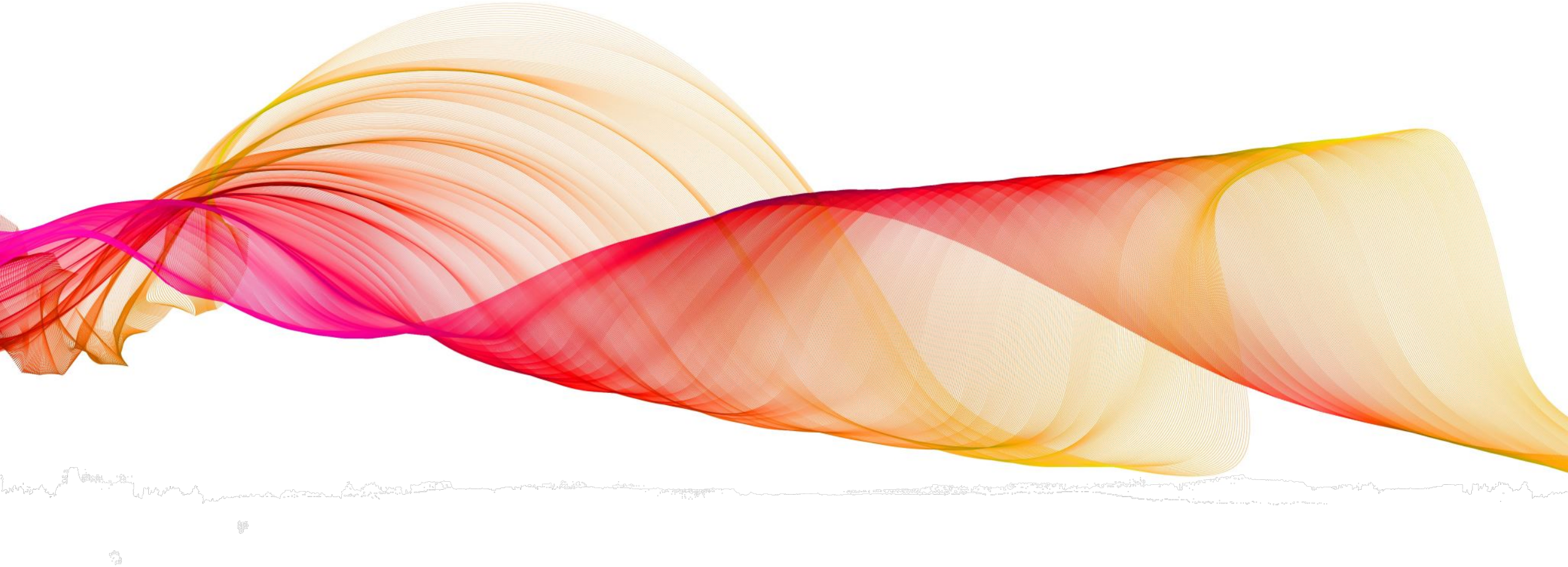

Host Genetics and COVID-19

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Johns Hopkins Bloomberg School of Public Health

February 4, 2021

Why consider genetics in the study of infectious disease?

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.

Infectious Disease: A complex trait?

Infectious Disease is a perfect example of a complex trait

- Environmental **Exposure**: Exposure to a pathogen is critical.
- Redundancy and Complexity of the immune system suggest **multiple genes** may be involved in immune response.
- The **pathogen** (virus, bacteria, parasite) may also have **genetic factors** that are important.

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**

3. Controlling Dose/Pathogen

- We learn from our mistakes…
- 1926, Lubeck Germany
- 249 babies injected with the same live dose of virulent M. tuberculosis instead of BCG.
- Babies too young to have significant prior exposure to mycobacteria, and not previously vaccinated to BCG.
- All got the same strain, same dose.

