**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Reference Number** | NT246 |
| **Submission Date** | 7/24/2017 |
| **Project Title** | Association Studies of Rare Variants in *HNF1B*, *UMOD, WT1* and *CFH* and Known Risk Alleleswith Chronic Kidney Disease in 25,000 eMERGE 3 participants |
| **Tentative Lead Investigator (first author)** | Miguel Verbitsky\* |
| **Tentative Senior Authors (last author)** | Krzysztof Kiryluk, Ali Gharavi |
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| **Sites Involved** | A network-wide study (all sites invited to participate).  |
| **Background / Significance** | Chronic kidney disease (CKD) affects 14% of the US population. Common variants in over 50 loci are known to affect kidney function but these explain only a small proportion of the variance in this trait. We have nominated the *HNF1B*, *UMOD* and *CFH*genes and 50 known CKD risk variants for E3 sequencing. *HNF1B*, *UMOD* and *CFH*cause Mendelian forms of nephropathy with pleotropic effects on other organ systems. *WT1*, one of the ACMG actionable genes is also associated with Mendelian forms of kidney disease. We hypothesize that 1) rare variants in *HNF1B*, *UMOD* , *WT1* and *CFH*will be enriched in E3 participants with CKD as defined by our newly developed CKD e-algorithm. 2) these same variants will be associated with other metabolic and clinical traits such as hypertension, diabetes, hyperuricemia/gout, hypomagnesemia, blood pressure variation (*UMOD* and *HNF1B, WT1*), or macular degeneration/autoimmunity (*CFH*), and perhaps intellectual disability (*HNF1B*) as defined by ICD9 and PheWAS codes (3) *HNF1B*, *UMOD* , *WT1* and *CFH*have additional pleiotropic effects and novel phenotypic associations will be discovered with an exploratory PheWAS . 4) CKD risk variants typed on the EmergeSeq panel will be associated CKD as defined by the new e-algorithm. |
| **Outline of Project** | 1. Determine the frequency of pathogenic/likely pathogenic variants in *HNF1B*, *CFH*, *UMOD, WT1,* and *APOL1* risk alleles among E3 sequenced participants with CKD
2. Gene- and variant–based burden tests in CKD and phenotypes known to be associated with *APOL1*, *HNF1B*, *UMOD, WT1,* and *CFH* mutations among E3 sequenced participants
3. PheWAS of rare variants in *UMOD, HNF1B,* *WT1,*  and *CFH* in among E3 sequenced participants
4. Testing the combined effect of rare variants and common CKD risk alleles from published GWAS studies that were included on the EmergeSeq panel.
5. Manuscript preparation and submission.
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| **Desired****Variables (essential for analysis****indicated by \*)** | * CKD electronic phenotype (e3, developed by Columbia)
* Autoimmunity electronic phenotype (e3, developed by Columbia)
* Hypertension and diabetes phenotypes
* Uric acid, Magnesium, Calcium, Hemoglobin, and Albumin levels
* HgbA1C
* Age, sex, race/ethnicity\*
* PheWAS codes
* ICD9 and ICD10 codes
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| **Desired data** | * *UMOD, HNF1B and CFH* sequence data in E3 participants (EMERGE-seq panel data)
* Sequence data for CKD risk SNPs typed on EMERGE-seq, including APOL1 G1/G2 variants
* CKD electronic phenotype (e3, developed by Columbia
* PheWAS and ICD9/10 codes
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| **Planned Statistical Analyses** |  1. Identification of rare coding variants in *HNF1B*, *UMOD, WT1* and *CFH*
2. Rare variant burden tests to detect associations with phenotypes
3. Common CKD risk allele analyses in association with the phenotype, including genetic risk score analyses and tests of effect modification for the rare variants detected above.
4. PheWAS of rare variants in *UMOD, HNF1B,* *WT1,* and *CFH* in among E3 sequenced participants
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| **Ethical considerations** | There are no additional risks involved. The data will be stored at a secured location in the data storage system of the Gharavi and Kiryluk labs. No data will be shared with unauthorized third parties. Patient identity will not be compromised by the proposed analysis. We will also abide by the EMERGE guidelines in this regard. |
| **Target Journal** | TBD, depending on the findings |
| **Milestones\*\*** | Total Duration of the study: 2 years |

**\*\*** This section should include: Timeline for completion of project, including approval, project duration, first and second draft of the paper and submission.