Genomics and Pharmacogenomics of Susceptibility and Severity of COVID-19 in the UK Biobank

Presented by:
Yan Gong, PhD
Associate Professor
Center for Pharmacogenomics and Precision Medicine
UF College of Pharmacy, Email: gong@cop.ufl.edu
• Aims to improve the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses
• ~500,000 volunteer participants of age 40-69 recruited between 2006 and 2010.
• Heath and well-being information are longitudinally followed
• Data available:
  • Electronic health records (demographics, clinical, treatments, medications, critical care, etc)
  • Genome-wide genotype data (~488,000)
  • Whole-exome sequencing data (~150,000 by end of 2020, all pts by end of 2021)
  • Whole genome sequencing data (~50,000 now, all pts by the end of 2022)
  • Biomarkers
  • Metabolomics (NMR)
  • .....
COVID-19 Data in UK Biobank

- COVID-19 data made available to all UKB approved researchers.
- Updated on a weekly basis:
  - Results of COVID-19 tests for UK Biobank participants (both positive and negative test results)
- Updated on a monthly basis:
  - GP (primary care) data provided directly by the system suppliers
  - Hospital inpatient data
  - Death data
  - Critical care data
Specific Aims

Aim 1: Identify genetic and nongenetic risk factors associated with the susceptibility of SARS-CoV-2 infection.

- 1a. Nongenetic risk factors
- 1b. Genetic risk factors will be assessed through genome-wide association study
- 1c. ACE2 polymorphisms will be assessed

Aim 2: Determine the genomic and pharmacogenomic risk factors for death or hospitalization in COVID-19 patients.

- 2a. Determine the genomic risk factor for severity of the disease.
- 2b. Determine the association of ACE2 polymorphisms with the severity of the disease.
- 2c. Determine the pharmacogenomic association of patients treated with ACE inhibitors and/or ARBs.
Phenotype Definitions

SARS-CoV-2 infection (Aim 1)

- Laboratory confirmation of SARS-CoV-2 infection (RNA and/or serology based) or
- ICD/administrative/EHR coding-based definition of SARS-CoV-2 infection where large-scale & rapid clinical testing unavailable.

Severity of COVID-19 (Aim 2)

- Death
- or hospitalization with respiratory support:
  - intubation,
  - continuous positive airway pressure ventilation (CPAP),
  - continuous negative pressure ventilation (CPN) or
  - biphasic positive airway pressure ventilation (BiPAP).
Preliminary Results: 09/15/20 Update

Aim 1 a. Nongenetic risk factors for SARS-CoV-2 infection

- **18,221 tested including 1,713 (9.4%) positive**

<table>
<thead>
<tr>
<th></th>
<th>COVID-19 positive</th>
<th>Negative</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1,713)</td>
<td>(n= 16,508)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>56.1 (9.1)</td>
<td>58.1 (8.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>897 (52.4%)</td>
<td>7884 (47.8%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White</td>
<td>1481 (86.5%)</td>
<td>15403 (93.3%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>87 (5.1%)</td>
<td>309 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>78 (4.6%)</td>
<td>375 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Other/mixed</td>
<td>67 (3.9%)</td>
<td>421 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>618 (36.1%)</td>
<td>6049 (36.6%)</td>
<td>0.644</td>
</tr>
<tr>
<td>Cancer</td>
<td>294 (17.2%)</td>
<td>3598 (21.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>181 (10.6%)</td>
<td>1438 (8.7%)</td>
<td>0.010</td>
</tr>
</tbody>
</table>
### Aim 1 Preliminary Results

#### Aim 1b. Genetic risk factors for SARS-CoV-2 infection

In participants of European ancestry:

<table>
<thead>
<tr>
<th>SNP</th>
<th>CHR</th>
<th>Gene</th>
<th>MAF</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2290351</td>
<td>15</td>
<td>AP3S2</td>
<td>0.22</td>
<td>1.23</td>
<td>1.12-1.35</td>
<td>5.89*10^-06</td>
</tr>
<tr>
<td>rs769449</td>
<td>19</td>
<td>ApoE</td>
<td>0.13</td>
<td>1.28</td>
<td>1.15-1.42</td>
<td>6.87*10^-06</td>
</tr>
<tr>
<td>rs877863</td>
<td>15</td>
<td>RORA</td>
<td>0.49</td>
<td>1.19</td>
<td>1.10-1.29</td>
<td>8.98*10^-06</td>
</tr>
</tbody>
</table>

MAF: minor allele frequency  
*OR: odds ratio from logistic regression adjusting for age, sex and principal components

Accepted as a late-breaking poster at American Society of Human Genetics (ASHG) virtual meeting on Oct 27-30, 2020

