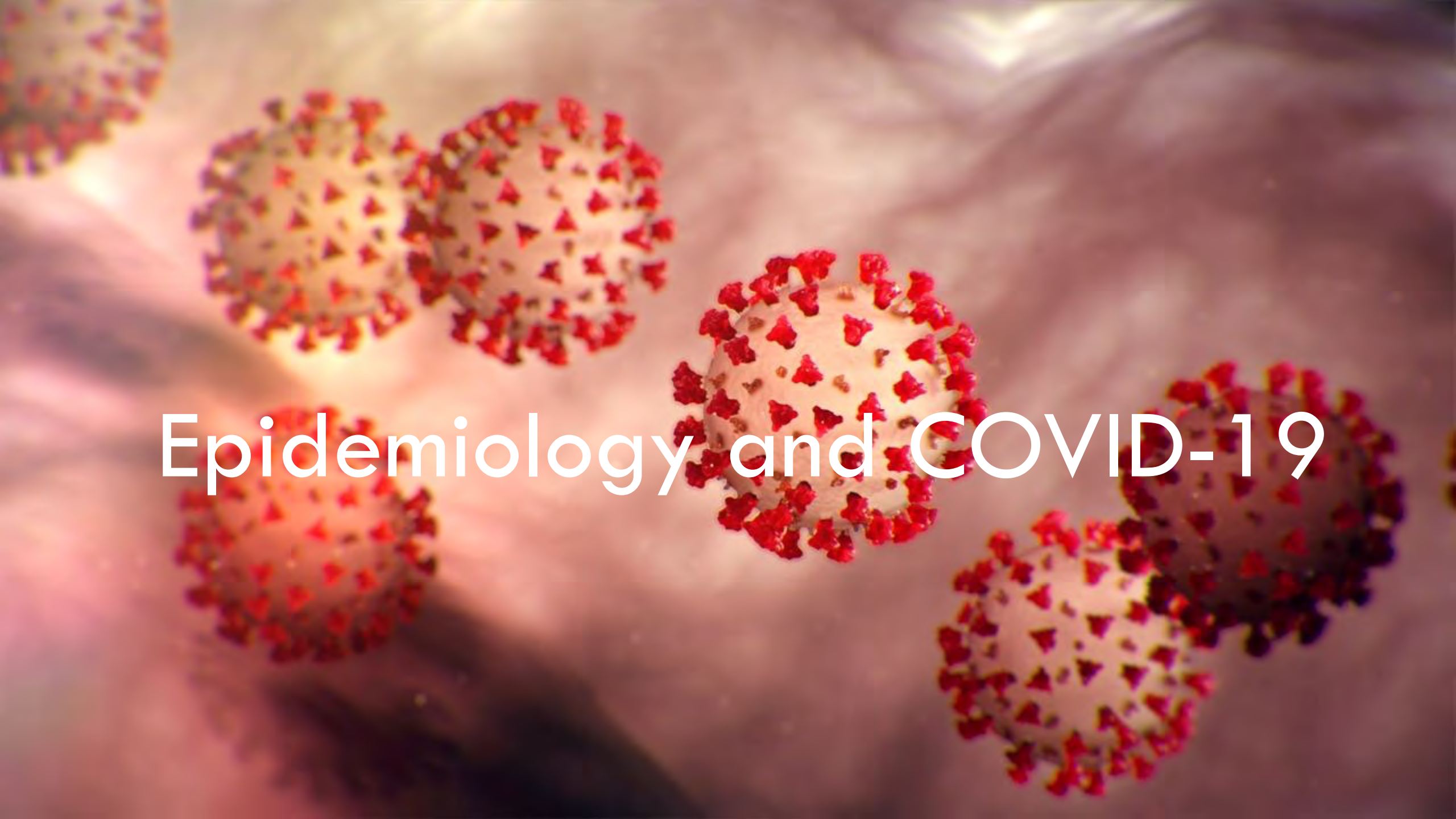
Impact of Host Genomics on COVID-19: What We Know and Don't Know

Priya Duggal, PhD, MPH

Johns Hopkins Bloomberg School of Public Health

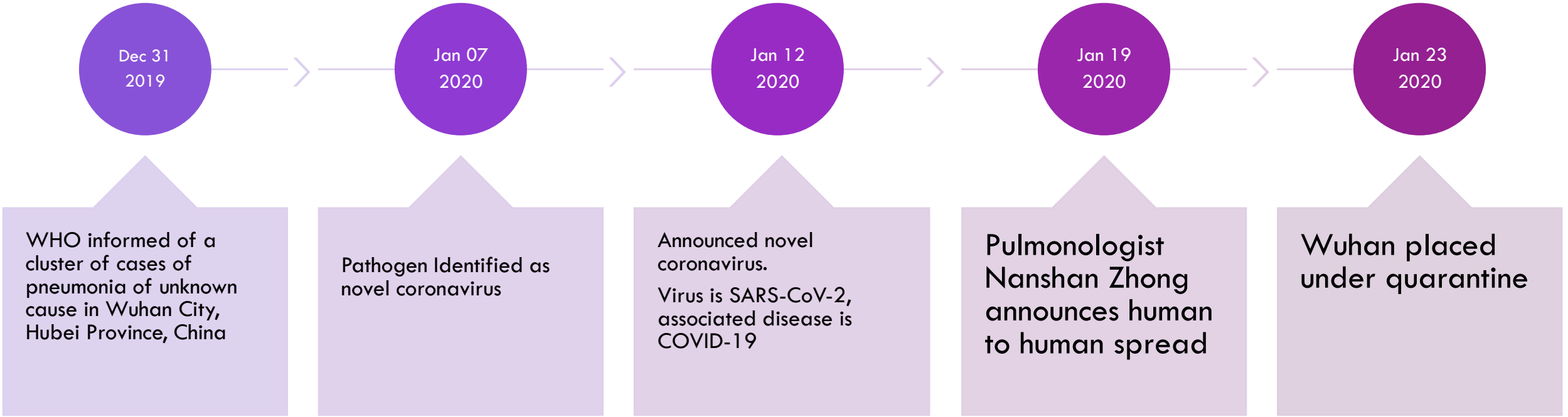
July 23, 2020

CDC



Epidemiology and COVID-19

Early COVID-19 Timeline



COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

Total Confirmed
15,250,804

Confirmed Cases by Country/Region/Sovereignty

- 3,971,343 US
- 2,227,514 Brazil
- 1,238,798 India
- 793,720 Russia
- 394,948 South Africa
- 366,550 Peru
- 362,274 Mexico
- 334,683 Chile
- 297,952 United Kingdom
- 281,413 Iran
- 269,191 Pakistan
- 267,551 Spain
- 258,156 Saudi Arabia
- 245,032 Italy
- 222,402 Turkey
- 218,428 Colombia
- 216,110 Bangladesh
- 215,605 France
- 204,484 Germany
- 141,900 Argentina
- 113,790 Canada
- 107,871 Qatar

Admin0 | Admin1 | Admin2

Last Updated at (M/D/YYYY)
7/23/2020, 6:34:51 AM

Cumulative Confirmed Cases | Active Cases | Incidence Rate | Case-Fatality Ratio | Testing Rate | Hospitalization Rate

188
countries/regions

Lancet Inf Dis Article: Here. Mobile Version: Here.
Lead by JHU CSSE. Technical Support: Esri Living Atlas team and JHU APL. Financial Support: JHU, NSF, Bloomberg Philanthropies and Stavros Niarchos Foundation. Resource support: Slack, Github and AWS. Click *here* to **donate** to the CSSE dashboard team, and other JHU COVID-19 Research Efforts. FAQ. Read more in this blog. Contact US.

Data sources: Full list available *here*.