76 babies died, 173 babies survived

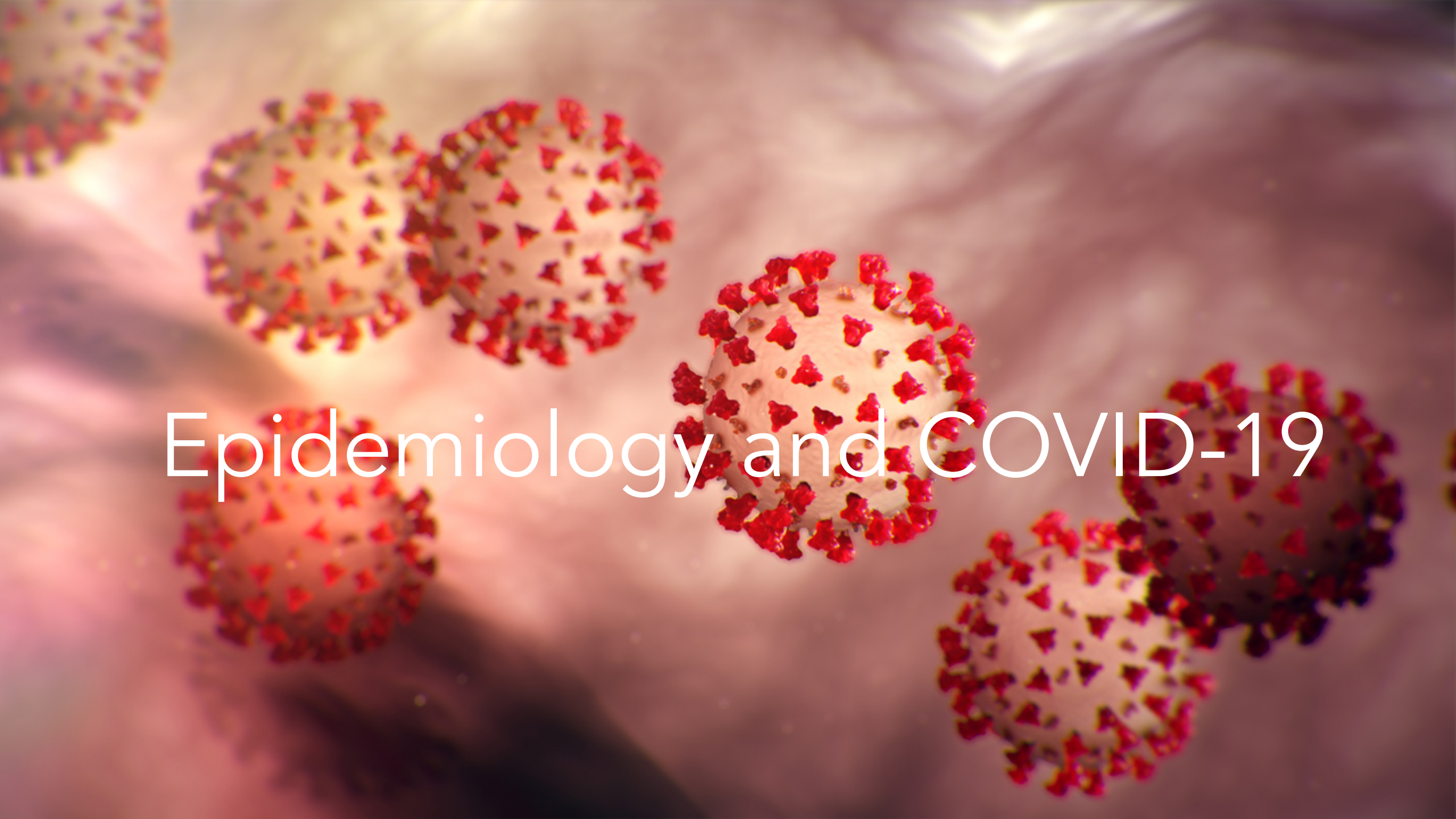
Driven by 2 main questions

Do you get infected?

Do you get disease?

What makes infectious diseases different?

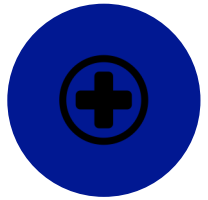
EXPOSURE


Epidemiology and COVID-19

Typical Presentations of COVID-19 for a disease that doesn't seem so typical…

Asymptomatic

Mild Infections



Hospitalized Infections. Disease progression with ICU monitoring and multiple organ manifestations

Multi-inflammatory Syndrome

Children and Adults

Post Acute Symptoms
"Long Haulers"

A LOT OF HETEROGENEITY

Asymptomatics & Mild Infections

- Asymptomatic individuals have longer duration of viral shedding
- Asymptomatic individuals have weaker immune response
- Some asymptomatic individuals have organ involvement but with no symptoms (see lungs)
- Mild infections report fatigue, shortness of breath 3 months post infection
- No free pass. Infection across the severity spectrum associated with organ involvement and potentially long term sequelae.