Luna Chen
Aim 1 Preliminary Results

Aim 1b. Genetic risk factors for SARS-CoV-2 infection

- ApoE encodes Apolipoprotein E.
- This locus was previously associated with COVID19 in a candidate gene study in the UK Biobank.
- Associated with Alzheimer’s disease
- Associated with abundance of multiple proteins such as C-reactive protein, low-density lipid lipoproteins (LDL) and total cholesterol (TC).
- ApoE gene is highly co-expressed with ACE2 which is receptor for cell entry of the SARS-Cov-2 virus in type II alveolar cells in the lungs.

rs769449 in the ApoE region

ACE2: Angiotensin converting enzyme 2
TMPSRSS2: transmembrane protease serine 2
AGT: angiotensinogen
Aim 1 Preliminary Results

Aim 1b. Genetic risk factors for SARS-CoV-2 infection

- rs2290351 AP3S2
  - AP3S2 encodes adaptor related protein complex 3 subunit sigma 2
  - eQTL for ANPEP (alanyl aminopeptidase) in the lung (1.59*10^-8)

- rs877863 RORA
  - RORA encodes retinoic acid receptor-related orphan receptor-α
  - Regulates lipid homeostasis by mediating lipid metabolism.

Accepted as a late-breaking poster at American Society of Human Genetics (ASHG) virtual meeting on Oct 27-30, 2020
Aim 1 Preliminary Results

Aim 1b. Genetic risk factors for SARS-CoV-2 infection

- All three genes are related to lipid metabolism through direct or indirect interactions with the low-density lipoprotein receptor (LDLR) or lipase C (LIPC).
- Dyslipidemia including high TC have previously been associated with increased susceptibility for COVID19 in Chinese individuals.

Accepted as a late-breaking poster at American Society of Human Genetics (ASHG) virtual meeting on Oct 27-30, 2020
Aim 1 Preliminary Results

Aim 1c. Association of ACE2 polymorphisms with SARS-CoV-2 infection

- XWAS: an analysis approach that considered X-inactivation.
- The rare ACE2 missense variants (Ser19Pro, Glu23Lys, Thr27Ala…) were not captured in GWAS.
- 7 ACE2 SNPs were in the GWAS dataset:
  - None were significantly associated with the susceptibility of SARS-CoV-2 infection.
  - The top SNP rs2106809 (A>G), which was associated with hypertension, had odds ratio (OR) 0.94 with the 95% Confidence Interval (CI) (0.86 – 1.02) (p = 0.148).

<table>
<thead>
<tr>
<th>SNP</th>
<th>Alleles</th>
<th>MAF</th>
<th>OR</th>
<th>L95</th>
<th>U95</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2106809</td>
<td>G/A</td>
<td>0.19</td>
<td>0.94</td>
<td>0.86</td>
<td>1.02</td>
<td>0.148</td>
</tr>
<tr>
<td>rs4646116</td>
<td>C/T</td>
<td>0.007</td>
<td>0.76</td>
<td>0.47</td>
<td>1.24</td>
<td>0.278</td>
</tr>
<tr>
<td>rs35803318</td>
<td>T/C</td>
<td>0.04</td>
<td>1.08</td>
<td>0.93</td>
<td>1.25</td>
<td>0.326</td>
</tr>
<tr>
<td>rs142443432</td>
<td>C/T</td>
<td>0.00</td>
<td>0.61</td>
<td>0.18</td>
<td>2.03</td>
<td>0.421</td>
</tr>
<tr>
<td>rs2023802</td>
<td>G/A</td>
<td>0.37</td>
<td>1.02</td>
<td>0.95</td>
<td>1.09</td>
<td>0.557</td>
</tr>
<tr>
<td>rs148771870</td>
<td>T/C</td>
<td>0.003</td>
<td>0.90</td>
<td>0.47</td>
<td>1.72</td>
<td>0.759</td>
</tr>
<tr>
<td>rs41303171</td>
<td>C/T</td>
<td>0.03</td>
<td>0.98</td>
<td>0.80</td>
<td>1.21</td>
<td>0.875</td>
</tr>
</tbody>
</table>
Aim 2 Preliminary Results

- Among the 1,713 COVID-19 positive patients:
  - 331 (19.3%) died
  - 112 (6.5%) had critical care after COVID-19 diagnosis
  - 106 (6.2%) with respiratory support
  - 391 (22.8%) were severe: death/respiratory support
- Nongenetic predictors of severity:
  - Age (decade): ORadj: 2.31 (1.97-2.71), p < 0.0001
  - Male: 1.66 (1.30-2.13), p < 0.0001
  - Hypertension, 1.28 (1.00-1.64), p = 0.05
  - Cancer: 1.31 (0.97-1.75), p = 0.07
Aim 2 Preliminary Results

Aim 2a. Determine the genomic risk factor for severity of the disease.