Global Deaths
623,897

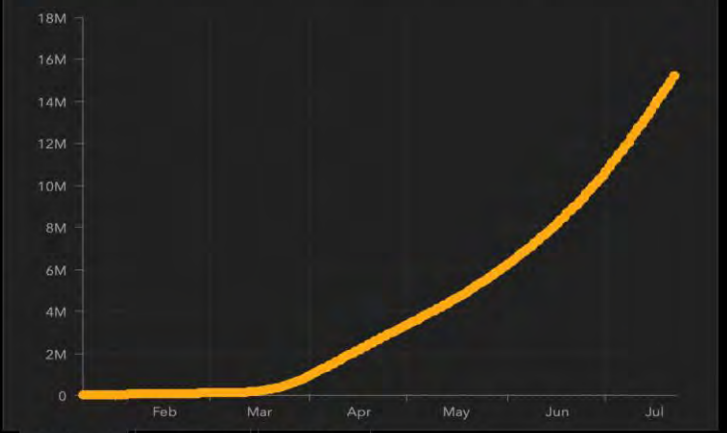
- 143,193 deaths US
- 82,771 deaths Brazil
- 45,586 deaths United Kingdom
- 41,190 deaths Mexico
- 35,082 deaths Italy
- 30,175 deaths France
- 29,861 deaths India
- 28,426 deaths Spain
- 14,853 deaths Iran
- 13,767 deaths Peru

Global Deaths | Global Recovered

US State Level
Deaths, Recovered

- 32,558 deaths, 72,386 recovered New York US
- 15,707 deaths, 31,850 recovered New Jersey US
- 8,468 deaths, 96,452 recovered Massachusetts US
- 8,047 deaths, recovered California US
- 7,540 deaths, recovered Illinois US
- 7,077 deaths, 77,547 recovered Pennsylvania US
- 6,388 deaths, 55,162 recovered Michigan US
- 5,345 deaths, recovered Florida US
- 4,439 deaths, 195,315 recovered Texas US
- 4,406 deaths, 8,466 recovered Connecticut US

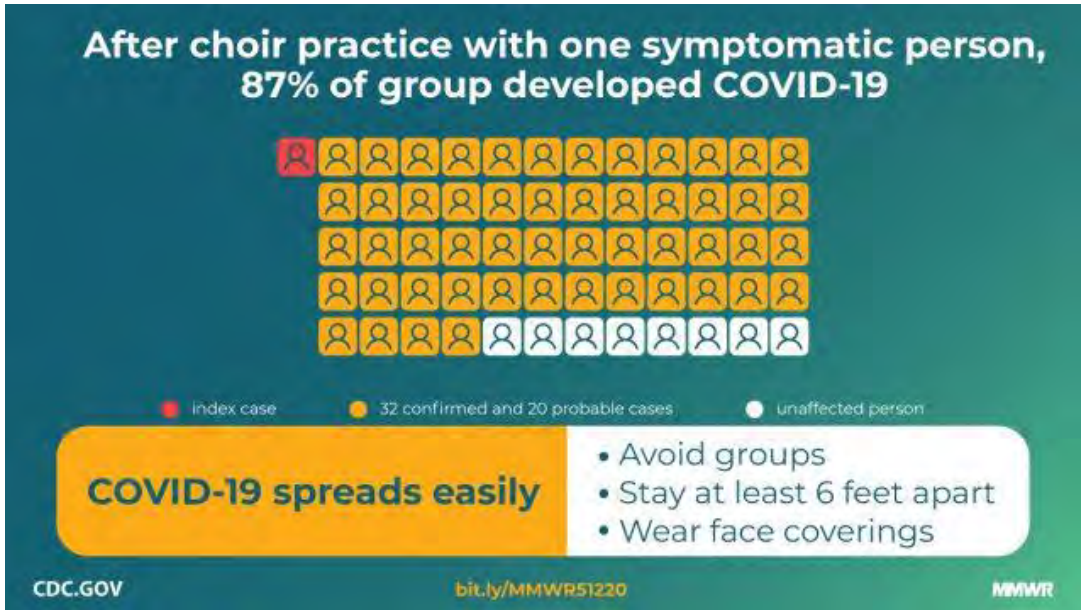
US Deaths, Recovered



Confirmed | Logarithmic | Daily Cases

Transmission

- This is a respiratory illness.
- Spread through droplets which includes close contact with people who are sick, including talking!
- It also resides on surfaces and may be airborne, both can impact exposure to another person even if they are not in the same room at the same time.
- Asymptomatic or pre-symptomatic transmission does occur. This means, unlike influenza, you cannot rely on coughing or sneezing to indicate someone is transmitting.

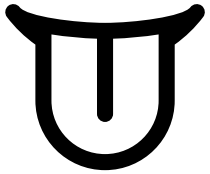
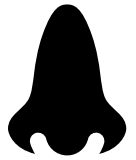
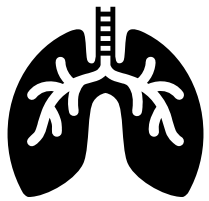


Typical Symptoms 2-14 days after exposure

- Fever
- Chills
- Cough
- Shortness of Breath
- Repeated Shaking with Chills

- Muscle Pain
- Headache
- Sore Throat
- New Loss of Taste or Smell
- Diarrhea

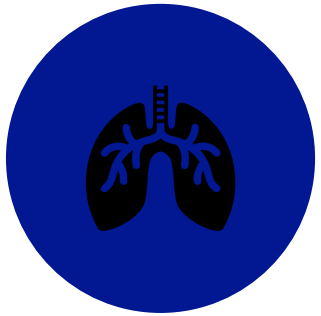


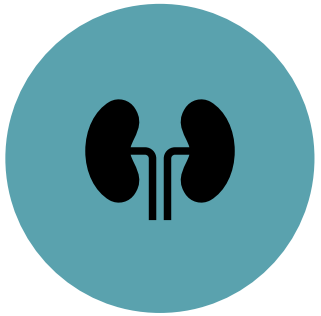
Typical severe presentation requiring hospitalization

Day 1: Patient may have mild symptoms

Day 5: Patient has difficulty breathing



Day 8: Patient may develop an acute respiratory distress syndrome (fluids builds up in lungs) 15% of cases will develop this.



Day 10: Disease progression may require ICU admittance for breathing. But also other manifestations (heart, kidney, stroke etc)

Asymptomatics & Mild Infections

- Some asymptomatic individuals have organ involvement but with no symptoms (see lungs)
- Mild infections report fatigue, shortness of breath 3 months post infection

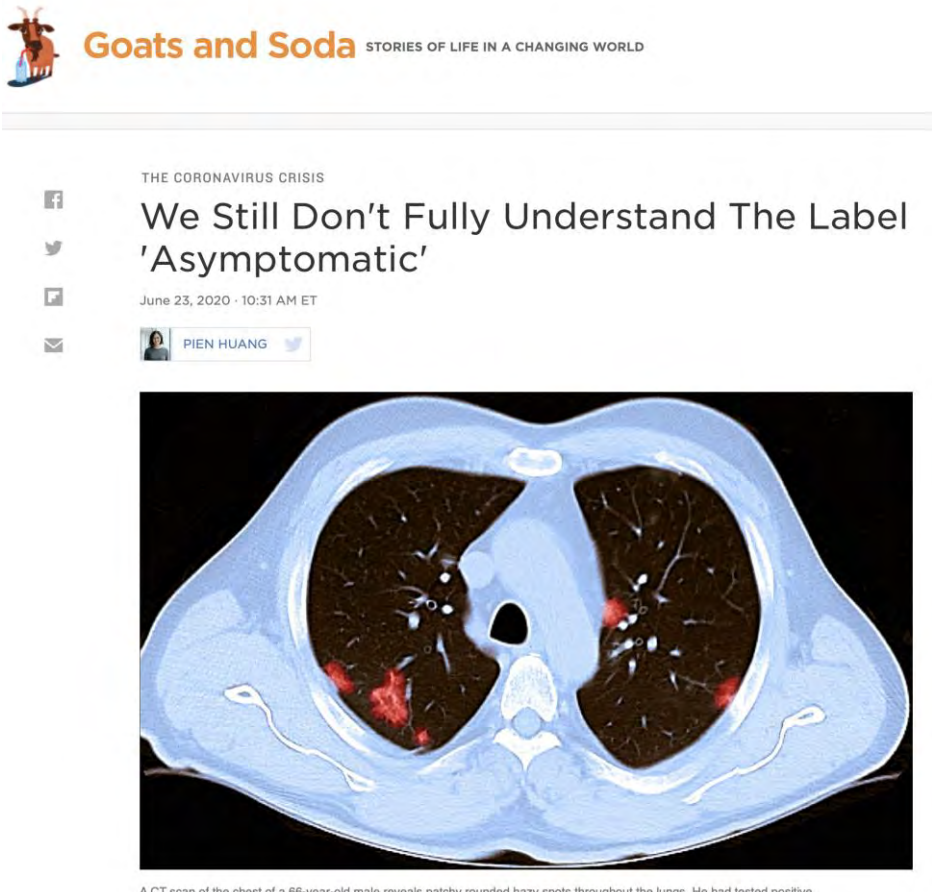

nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-0965-6

Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections

Quan-Xin Long[1,8], Xiao-Jun Tang[2,8], Qiu-Lin Shi[2,8], Qin Li[3,8], Hai-Jun Deng[1,8], Jun Yuan[1], Jie-Li Hu[1], Wei Xu[2], Yong Zhang[2], Fa-Jin Lv[4], Kun Su[5], Fan Zhang[5], Jiang Gong[5], Bo Wu[6], Xia-Mao Liu[7], Jin-Jing Li[7], Jing-Fu Qiu[2,5], Juan Chen[1,2] and Ai-Long Huang[1,2]


Goats and Soda STORIES OF LIFE IN A CHANGING WORLD

THE CORONAVIRUS CRISIS

We Still Don't Fully Understand The Label 'Asymptomatic'

June 23, 2020 · 10:31 AM ET

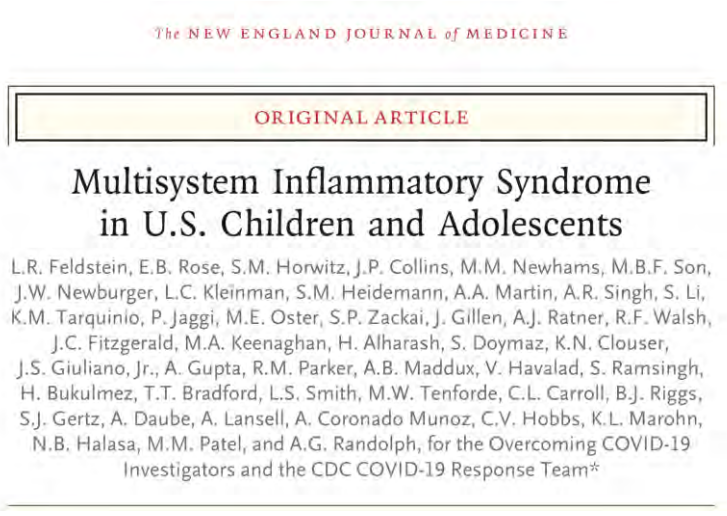
PIEN HUANG

"I suspect that, if you followed up with these asymptomatic people in several months, most of their CT scans would be completely normal unless they were known to later develop symptoms," Taylor-Cousar says.