nature medicine

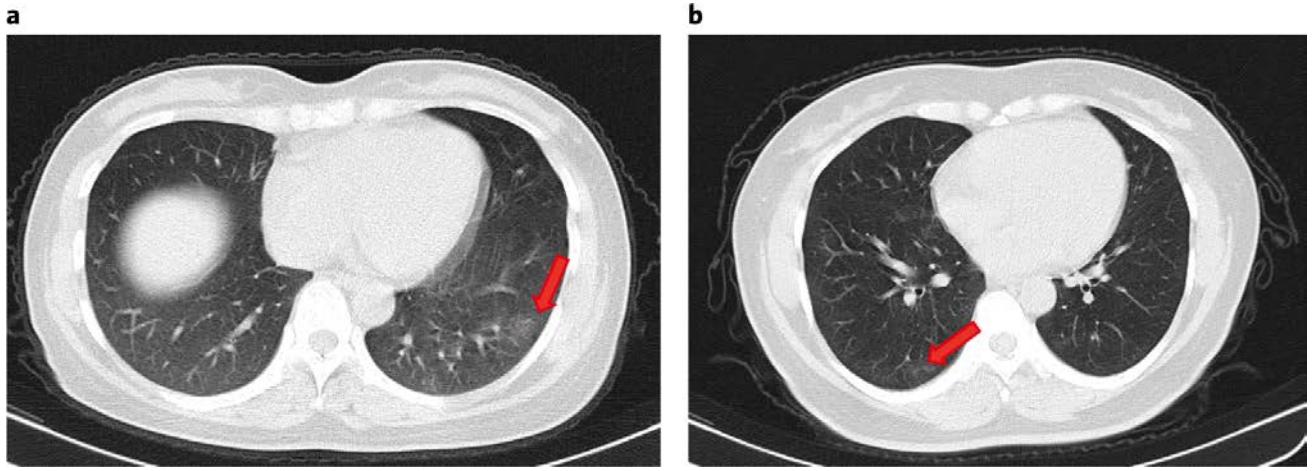
LETTERS

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

Check for updates

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[3], Fan Zhang[5], Jiang Gong[5], Bo Wu[6], Xia-Mao Liu[7], Jin-Jing Li[7], Jing-Fu Qiu[2]✉, Juan Chen[1]✉ and Ai-Long Huang[1]✉



Risk Factors for Severe Disease

Older Age

Male Sex

Comorbidities

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*

Viral genetics does not seem to play a role in severity of disease, yet.

So is there a place for host genetics?

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/First Responders
  - Household members of known cases
  - Intensely followed cohorts (like withSTD/HIV high risk individuals)

Do you get disease (severity)?

- This is about the *heterogeneity* in disease.