- The most significant SNP discovered in the European participants and replicated in African ancestry participants was an intronic variant rs6985555 (T>C) in Poly (U) Binding Splicing Factor 60 (PUF60) gene on 8q24.3.

Abstract submitted to American Society of Clinical Pharmacology and Therapeutics (ASCPT) 2021 virtual meeting
Aim 2 Preliminary Results

Aim 2a. Determine the genomic risk factor for severity of the disease.

rs6985555 and mortality in COVID-19 patients

- The PUF60 gene is a DNA- and RNA-binding protein, involved in different nuclear processes as pre-mRNA splicing, apoptosis and is associated with cardiac, seizure, and recurrent respiratory infection.
- rs6985555 is an eQTL for nuclear receptor-binding protein 2 (NRBP2), which was associated with left ventricular dysfunction in dilated cardiomyopathy.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>1.75 (1.40-2.19), p=7.9*10^{-7}</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>3.03 (1.14-8.02), p=0.025</td>
<td></td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1.79 (1.40-2.18), p=1.1*10^{-7}</td>
<td></td>
</tr>
</tbody>
</table>

Abstract submitted to American Society of Clinical Pharmacology and Therapeutics (ASCPT) 2021 virtual meeting
Aim 2 Preliminary Results

Aim 2b. Association of ACE2 polymorphisms with severity of COVID-19

- XWAS: an analysis approach that considered X-inactivation
- 6 ACE2 SNPs evaluated:
  - Intronic SNP rs2023802 was nominally associated with a higher risk of death in COVID-19 patients.
  - rs2023802 is a nonsense mediated decay transcript variant, which affects the ACE2 gene expression by regulating stability of the ACE2 gene transcript (ENST00000649243).

<table>
<thead>
<tr>
<th>SNP</th>
<th>Alleles</th>
<th>MAF</th>
<th>OR</th>
<th>L95</th>
<th>U95</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2023802</td>
<td>G/A</td>
<td>0.377</td>
<td>1.205</td>
<td>1.025</td>
<td>1.417</td>
<td>0.024</td>
</tr>
<tr>
<td>rs142443432</td>
<td>C/T</td>
<td>0.001</td>
<td>9.878</td>
<td>0.5887</td>
<td>165.8</td>
<td>0.1114</td>
</tr>
<tr>
<td>rs41303171</td>
<td>C/T</td>
<td>0.023</td>
<td>1.31</td>
<td>0.7838</td>
<td>2.19</td>
<td>0.3028</td>
</tr>
<tr>
<td>rs4646116</td>
<td>C/T</td>
<td>0.005</td>
<td>0.5028</td>
<td>0.07135</td>
<td>3.543</td>
<td>0.4901</td>
</tr>
<tr>
<td>rs2106809</td>
<td>G/A</td>
<td>0.176</td>
<td>0.9466</td>
<td>0.7644</td>
<td>1.172</td>
<td>0.6147</td>
</tr>
<tr>
<td>rs35803318</td>
<td>T/C</td>
<td>0.049</td>
<td>1.034</td>
<td>0.7284</td>
<td>1.469</td>
<td>0.8504</td>
</tr>
</tbody>
</table>
We verified ApoE and identified two additional lipid-related loci to be potentially associated with susceptibility of SARS-Cov-2 infection, indicating a potential link between lipid metabolisms and COVID-19.

We also identified a genetic variant in PUF60 associated with mortality in COVID-19 patients.

There was no evidence that ACE2 variants are associated with susceptibility.

One ACE2 SNP was nominally associated with higher mortality in COVID-19 patients.

Further investigations are warranted to understand the implications of these associations.
Ongoing Analysis

• Incorporate the Whole-exome sequencing data for ACE2 variants analysis
• Pharmacogenomics analysis in patients treated with ACEI/ARB
• Participate in the global COVID-19 Host Genetic Initiative.
  • Global human genetics community to generate, share, and analyze data to learn the genetic determinants of COVID-19 susceptibility, severity and outcomes.
  • Generate hypotheses for drug repurposing, identifying high risk individuals
  • Contributing to the global knowledge of COVID-19
• 220 registered studies including 55 from US
Acknowledgements

The team
• Dr. Rhonda Cooper-DeHoff
• Dr. Qing Lu
• Dr. Marwa Tantawy
• Dr. Guang Yang
• Ms. Yiqing (Luna) Chen
• Dr. Carl Pepine
• Dr. Taimour Langaee

UF Research Computing
• Matt Gitzendanner

UK Biobank
• Project number: #34697
• All UKB participants

Funding supports
• CTSI-UFII Pilot Fund
• CTSI COVID-19 Rapid Response Fund
• UF Health Cancer Center
• UF College of Pharmacy