In the midst of an infection, however, doctors can't predict how an individual's case will progress. "There's no way to know who is going to stop with an asymptomatic infection and likely recover completely and who is likely to go on to more severe infection," Schluger says.

Multisystem Inflammatory Syndrome in Children

- Rare (n=1000)
- Temporally associated with COVID-19
- Median age 7.5-11.6 years in US, French and Italian reports
- Male: 62-70%
- ~70% previously healthy
- 20% received invasive mechanical ventilator support
- ~70% had 4 organ system involvement


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

L.R. Feldstein, E.B. Rose, S.M. Horwitz, J.P. Collins, M.M. Newhams, M.B.F. Son, J.W. Newburger, L.C. Kleinman, S.M. Heidemann, A.A. Martin, A.R. Singh, S. Li, K.M. Tarquinio, P. Jaggi, M.E. Oster, S.P. Zackai, J. Gillen, A.J. Ratner, R.F. Walsh, J.C. Fitzgerald, M.A. Keenaghan, H. Alharash, S. Doymaz, K.N. Clouser, J.S. Giuliano, Jr., A. Gupta, R.M. Parker, A.B. Maddux, V. Havalad, S. Ramsingh, H. Bukulmez, T.T. Bradford, L.S. Smith, M.W. Tenforde, C.L. Carroll, B.J. Riggs, S.J. Gertz, A. Daube, A. Lansell, A. Coronado Munoz, C.V. Hobbs, K.L. Marohn, N.B. Halasa, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team*

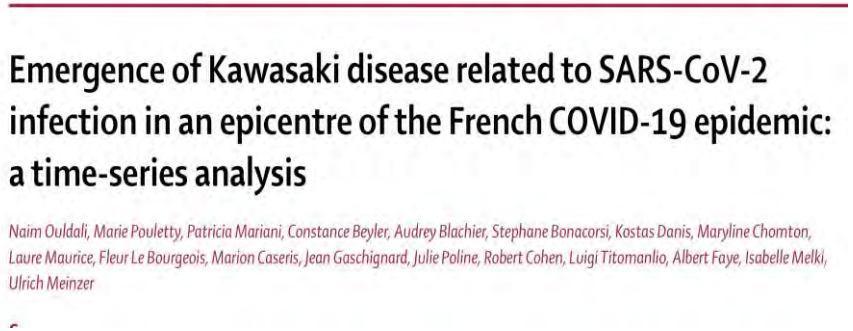

THE LANCET
Child & Adolescent Health

COMMENT | ONLINE FIRST

Kawasaki disease in the COVID-19 era: a distinct clinical phenotype?

Kai-Qian Kam • Jacqueline S M Ong • Jan Hau Lee

Published: July 02, 2020 • DOI: https://doi.org/10.1016/S2352-4642(20)30207-8 • Check for updates


Emergence of Kawasaki disease related to SARS-CoV-2 infection in an epicentre of the French COVID-19 epidemic: a time-series analysis

Naim Ouldali, Marie Pouletty, Patricia Mariani, Constance Beyler, Audrey Blachier, Stephane Bonacorsi, Kostas Danis, Maryline Chomton, Laure Maurice, Fleur Le Bourgeois, Marion Caseris, Jean Gaschignard, Julie Poline, Robert Cohen, Luigi Titomanlio, Albert Faye, Isabelle Melki, Ulrich Meinzer

But its clear there is nothing typical about COVID-19

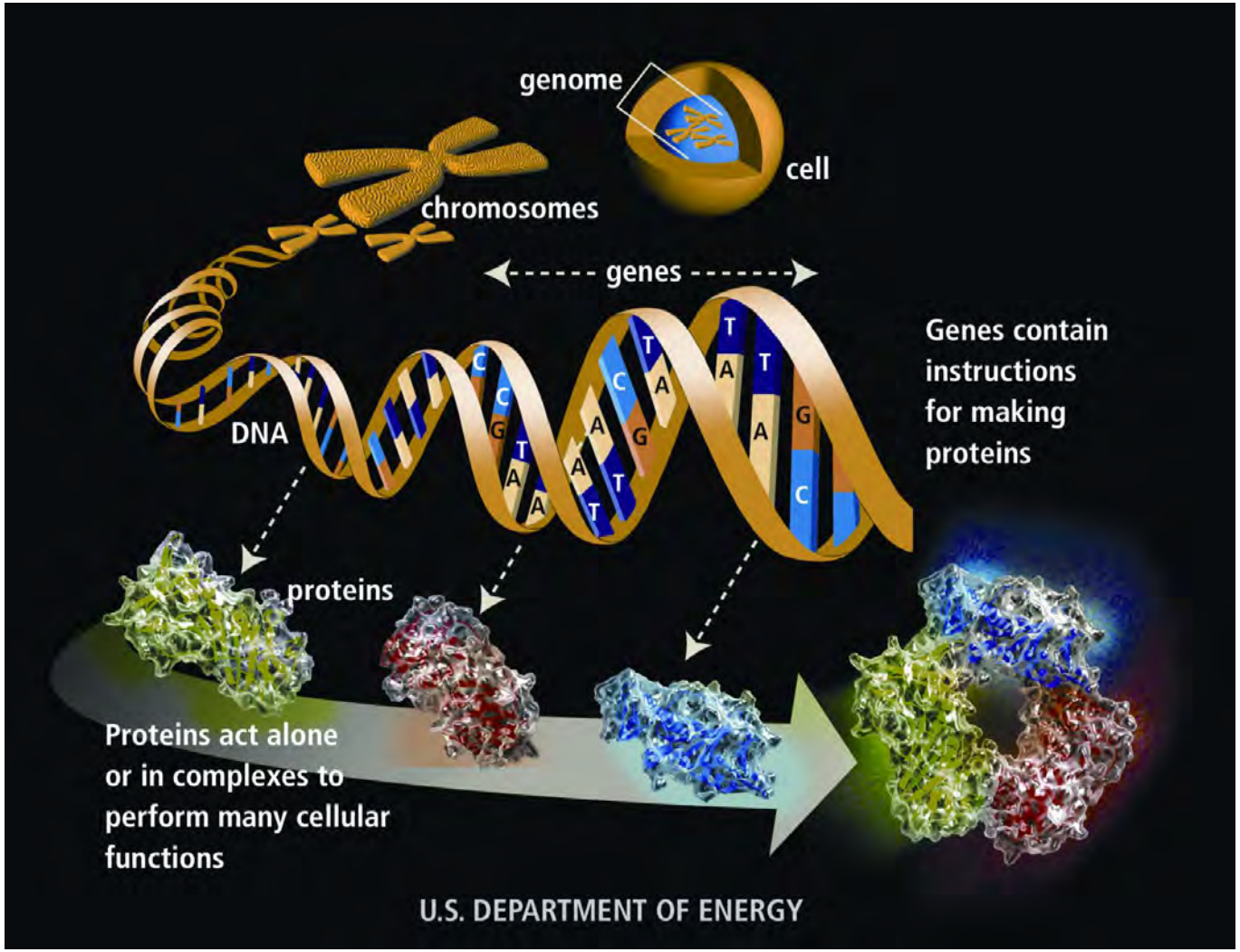
"I have never seen infection in which you have such a broad range literally no symptoms at all in a substantial proportion of the population to some who get ill with minor symptoms to some who get ill enough to be in bed for weeks,"

"Others get hospitalized, require oxygen, intensive care, ventilation and death. The involvement with the same pathogen is very unique."