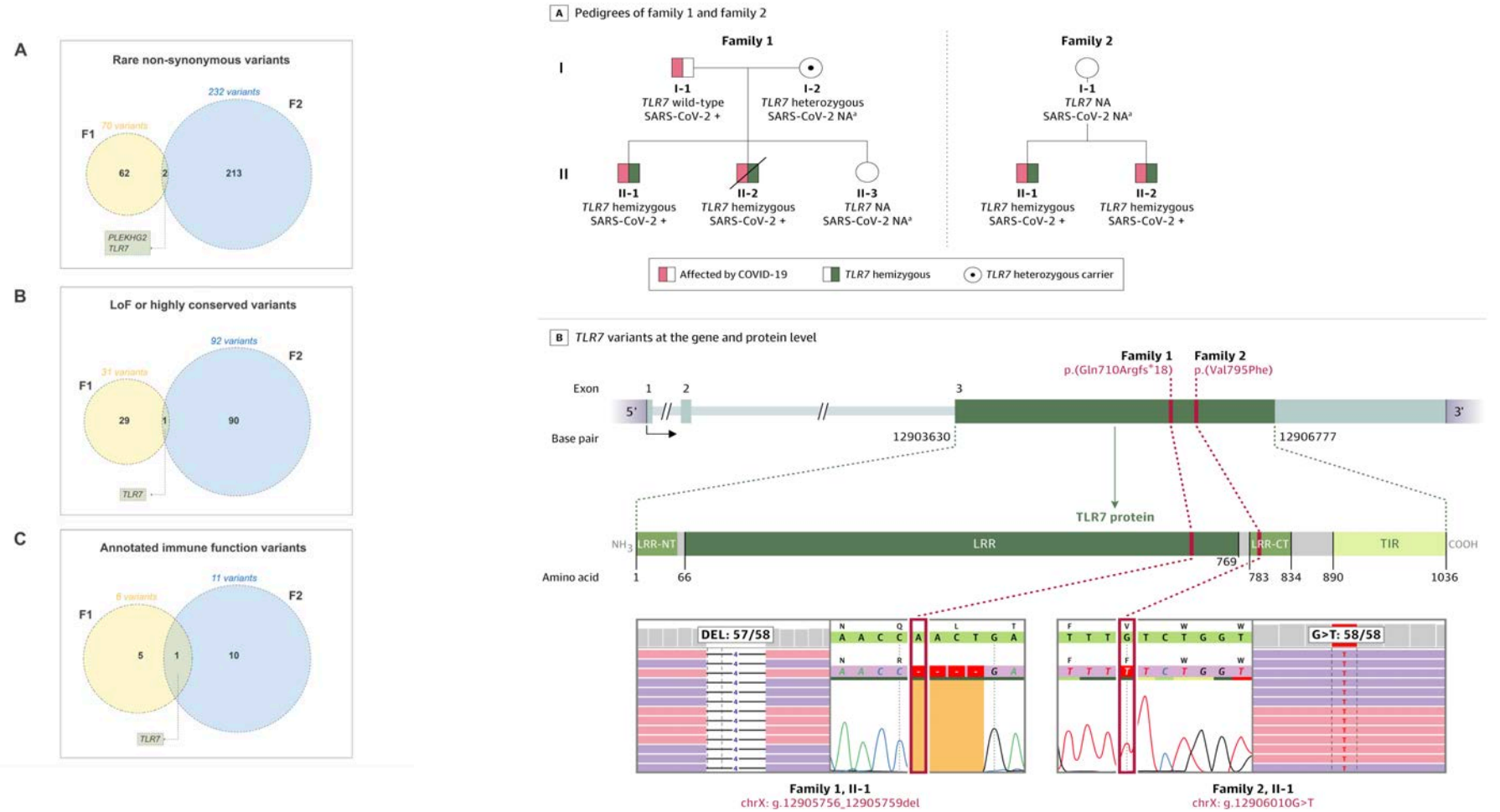
Study Design

- 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.

Types of suitable genetic studies based on underlying hypothesis..

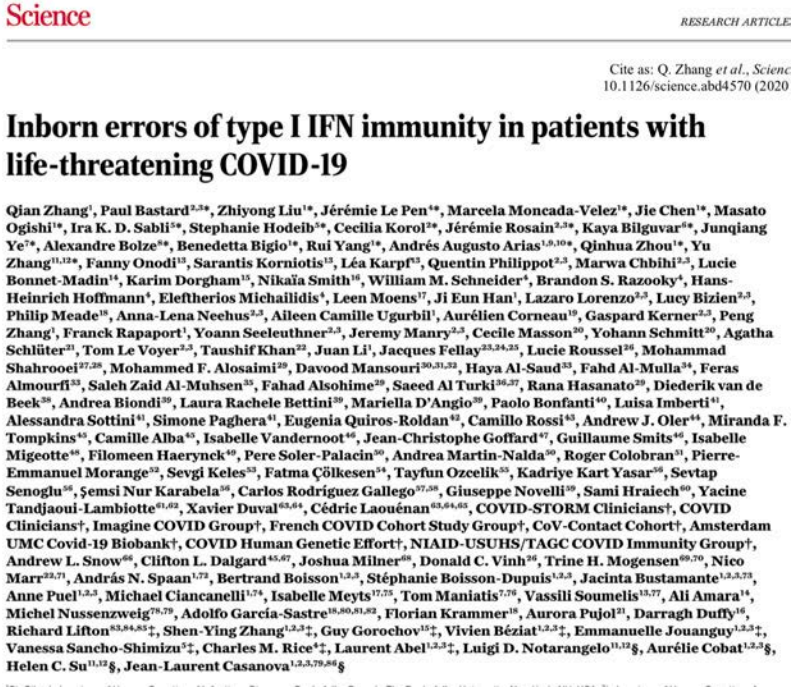
- Rare Disease
  - Family based or multiple affecteds with rare outcomes and exome/WGS
- Common Disease
  - population based GWAS or exome sequencing

