Genomics of Vaccine-Induced Myocarditis

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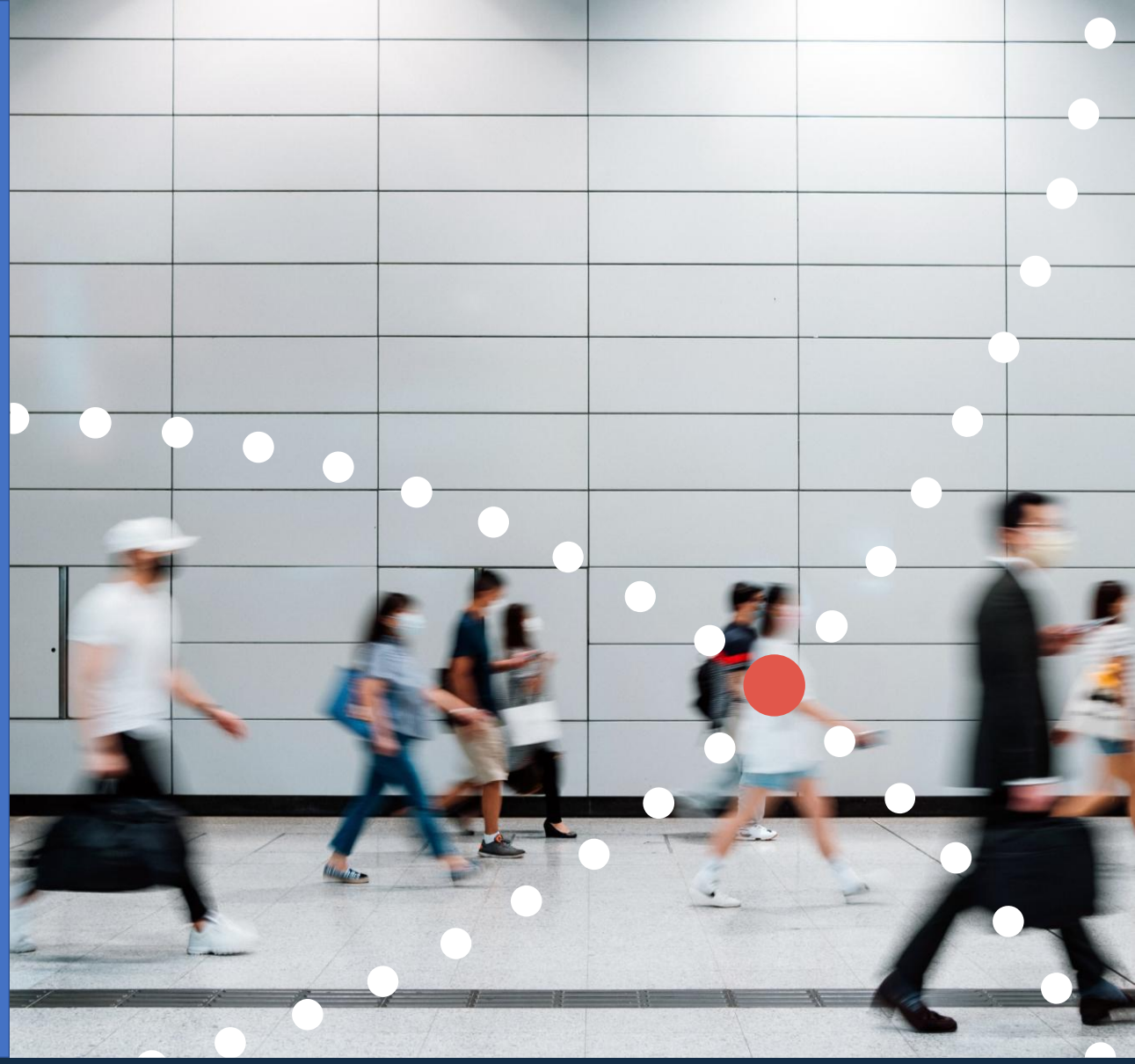

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Co-Directors

Global Vaccine Data Network™

the GVDN:
A collaborative Network of 32 countries and growing

Argentina
Australia
Brazil
Canada
Chile
China
Denmark
England

Ethiopia
Finland
France
Ghana
Hong Kong
India
Indonesia

Japan
Korea, Republic of
New Zealand
Scotland
Taiwan
USA
VAC4EU

South Africa
and the
Alive collaboration
countries: DRC Congo
Ethiopia, Ghana,
Kenya, Malawi,
Mali, Mozambique,
Nigeria, Rwanda