Anthony Fauci, July 21, 2020

…except disease heterogeneity


Host Genetics and COVID-19



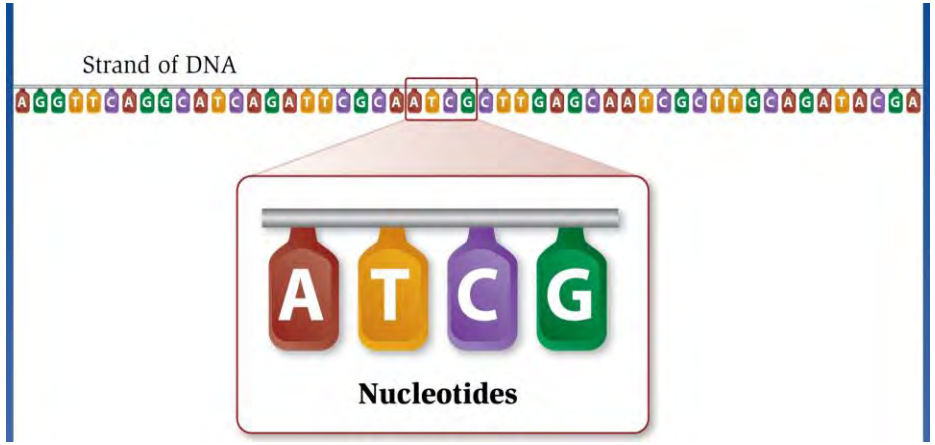
Cells use DNA that codes genes to create proteins (Myoglobin, Collagen, etc)

These proteins work together and interactively to facilitate cell function

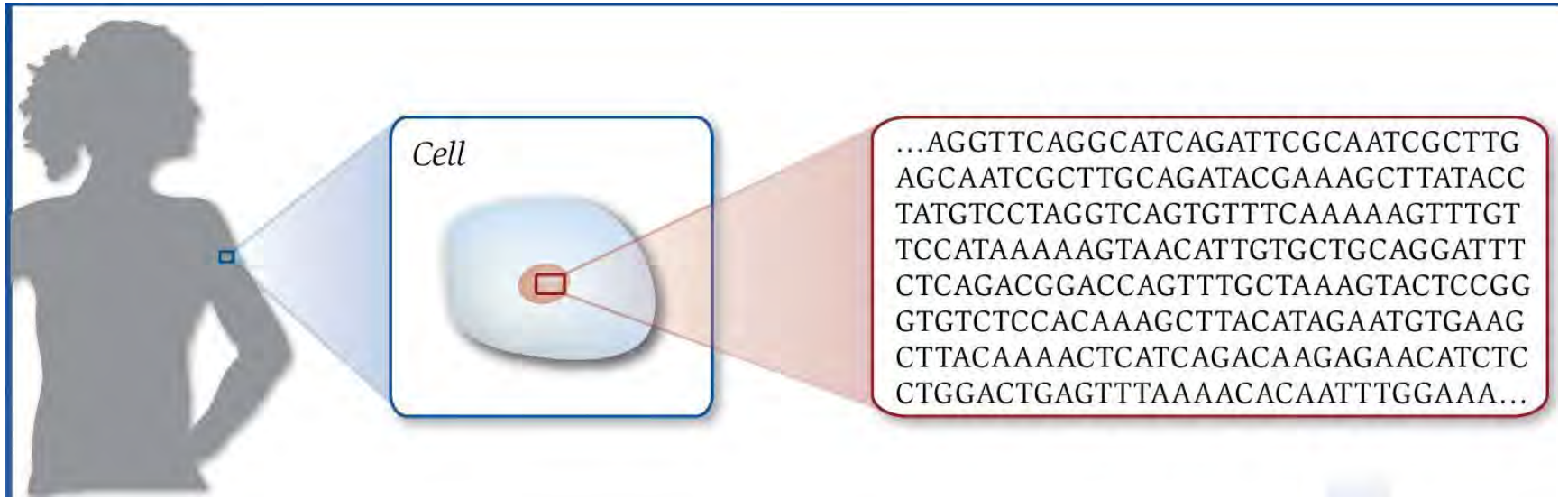
Central Dogma of Genetics

DNA → RNA → Protein

DNA, our building blocks

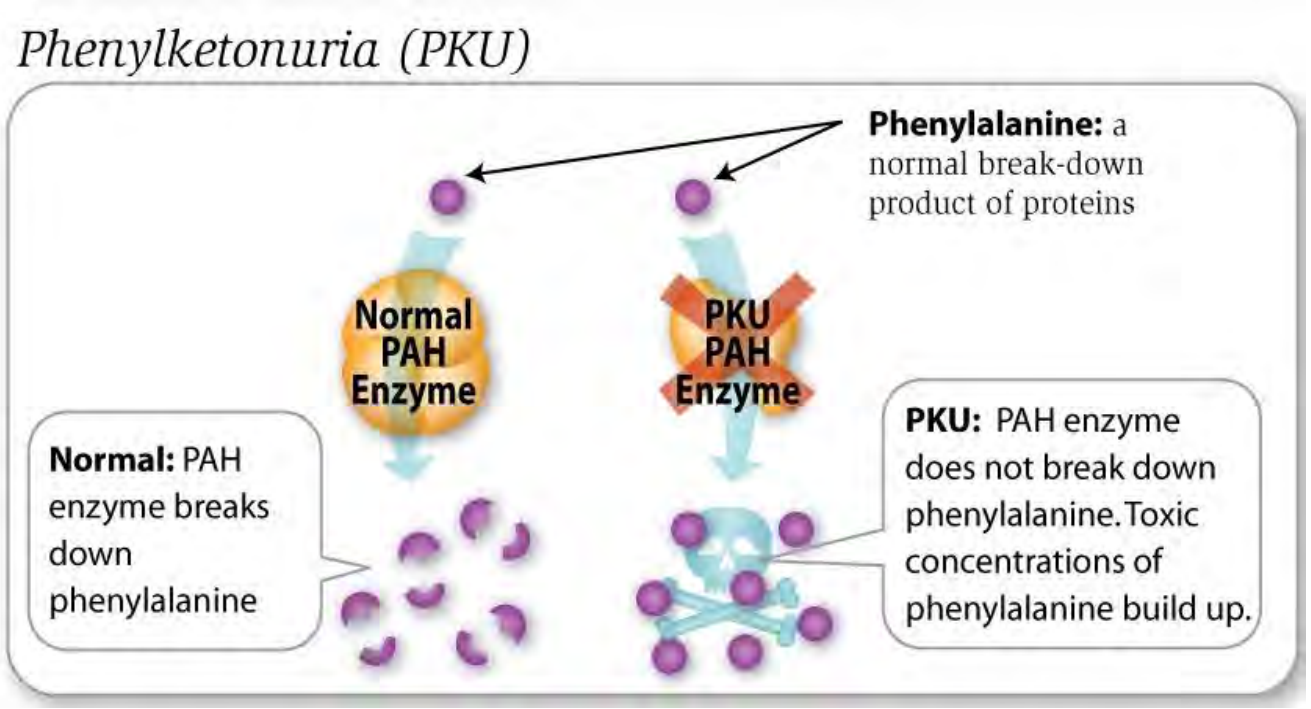


The human genome contains ~3 billion nucleotides
(= 200 1000 page phone books)



Slides courtesy of NIH

Differences in protein function



NHGRI/NIH

Any two humans have 99.9% genetically identical sequence…so why are we studying our genes?

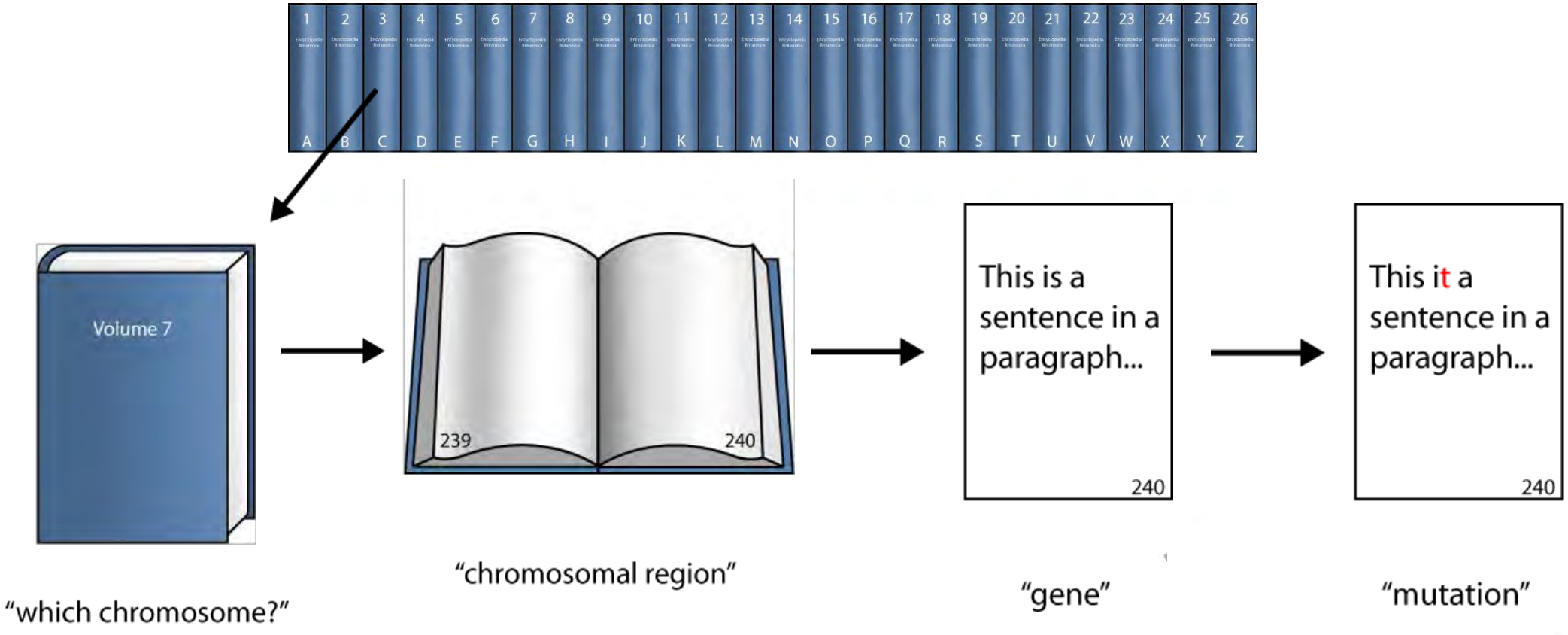
This results in 1 difference every 1000 nucleotides, resulting in ~3 million nucleotide differences between any 2 people.