From: **Presence of Genetic Variants Among Young Men With Severe COVID-19**
JAMA. 2020;324(7):663-673. doi:10.1001/jama.2020.13719



Identification of TLR7 Variants in 4 Patients From 2 Families With Severe Coronavirus Disease 2019 (COVID-19) Patients II-1 and II-2 from family 1 lived in separate households, patients II-1 and II-2 from family 2 were housed together. Circles represent female family members; squares, males. A slash symbol represents a deceased individual. Panel B shows the TLR7 variants in each family at the gene and protein level in a schematic representation. The TLR7 protein structure is shown with leucine-rich repeat region (LRR), N- and C-termini (LRR-NT, LRR-CT) and the toll-interleukin receptor (TIR) homology domain. The exon-intron structure depicts the coding exon 3 of TLR7 with the identified variants by exome sequencing and Sanger sequencing validation as shown in the highlighted sections below. Red boxes depict positions of the variants ChrX(GRCh37):g.12905756_12905759del and ChrX(GRCh37):g.12906010G>T). NA indicates not assessed.

[a]At the time of evaluation, testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was not routinely performed.



Science RESEARCH ARTICLE

Cite as: Q. Zhang *et al.*, *Scienc*
10.1126/science.abd4570 (2020

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Qian Zhang[1], Paul Bastard[2,3]*, Zhiyong Liu[1]*, Jérémie Le Pen[4]*, Marcela Moncada-Velez[1]*, Jie Chen[1]*, Masato Ogishi[1]*, Ira K. D. Sabli[5]*, Stephanie Hodeib[5]*, Cecilia Korol[2]*, Jérémie Rosain[2,3]*, Kaya Bilguvar[6]*, Junqiang Ye[7]*, Alexandre Bolze[6]*, Benedetta Bigio[1]*, Rui Yang[1]*, Andrés Augusto Arias[1,9,10]*, Qinhua Zhou[1]*, Yu Zhang[11,12]*, Fanny Onodi[13], Sarantis Korniotis[13], Léa Karpf[13], Quentin Philippot[2,3], Marwa Chbihi[2,3], Lucie Bonnet-Madin[14], Karim Dorgham[15], Nikaïa Smith[16], William M. Schneider[4], Brandon S. Razooky[4], Hans-Heinrich Hoffmann[4], Eleftherios Michailidis[4], Leen Moens[17], Ji Eun Han[1], Lazaro Lorenzo[2,3], Lucy Bizien[2,3], Philip Meade[18], Anna-Lena Neehus[2,3], Aileen Camille Ugurbil[1], Aurélien Corneau[19], Gaspard Kerner[2,3], Peng Zhang[1], Franck Rapaport[1], Yoann Seeleuthner[2,3], Jeremy Manry[2,3], Cecile Masson[20], Yohann Schmitt[20], Agatha Schlüter[21], Tom Le Voyer[2,3], Taushif Khan[22], Juan Li[1], Jacques Fellay[23,24,25], Lucie Roussel[26], Mohammad Shahrooei[27,28], Mohammed F. Alosaimi[29], Davood Mansouri[30,31,32], Haya Al-Saud[33], Fahd Al-Mulla[34], Feras Almourfi[33], Saleh Zaid Al-Muhsen[35], Fahad Alsohime[29], Saeed Al Turki[36,37], Rana Hasanato[29], Diederik van de Beek[38], Andrea Biondi[39], Laura Rachele Bettini[39], Mariella D'Angio[39], Paolo Bonfanti[40], Luisa Imberti[41], Alessandra Sottini[41], Simone Paghera[41], Eugenia Quiros-Roldan[42], Camillo Rossi[43], Andrew J. Oler[44], Miranda F. Tompkins[45], Camille Alba[45], Isabelle Vandernoot[46], Jean-Christophe Goffard[47], Guillaume Smits[46], Isabelle Migeotte[48], Filomeen Haerynck[49], Pere Soler-Palacin[50], Andrea Martin-Nalda[50], Roger Colobran[51], Pierre-Emmanuel Morange[52], Sevgi Keles[53], Fatma Çölkesen[54], Tayfun Ozcelik[55], Kadriye Kart Yasar[56], Sevtap Senoglu[56], Şemsi Nur Karabela[56], Carlos Rodríguez Gallego[57,58], Giuseppe Novelli[59], Sami Hraiech[60], Yacine Tandjaoui-Lambiotte[61,62], Xavier Duval[63,64], Cédric Laouénan[63,64,65], COVID-STORM Clinicians†, COVID Clinicians†, Imagine COVID Group†, French COVID Cohort Study Group†, CoV-Contact Cohort†, Amsterdam UMC Covid-19 Biobank†, COVID Human Genetic Effort†, NIAID-USUHS/TAGC COVID Immunity Group†, Andrew L. Snow[66], Clifton L. Dalgard[45,67], Joshua Milner[68], Donald C. Vinh[26], Trine H. Mogensen[69,70], Nico Marr[22,71], András N. Spaan[1,72], Bertrand Boisson[1,2,3], Stéphanie Boisson-Dupuis[1,2,3], Jacinta Bustamante[1,2,3,73], Anne Puel[1,2,3], Michael Ciancanelli[1,74], Isabelle Meyts[17,75], Tom Maniatis[7,76], Vassili Soumelis[13,77], Ali Amara[14], Michel Nussenzweig[78,79], Adolfo García-Sastre[18,80,81,82], Florian Krammer[18], Aurora Pujol[21], Darragh Duffy[16], Richard Lifton[83,84,85]‡, Shen-Ying Zhang[1,2,3]‡, Guy Gorochov[15]‡, Vivien Béziat[1,2,3]‡, Emmanuelle Jouanguy[1,2,3]‡, Vanessa Sancho-Shimizu[5]‡, Charles M. Rice[4]‡, Laurent Abel[1,2,3]‡, Luigi D. Notarangelo[11,12]§, Aurélie Cobat[1,2,3]§, Helen C. Su[11,12]§, Jean-Laurent Casanova[1,2,3,79,86]§

