Genetic study of vaccine-induced myocarditis

Alexandre Bolze and Elena Hsieh
on behalf of the COVID Human Genetic Effort

16 January 2023, EMA workshop

COVID Human Genetic Effort (HGE):
Discover the Genetic & Immunological Basis of SARS-CoV-2 Severe Infection Outcomes

A "Think Tank" focused on vaccine-induced myocarditis

COMMENTARY

Decoding the Human Genetic and Immunological Basis of COVID-19 mRNA Vaccine-Induced Myocarditis

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Hypothesis: Germline Genetic Variants Increase the Risk to Develop Vaccine-Induced Myocarditis

Rare variants in genes coding for sarcomere (e.g. *TTN*)
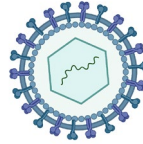
Viral infection

Myocarditis

HLA-C*07:01

Clozapine

Myocarditis

HLA-A*03:01

COVID-19 mRNA vaccine

Fever and chills

HLA-A*03:01 as a Risk Factor for More Severe Side Effects following COVID-19 mRNA Vaccination

Study design

17,440 research participants

Cases (n = 2,266)
{severe or extreme difficulties with daily routine}

vs.

Controls (n = 8,002)
{none or mild difficulties with daily routine}

Genetic association results

HLA-A*03:01 was the top hit
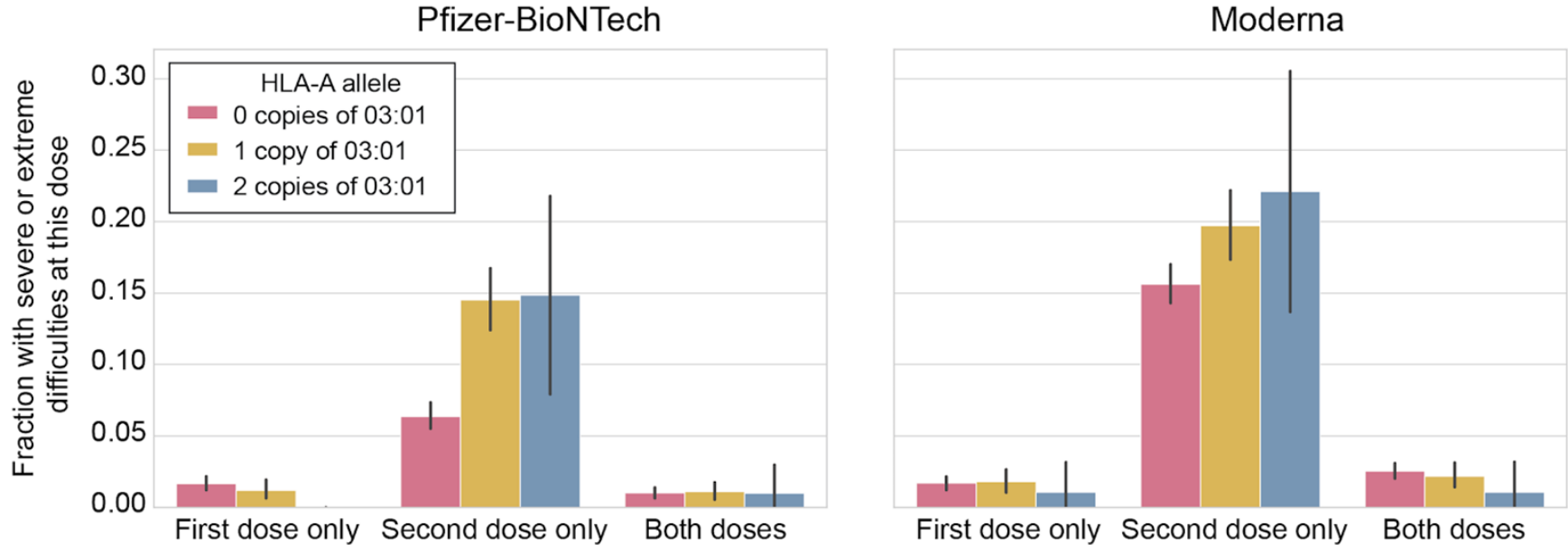
p-value = 5.00 E-11
Odds Ratio = 1.6 (CI: 1.4 - 1.8)

Replication by 23andMe:
{any reaction vs. no reaction}
p = 2.00E-205
OR = 1.34

Bolze et al., *HGGA*, 2022

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The Effect of HLA-A*03:01 Risk Factor is only evident after the Second Dose

Potential mechanisms:
via T Cell Receptors (TCR) on CD8+ T cells
or Killer cells Ig-like Receptors (KIR) on NK cells

Recruitment Criteria of Participants in the Study

Physician network

Inclusion criteria are not too restrictive

- Diagnosis of myocarditis by a cardiologist
- Symptoms within 14 days post vaccination (any dose)
- Elevated troponin levels or elevated CPK-MB
- Abnormal EKG or MRI

Exclusion criteria

- On treatment with clozapine
- SARS-CoV-2 infection within 6 weeks prior to myocarditis

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Status

~ 100 patients identified

50 enrolled in the study

2 twins

2 unrelated patients with multiple events of myocarditis (1st event was after vaccination)

——

1 'severe' group & 1 'less severe' ?

Sequencing & Analytical Plan

Whole exome or genome sequencing for all patients

- Sequencing of vaccinated parents in rare cases
- 30+ sequenced so far
- >> 10X controls using individuals who responded to vaccination survey

Gene burden tests & HLA associations

- Genome-wide approach: ~20,000 genes and 200 HLA alleles
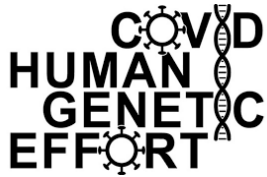- Candidate genes: *TTN*, Inflammation pathway, HLA-A*03:01

Other

- Look for expansion of TCR Vbeta 21.3+ CD4+ & CD8+ T cells (like MIS-C)
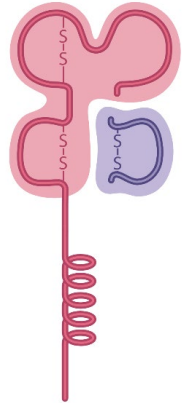
Acknowledgements & Future Collaborations

All <u>research participants</u>
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Helen Su
Yelena Nemirovskaya   **Joe Grzymski**
Shen-Ying Zhang
Trine Mogensen
Satoshi Okada

& many others

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