AAAACGTCAAGGGGACAGGGGTTTAACGGGTTTTACT
AGTCGATCGATTTGGGGGACTTTGAAATCAGATCAGAT
CAGATTTCAGGATATTTAGGGCTCTAG

AAAACGTCAAGGTGACAGGGGTTTAACGGGTTTTACT
AGTCGATCGATTTGGGGGACTTTGAAATCAGATCAGAT
CAGATTTCAGGATATTTAGGGCTCTAG

How to Find Genes Responsible for Human Disease

Difficult challenge to find a disease gene—like finding a misspelled word in a set of encyclopedias!



Genetic Epidemiology Approach

- Genotype individuals using large scale arrays or targeted candidate genes (Receptors, Cytokines etc)
- Sequence individuals (exome or whole genome)—ideal to get multiple affected families
- Compare polymorphisms (SNPs/SNVs) across the genome with case/control status
- We are looking for associations that may give us information on disease pathogenesis

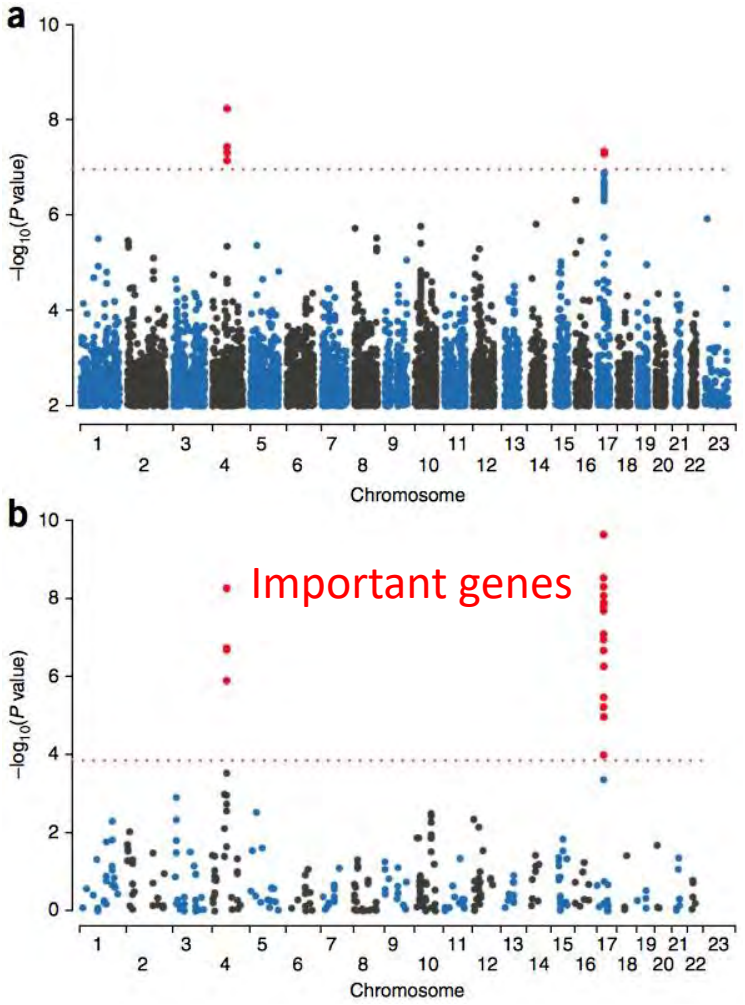
How do we do genetics?
One example: Genome Wide Association Study

Two-stage design

Stage 1: 500K Illumina panel in 1,700 cases and 4,000 controls

- Cochran-Armitage test for trend

Stage 2: replication in an independent cohort of 3,500 cases and 4,800 controls of the 384 most associated SNPs



Source: Simón-Sánchez, J., Schulte, C., Bras, J. M., et al. (2009, December). Genome-wide association study reveals genetic risk underlying Parkinson's disease. *Nat Genet, 41*, 12, 1308–1312.

If we can understand why people have different outcomes---we will better understand the immune response and eventually exploit this understanding for therapeutics and vaccines.

Our goals…are still to *better understand disease* so we can prevent and treat.

Things we look for to see if genetics might be playing a role…

- **Disease Heterogeneity**
- **Familial aggregation**
- **Pathogen Dose and Environment**

Reported Risk Factors for Severe Disease

Older Age

Male Sex

Comorbidities

Race

And yet…

Older people (even 102 years of age) recover

Younger people require mechanical ventilation and even die with no comorbidities.

Race appears to be a risk factor—but as a social risk factor *not biologic*

Things we look for to see if genetics might be playing a role….

- **Disease Heterogeneity**
  - Not explained by other risk factors (sex, age, comorbidities)
- **Familial aggregation**
  - Hard to assess with infectious diseases because of transmission
- **Pathogen Dose and Environment**
  - not major players (yet)

Driven by 2 main questions

Do you get infected?

Do you get disease?

What makes infectious diseases different?

EXPOSURE

We need to know who was exposed

Need careful and **comprehensive characterization** of infection and disease.

CONTROLS matter. If you call someone uninfected you need to know they were exposed & still uninfected.

Do you get infected (susceptibility)?

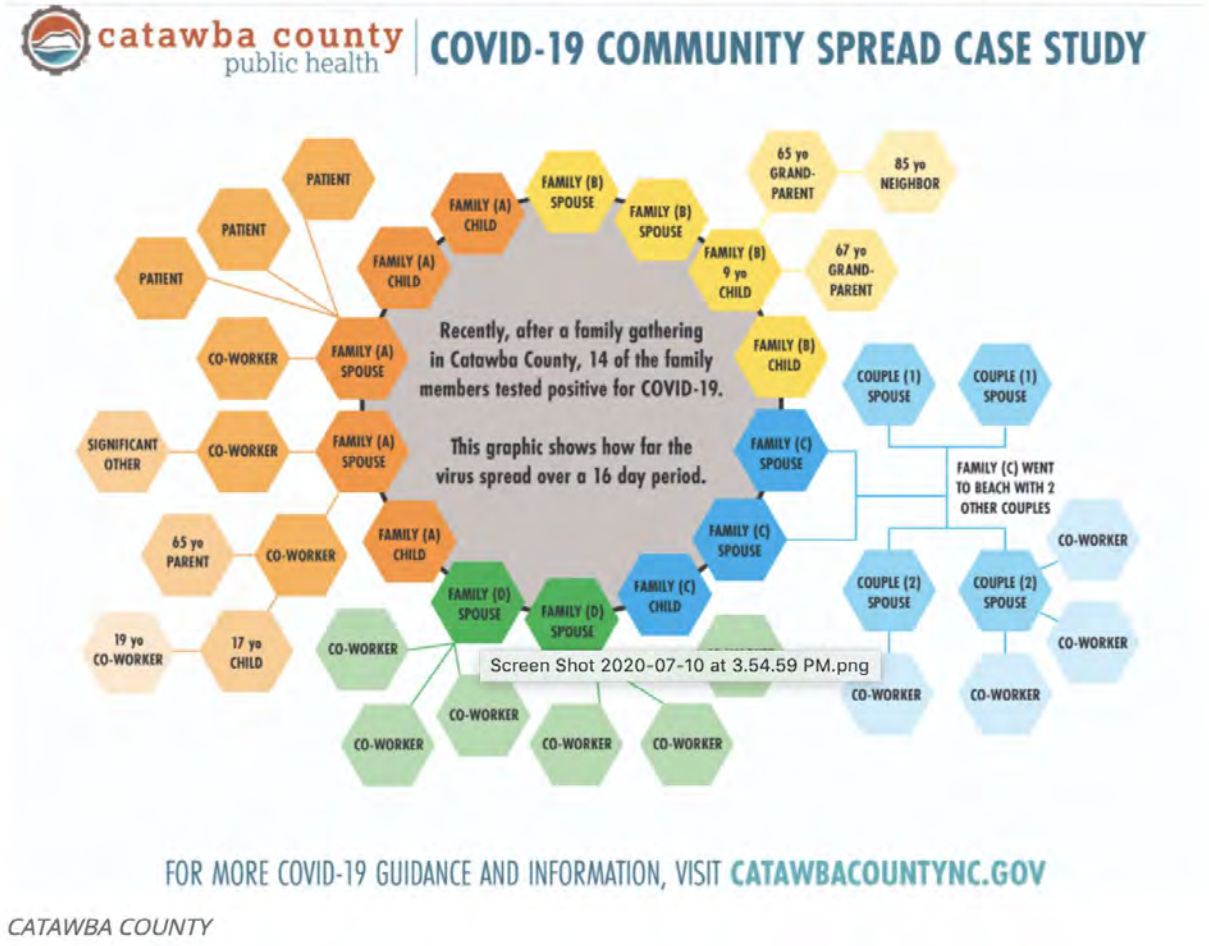
- This requires *detailed* information on the population under study
- **We need to know the non-infected were exposed, and yet still did not get infected**

