1.a. Full Title: Identification of genes that modulate the relationship between prevalent periodontal disease and risk for incident tooth loss.

b. Abbreviated Title (Length 26 characters): Perio*Genes=ToothLoss

2. Writing Group:
   Writing group members:
   James Beck
   University of North Carolina

   Kevin Moss
   University of North Carolina

   Kamaira Philips
   University of North Carolina

   Others to be invited
   ??

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

First author:
   Name: Jim Beck

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
3. **Timeline:** Six months for data analysis then six additional months for Manuscript Preparation

4. **Rationale:**
In the dental community, tooth loss is considered comparable to death when considered as an outcome. The UNC team has developed a new classification of periodontal disease based on Latent Class Analysis that groups people into mutually exclusive and exhaustive homogenous bins. This new definition of disease called Periodontal Profile Class (PPC) has already been shown to be associated with incident tooth loss (ARIC manuscript 2874) and incident stroke (MS 2886). We propose to continue this work to identify genes (SNPs) that may mediate the association between PPC and incident tooth loss.

5. **Main Hypothesis/Study Questions:**
1. Are there SNPs that are associated with incident tooth loss?
2. Do any of these SNPs mediate the association between PPC and tooth loss?
3. Do these SNPs add to the predictive model of PPC and incident tooth loss?

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).**

**Population:**
Our primary sample is the European American participants who have a periodontal exam at ARIC visit 4, incident tooth loss information (question from annual follow-up) and GWAS data. We will attempt to replicate our findings using the African American study participants.

**Outcome:**
Incident tooth loss defined as loosing 3 or more teeth over a ten-year period.

**Other variables:**
We will use age, sex, center, diabetes, smoking and education as our primary control variables. Ancestry Principal Components will be used when performing GWAS analysis.
Data Analysis:
Perform GWAS analysis with incident tooth loss as our phenotype in the EA and AA datasets. Candidate SNPs identified above will be used in Mediation Analysis to determine if the effect of periodontal disease on incident tooth loss is mediated by SNPs. This will be done in the EA’s and replicated in the AA’s.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X___ 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? _X__ Yes    ____ No
    (This file ICTDER 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? _X__ 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”? _X___ 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/mantrack/maintain/search/dtSearch.html

    _X_____ 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)? Manuscripts 2874, 2886, 2890, 2914, 2889, 3194, 2891.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X__ Yes    ____ No

11.b. If yes, is the proposal

    _X__  A. primarily the result of an ancillary study (list number* _1996.01_________)  
            ____  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 https://www2.csc.unc.edu/aric/approved-ancillary-studies
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/](http://publicaccess.nih.gov/) are posted in [http://www.csc.c.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.