COVID-19 mRNA Vaccine-induced Myocarditis Exome Sequencing Cohort

Clinical Elements for Brighton Collaboration Level 1 Myocarditis Cases (N=50)	
Age, [Mean (SD); range] [Median; IQR]	26.5 (13.5); 11 to 83 yr 21.5 yr; 18 to 31 yr
Biological sex, *n* (%)	Male (*n*=40, 80%), Female (*n*=10, 20%)
Self-reported ancestry, *n*	European (*n*=31); Australian (*n*=7); Unknown (not reported) (*n*=7); Egyptian (*n*=1); Lebanese (*n*=1); Admixed American (*n*=1); Indian (*n*=1); South African (*n*=1)
Vaccine manufacturer, *n* (%)	Pfizer (*n*=37, 74%); Moderna (*n*=13, 26%)
Dose, *n* (%)	1st does (*n*=10, 20%); 2nd dose (*n*=36, 72%); 3rd dose (*n*=4, 8%)
Vaccination to onset of myocarditis symptoms, [Median; IQR]*	4 days; 3 to 26 *available for 30 patients only

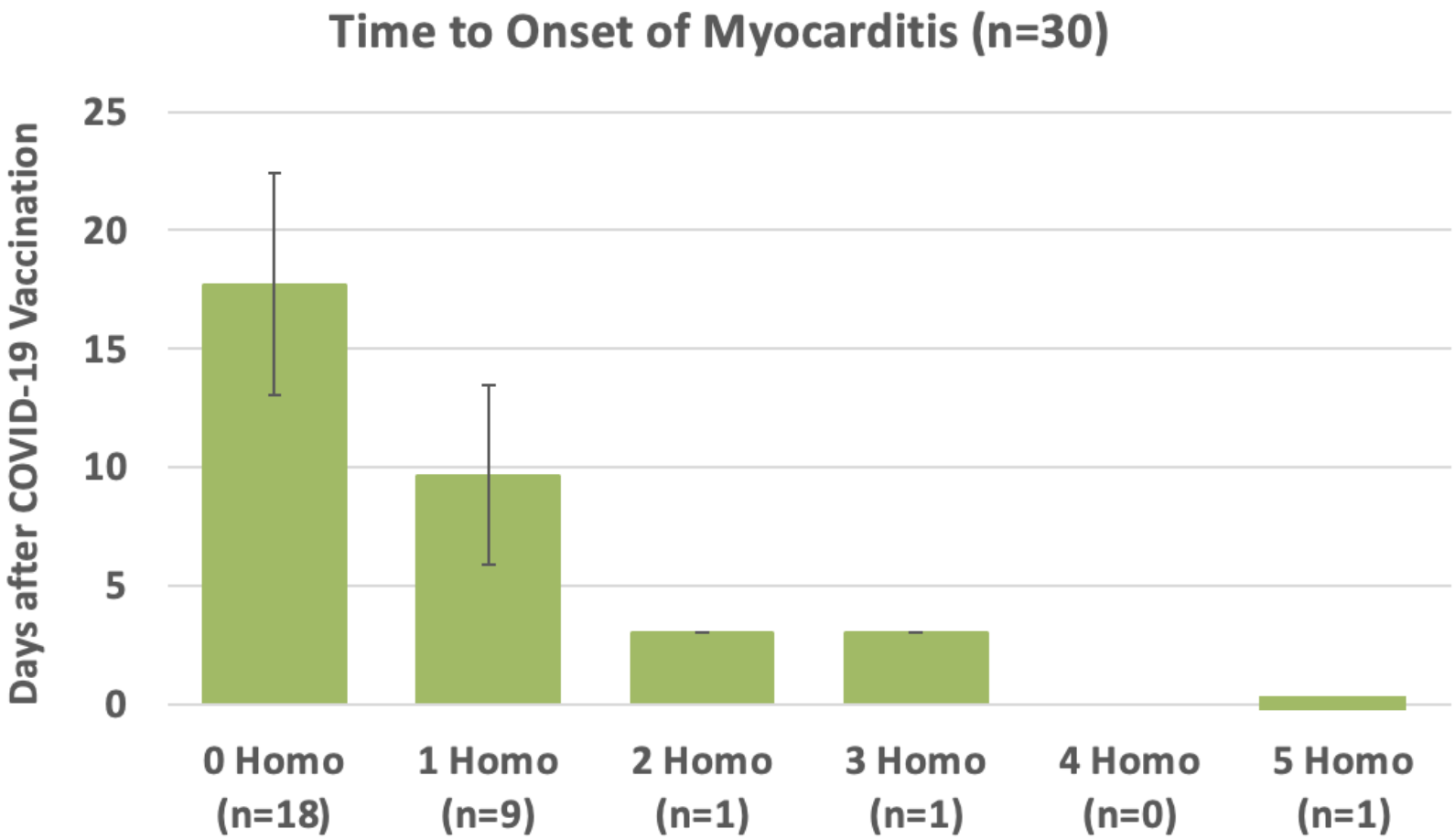
Methods

- 50 Brighton Collaboration Level 1 myocarditis cases were sequenced
- Exome-captured library preparation was sequenced with the Illumina NovaSeq 6000 system, reaching an average depth of 100x
- Reads were aligned to the GRch38 human reference genome
- 49 of 50 samples passed the quality control process
- Examine variant frequencies ≥ 50% in cases when global allele frequency (ClinVar) is ≤ 15%

7 variants across four genes identified with clear linkage to myocarditis development

No.	Gene	Function	SNP ID	Minor allele frequency (n=49)	Global allele frequency (n=5,008)	Fisher's exact *P*-value	Odds ratio (95% CI)
1	**LRP8**	Missense	rs5174	0.398	0.144 (T)	9.58×10^{-10}	3.92 (2.53 - 5.99)
