incident cancer, prevalent and incident diabetes, major CVD risk factors (smoking, lipids, blood pressure, insulin, glucose), hospitalization for liver disease, self-reported liver disease (visit 3).

**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 ICTDER02 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 ICTDER02 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 ICTDER02 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.csc.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)?**

**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**

**A. primarily the result of an ancillary study (list number\* 2003.10)**

**B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)\* \_\_\_\_\_)**

\*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

- 12. 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.**