Study Design

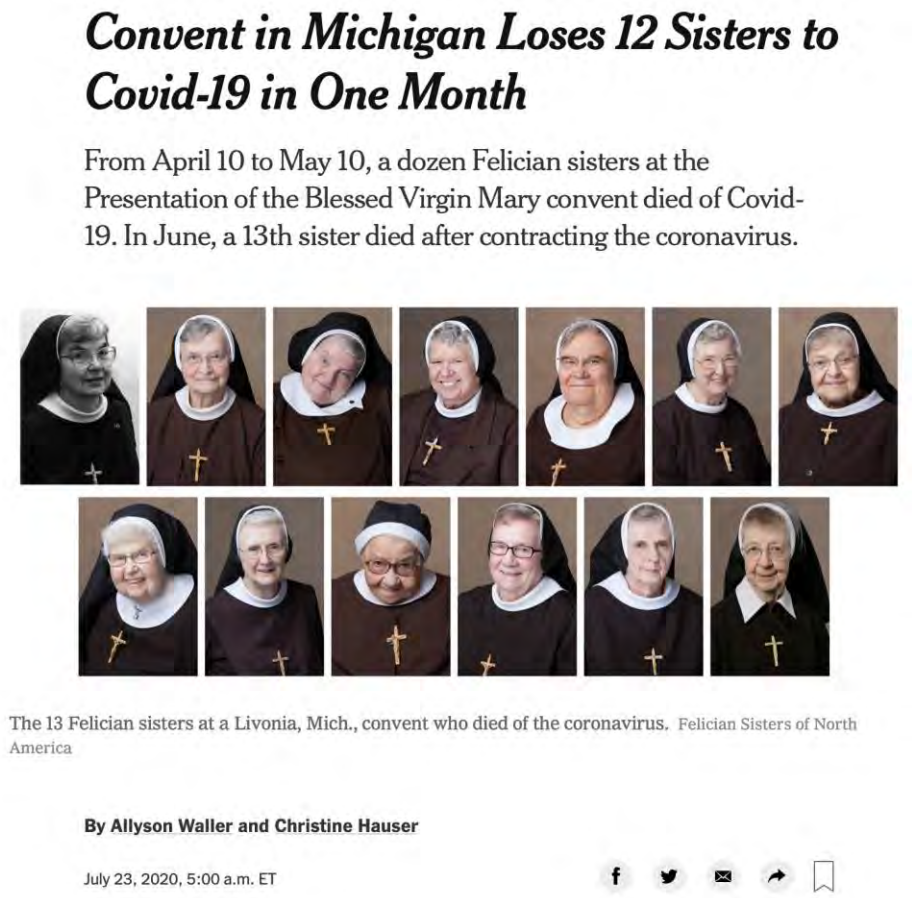
- Focus is typically on highly exposed individuals where you can document or infer that individuals were exposed

  - Health Care Workers/Essential Workers
  - Household members of known cases
  - Intensely followed cohorts (currently none for COVID-19)

Who gets infected? Who doesn't?



CATAWBA COUNTY



Convent in Michigan Loses 12 Sisters to Covid-19 in One Month

From April 10 to May 10, a dozen Felician sisters at the Presentation of the Blessed Virgin Mary convent died of Covid-19. In June, a 13th sister died after contracting the coronavirus.

The 13 Felician sisters at a Livonia, Mich., convent who died of the coronavirus. Felician Sisters of North America

By Allyson Waller and Christine Hauser

July 23, 2020, 5:00 a.m. ET

>24 people in attendance, 14 infected at the party

13 sisters died, 18 others infected, 65 total in convent

Do you get disease (severity)?

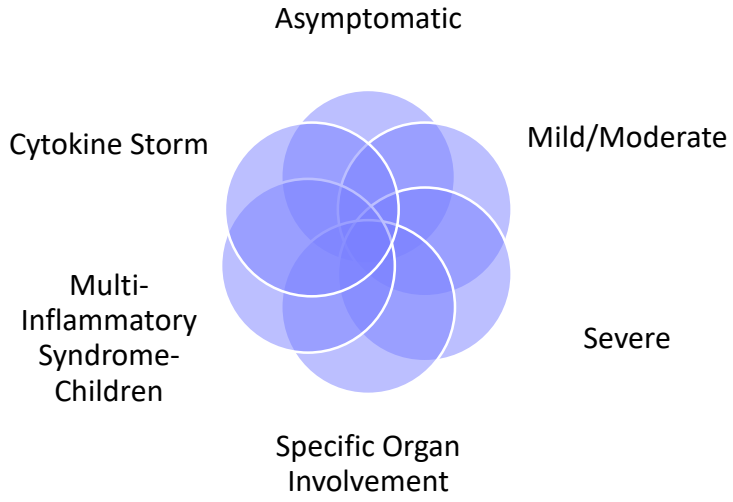
- This is about the *heterogeneity* in disease.

Study Design

- **We select cases and controls from among individuals who ALL have the infection**
  - **asymptomatic to severe/death**
  - **sample on distribution or extremes**
- Otherwise, you are comparing a severe case to someone who may have never had the opportunity to become a severe case.

COVID-19 Clinical Spectrum

- 80% of cases are mild not requiring hospitalizations
  - Long term sequelea?
  - Spectrum of symptoms
- Hospitalized cases heterogeneity
  - Oxygen needs
  - Penumonia
  - Organ involvement: Lungs, Hearts, Liver, Kidney, etc
- Children
  - Mild infections
  - Hospitalized Infections with oxygen needs
  - Multi-Inflammatory syndrome

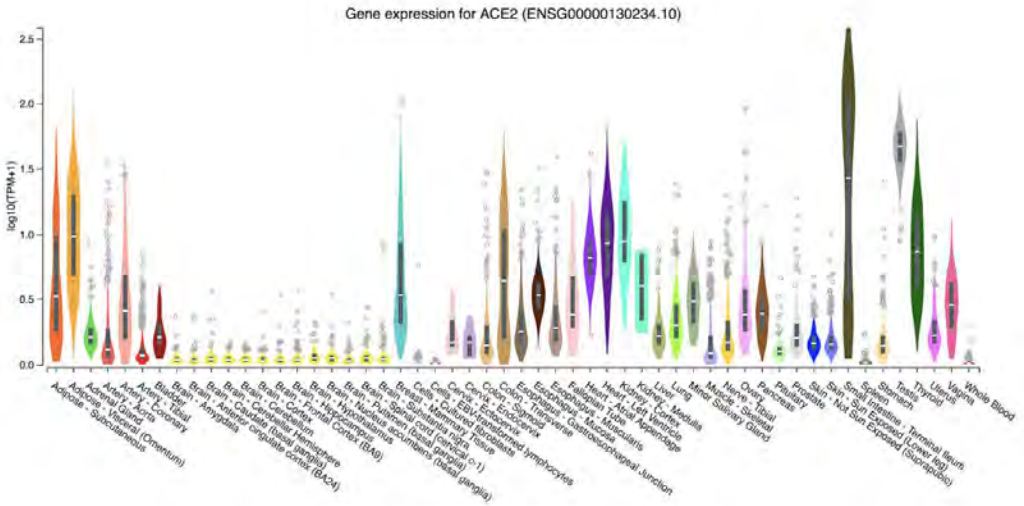


- No free pass. Although some have no real outcomes. Infection across the severity spectrum associated with organ involvement and potentially long term sequelae.