2	**VKORC1**	Intron	rs2884737	0.306	0.0914 (C)	2.44×10^{-9}	4.38 (2.74 - 6.87)
3	**AGTR1**	3 Prime UTR	rs5186	0.327	0.118 (C)	5.34×10^{-8}	3.63 (2.29 - 5.64)
4	ACAN	Missense	rs3817428	0.316	0.114 (G)	9.56×10^{-8}	3.59 (2.25 - 5.60)
5	SUMF1	Missense	rs2819590	0.306	0.117 (T)	5.24×10^{-7}	3.34 (2.09 - 5.23)
6	WDR62	Synonymous	rs2301734	0.316	0.125 (A)	6.93×10^{-7}	3.24 (2.04 - 5.05)
7	**TTN**	Missense	rs36051007	0.316	0.126 (T)	8.22×10^{-7}	3.21 (2.02 - 5.00)
8	**TTN**	Missense	rs35833641	0.316	0.127 (G)	9.74×10^{-7}	3.18 (2.00 - 4.96)
9	ANHX	Missense	rs36146434	0.316	0.129 (C)	1.40×10^{-6}	3.12 (1.96 - 4.86)
10	ALPP	Missense	rs1048988	0.327	0.141 (C)	3.02×10^{-6}	2.96 (1.87 - 4.60)
11	**TTN**	Missense	rs12463674	0.310	0.130 (G)	3.25×10^{-6}	3.01 (1.89 - 4.68)
12	EDARADD	3 Prime UTR	rs6428955	0.316	0.138 (T)	5.75×10^{-6}	2.90 (1.82 - 4.51)
13	MCPH1	Intron	rs1961222	0.330	0.150 (T)	7.24×10^{-6}	2.80 (1.78 - 4.32)
14	MSH6	Missense	rs1800935	0.306	0.135 (C)	1.12×10^{-5}	2.82 (1.77 - 4.42)
15	CHRNA5	Missense	rs16969968	0.316	0.150 (A)	4.47×10^{-5}	2.63 (1.65 - 4.10)
16	SUGP1	Stop Gained	rs11555053	0.306	0.149 (A)	8.74×10^{-5}	2.52 (1.57 - 3.94)
17	VPS53	Missense	rs11558129	0.296	0.145 (A)	0.000138	2.47 (1.54 - 3.88)
18	**TTN**	Missense	rs12464787	0.296	0.147 (A)	0.000152	2.45 (1.53 - 3.84)

An increase in the number of homozygous risk variants shortens the time to onset of myocarditis



LRP8 (LDL Receptor Related Protein 8)