Testing the hypothesis that severe COVID-19 maybe due to monogenic inborn errors of immunity to SARS_CoV-2 with complete/incomplete penetrance

- Enrolled 659 Patients (74.5% men), different ancestries between the ages of 1 month-99 years (median 52 years), plus 534 COVID-19 mild/asymptomatic controls.
- Sequenced their whole genome n=364 or exome n=295
- Hyp = variants at 13 loci (immune related and previously implicated in influenza severity) may be responsible for outcome.
- Identified 4 unrelated patients with LOF allelic variants of IRF7 or IFNAR1. Further tested overexpression of these genes and identified 8 genes with deleterious mutations
- None of the cases carried the same LOF, but a LOF in the pathway of genes.
- Functional evidence to support this pathway.

Genome Wide Association Studies and COVID-19

- Ellinghaus, NEJM
- Baillie, Nature
- 23&Me, under review
  - https://www.medrxiv.org/content/10.1101/2020.09.04.20188318v1.full.pdf
- Ancestry.com, under review
  - https://www.medrxiv.org/content/10.1101/2020.10.06.20205864v1


ORIGINAL ARTICLE

Genomewide Association Study of Severe Covid-19 with Respiratory Failure

The Severe Covid-19 GWAS Group*

Article Figures/Media Metrics

42 References 221 Citing Articles Letters

October 15, 2020
N Engl J Med 2020; 383:1522-1534
DOI: 10.1056/NEJMoa2020283
Chinese Translation 中文翻译


nature > articles > article

Article | Published: 11 December 2020

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Genetic mechanisms of critical illness in Covid-19

Erola Pairo-Castineira, Sara Clohisey, [...] J. Kenneth Baillie

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 or health volunteers (1255 Italy/950 Spain)