Tissue specific expression and genetic regulation of SARS-CoV-2 receptors ACE2 and TMPRSS2

Yuan He Follow
Mar 26 · 11 min read

Yuan He, Marios Arvanitis, Princy Parsana, Ashton Omdahl, Jessica Bonnie, Zeyu Chen, Christopher D. Brown, Alexis Battle



- Rare variants identified across populations
- But, no direct evidence of binding-resistant mutants in different populations
- ACE2 has **no** significant cis-eQTLs in tissues with high ACE2 expression, including lung, heart, kidney, and small intestine
- ACE2 is predicted to be highly loss of function variant intolerant indicating little effect of genetic variation on ACE2 function or expression

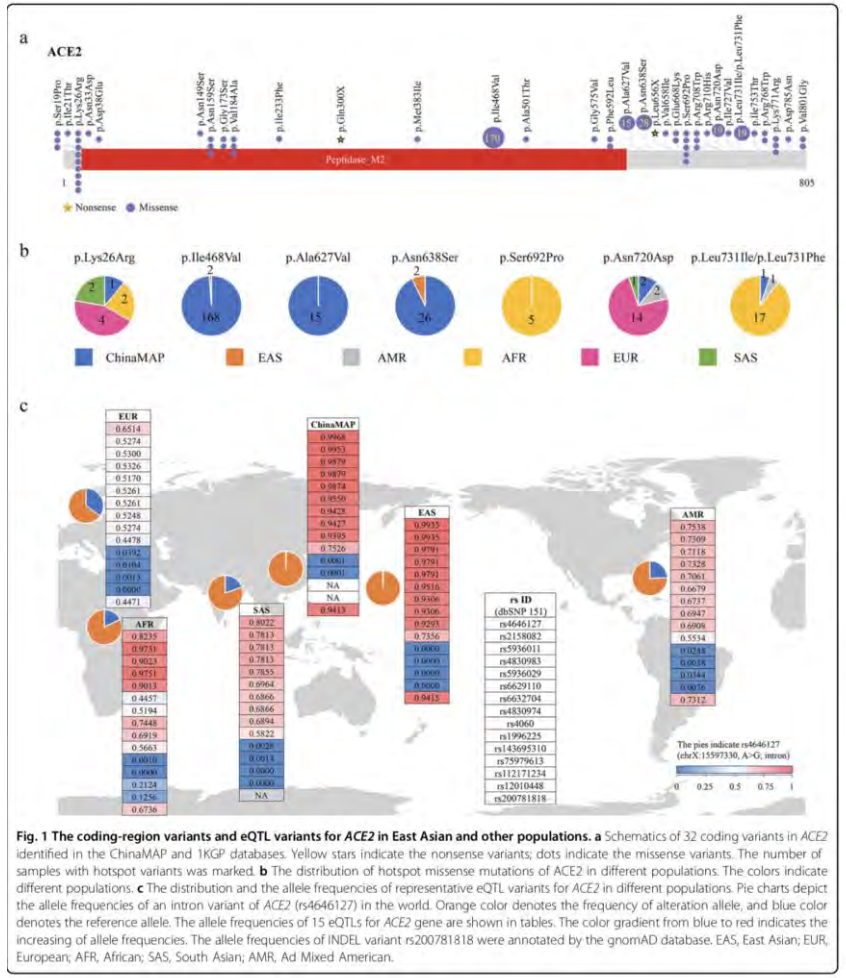


Fig. 1 The coding-region variants and eQTL variants for *ACE2* in East Asian and other populations. a Schematics of 32 coding variants in *ACE2* identified in the ChinaMAP and 1KGP databases. Yellow stars indicate the nonsense variants; dots indicate the missense variants. The number of samples with hotspot variants was marked. **b** The distribution of hotspot missense mutations of ACE2 in different populations. The colors indicate different populations. **c** The distribution and the allele frequencies of representative eQTL variants for *ACE2* in different populations. Pie charts depict the allele frequencies of an intron variant of *ACE2* (rs4646127) in the world. Orange color denotes the frequency of alteration allele, and blue color denotes the reference allele. The allele frequencies of 15 eQTLs for *ACE2* gene are shown in tables. The color gradient from blue to red indicates the increasing of allele frequencies. The allele frequencies of INDEL variant rs200781818 were annotated by the gnomAD database. EAS, East Asian; EUR, European; AFR, African; SAS, South Asian; AMR, Ad Mixed American.

Cao et al. *Cell Discovery* (2020)6:11
https://doi.org/10.1038/s41421-020-0147-1

Cell Discovery
www.nature.com/celldisc

CORRESPONDENCE Open Access

Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations

Yanan Cao, Lin Li, Zhimin Feng, Shengqing Wan, Peide Huang, Xiaohui Sun, Fang Wen, Xuanlin Huang, Guang Ning and Weiqing Wang

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genomewide Association Study of Severe Covid-19 with Respiratory Failure

The Severe Covid-19 GWAS Group*

ABSTRACT

Cases: Hospitalized COVID+ * (n=835 Italy/ 775 Spain)
Controls: Population based blood donors (1255 Italy/950 Spain)

*no information on comorbidities or treatment

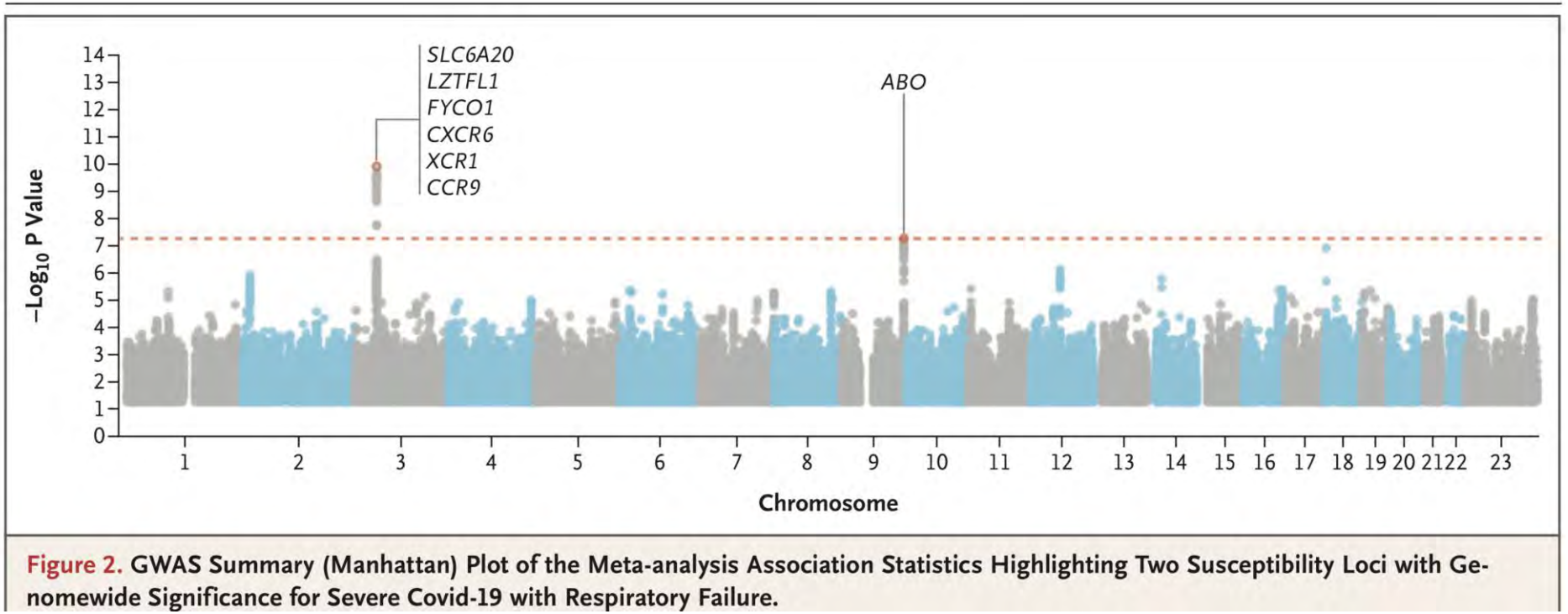


Figure 2. GWAS Summary (Manhattan) Plot of the Meta-analysis Association Statistics Highlighting Two Susceptibility Loci with Genomewide Significance for Severe Covid-19 with Respiratory Failure.