*no information on comorbidities or treatment

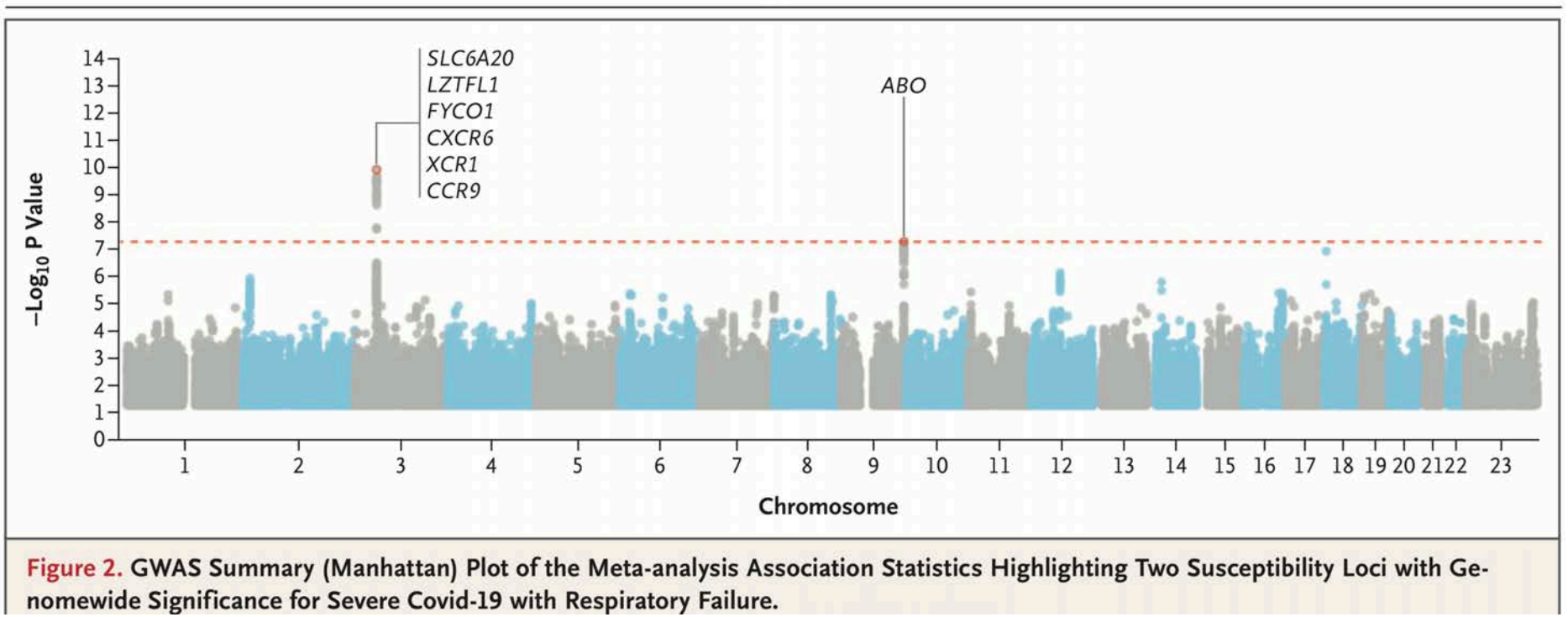
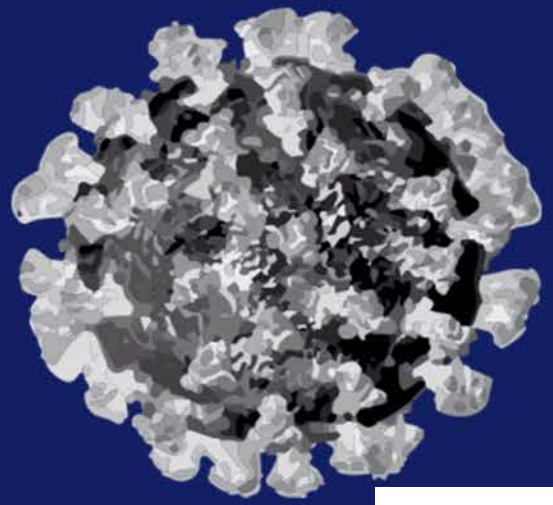


Figure 2. GWAS Summary (Manhattan) Plot of the Meta-analysis Association Statistics Highlighting Two Susceptibility Loci with Genomewide Significance for Severe Covid-19 with Respiratory Failure.



The COVID-19 Host Genetics Initiative

COVID-19 Host Genetics Initiative Coordination

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Matthew Solomonson

International Common Disease Alliance
Amy Trankiem
Kate Balaconis

A1_ALL

Very Severe Respi

alized COVID

Phenotype	Hospitalized covid vs. population
Population	Eur
Total Cases	9986
Total Controls	1877672

Phenotype

Population

Total Cases

Total Controls

A

Contributing Stu

Contributing Studies

Name	n_cases	n_controls
BQC19_EUR	244	396
BelCovid_EUR	363	1477
CU_EUR	453	2149
EstBB_EUR	90	196339
FinnGen_FIN	106	238605
GENCOVID_EUR	893	2443
GHS_Freeze_145_EUR	180	112862
LGDB_EUR	57	1531
UCLA_EUR	80	17514
UKBB_EUR	1670	328577
idipaz24genetics_EUR	106	75
Amsterdam_UMC_COVID_study_group_EUR	108	1413
SPGRX_EUR	311	302
DECODE_EUR	89	274322
MVP_EUR	436	2180
HOSTAGE_EUR	1610	2205
23ANDME_EUR	613	680416
BoSCO_EUR	212	512
FHoGID_EUR	362	259
Ancestry_EUR	250	1967
SweCovid_EUR	77	3748
genomicc_EUR	1676	8380

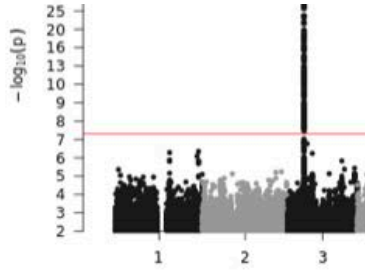
n_controls

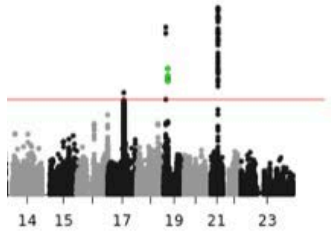
262

224

51

151





GRCh37 liftover: COVID19_HGI_B2_ALL_eur_leave_23andme_20210107.b37.txt.gz

Summary: GWAS and COVID-19

- **Interesting findings.** Especially, chromosome 3 gene cluster that has been replicated using population controls.

- **But, what does it all mean?** Comparing cases to population controls? Without accounting for exposure, and often co-morbidities. It's a gene for something, but for COVID-19 severity?

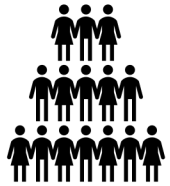
- **And COVID-19 susceptibility**…comparing COVID+ to COVID- with no epidemiologic follow up is not ok. The ABO locus finding needs to be considered in this light.

- **Nearly all European ancestry focused studies**. The virus is not focused on one ancestry and yet all the research is…

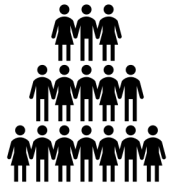
- **What we need:**
  - Diverse and representative samples to really disentangle what is happening.
  - Understanding who is testing positive and WHY. Social and structural issues are at play in terms of risk and not addressed. Even education emerges in the correlation analyses, but not addressed.

What are we doing at Johns Hopkins?

JHH and Affiliated Hospitalized Patients



JHH and Affiliated Ambulatory Patients



Genotyping at CIDR

Main goals:

1. increase diversity of population sampled
2. Severity of infection in light of comorbidities and exposure
3. Cytokine response
4. Antibody response
5. Long Term outcomes

COVID-19. What should we look at?

We need to be driven by the question.

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

What makes these individuals different?

Associations with cytokines, inflammatory markers.

Can we identify early associations with biomarkers?

Associations with viral pathogen.

Is there host-pathogen interaction?

Pharmacogenetics for clinical trials.

Does host genetics alter clinical trial meds?

Associations with humoral and T cell immunity?

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

Linking genetics with genomics.

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

In Sum:

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.

EXISTING RESOURCES: Biobanks, existing case-control studies and cohorts often cannot be used without additional efforts.

Acknowledgements

GENES AND ID

COVIDgene

Johns Hopkins COVID Long Study
www.covid-long.com

Genes and ID research team at JHSPH

Hannah Manley, Tristan Penson, Cristian Valencia, Dylan Duchen, Rebecca Munday, Steven Clipman, Poonum Korpe, Candelaria Vergara, Genevieve Wojcik

COVIDGene Team

Hannah Manley, Tristan Penson, Leon Hsieh, Dylan Duchen, Rebecca Munday, Steven Clipman, Candelaria Vergara, Cristian Valencia, Genevieve Wojcik, Andrea Cox, Chloe Thio, Shruti Mehta,Laura Kasch-Semenza, David Thomas