The COVID19-HGI in numbers https://www.covid19hg.org/

- **1128 members**
- 69,255 unique users on the website
- 243,118 page view

Scientists

Andrea Ganna and Mark Daly

- **201 studies from 51 countries**
- **16 (+3) "contributing studies"**

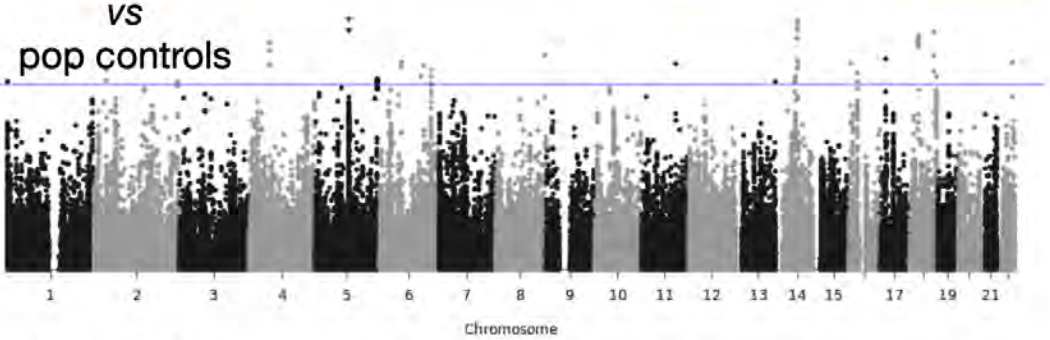
Studies

Countries that have shared results:

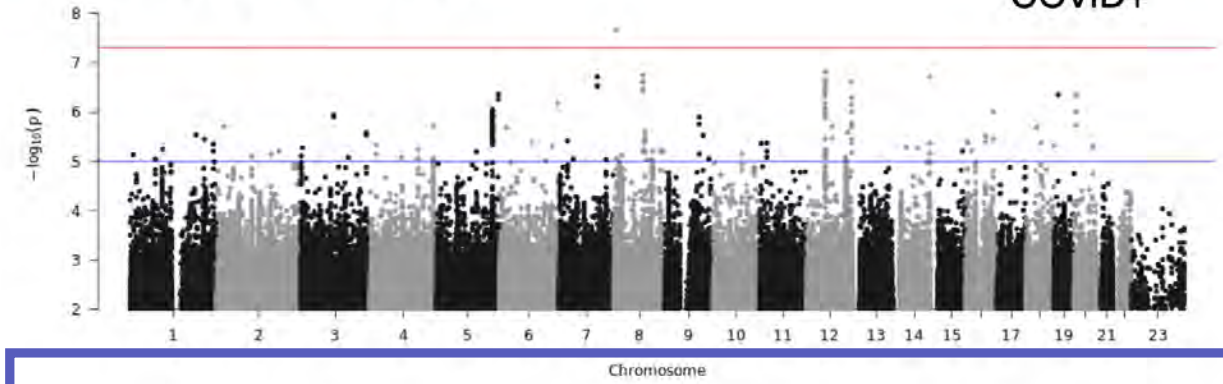
UK (4 studies), Iceland, Italy (2), Spain, Netherlands (2), Finland, USA (2), Qatar, Brazil, Belgium, Scotland, Korea

Results meta-analysis V3

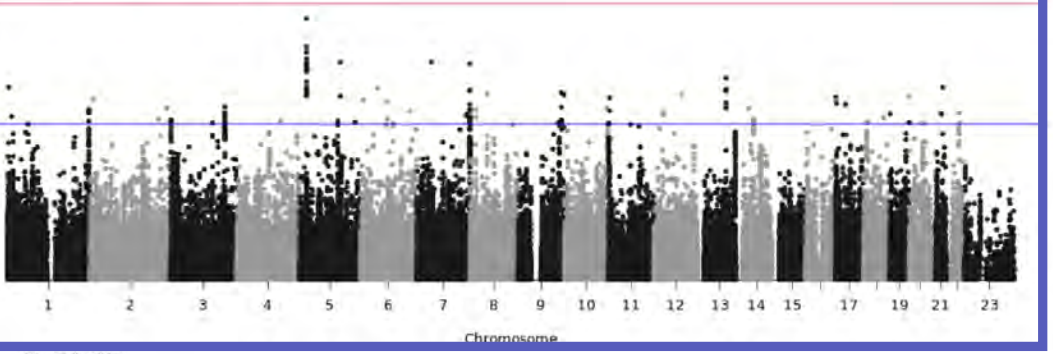
Severe Hosp COVID+ *vs* pop controls



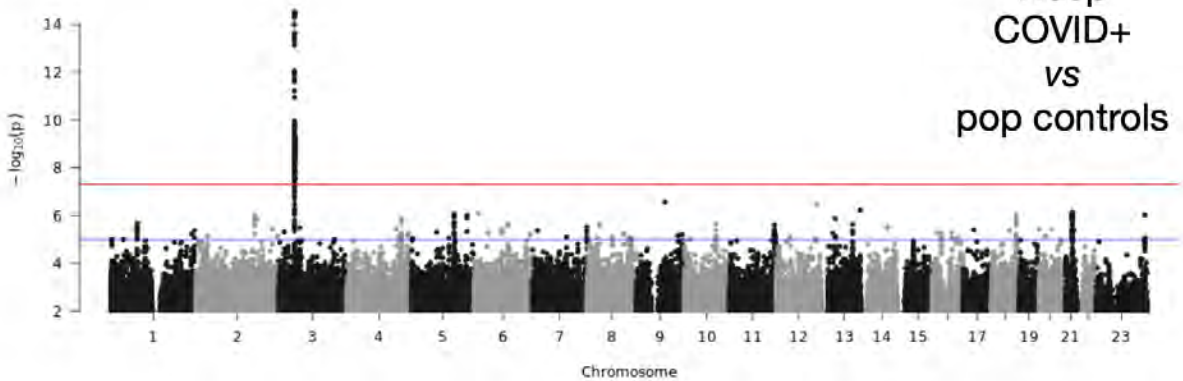
Predicted COVID+



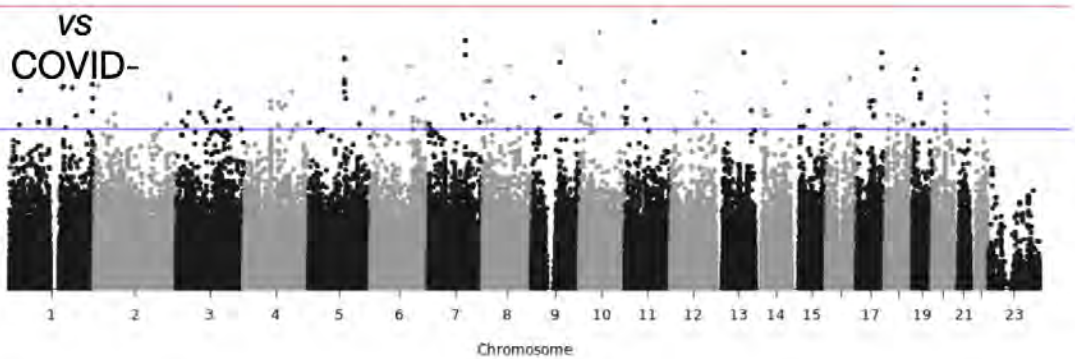
Hosp COVID+ *vs* non-Hosp COVID+



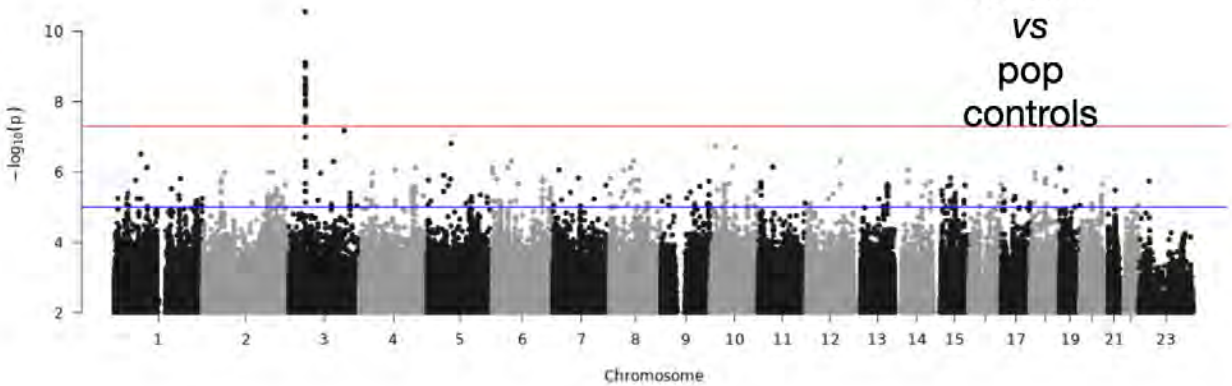
Hosp COVID+ *vs* pop controls



COVID + *vs* COVID-

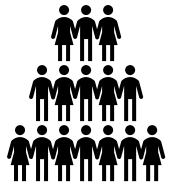


COVID+ *vs* pop controls

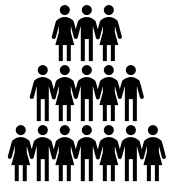


What are we doing at Johns Hopkins?

Hospitalized



Ambulatory



Genotyping

Main Aim to identify genes that are associated with severe or mild disease

What else should we look at?

We need to be driven by the question.

Rare cases of particular outcomes (MIS-C, clotting, kidney damage)

What makes these individuals different?

Associations with cytokines, inflammatory markers.

Can we identify early associations with biomarkers?

Associations with humoral and T cell immunity?

Does genetics influence the antibody or T cell response to infection or reinfection?

Pharmacogenetics for clinical trials.

Does host genetics alter clinical trial meds?

Linking genetics with genomics.

Evaluating genetics, epigenetic, transcriptomics and others to tell a more complete story

Associations with viral pathogen.

Is there host-pathogen interaction?

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COVIDGene Team

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