- Expressed in the heart, endothelium, vascular smooth muscle, and platelets

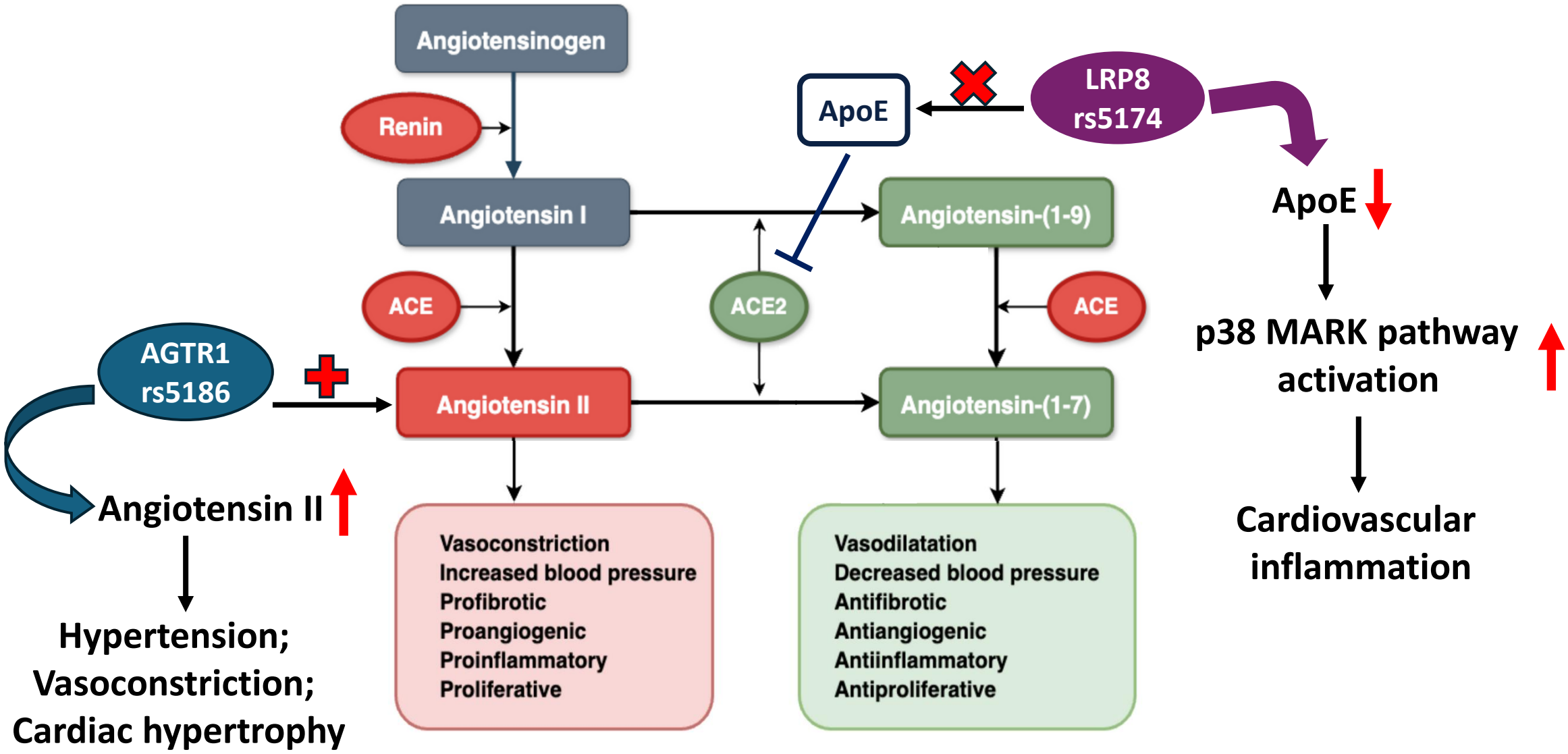
- R952Q variant (rs5174) is linked to cardiovascular inflammation and immune response, particularly in coronary artery disease (CAD) and myocardial infarction (MI) (OR: 1.31–1.42, $P<0.05$)

- Among 49 Brighton Level 1 myocarditis cases, 10 are homozygous for the risk allele (TT) and 19 are heterozygous (CT) for rs5174.

AGTR1 (Angiotensin II Type 1 Receptor)

- Patients with AGTR1 rs5186 risk CC genotype display both increased LDL and triglycerides
- AC and CC genotypes are associated with ≥90% left anterior descending artery stenosis [OR: 1.94 (1.059-3.552, *P*=0.032)].
- The C allele is associated with MI susceptibility [OR:1.12 (1.01-1.25); *P*=0.03] and essential arterial hypertension severity (*P*=0.033).
- Among 49 Brighton Level 1 myocarditis cases, 4 are homozygous for the risk allele (CC) and 24 are heterozygous (AC) for rs5186.

LRP8 & AGTR1 in Renin-Angiotensin System (RAS)

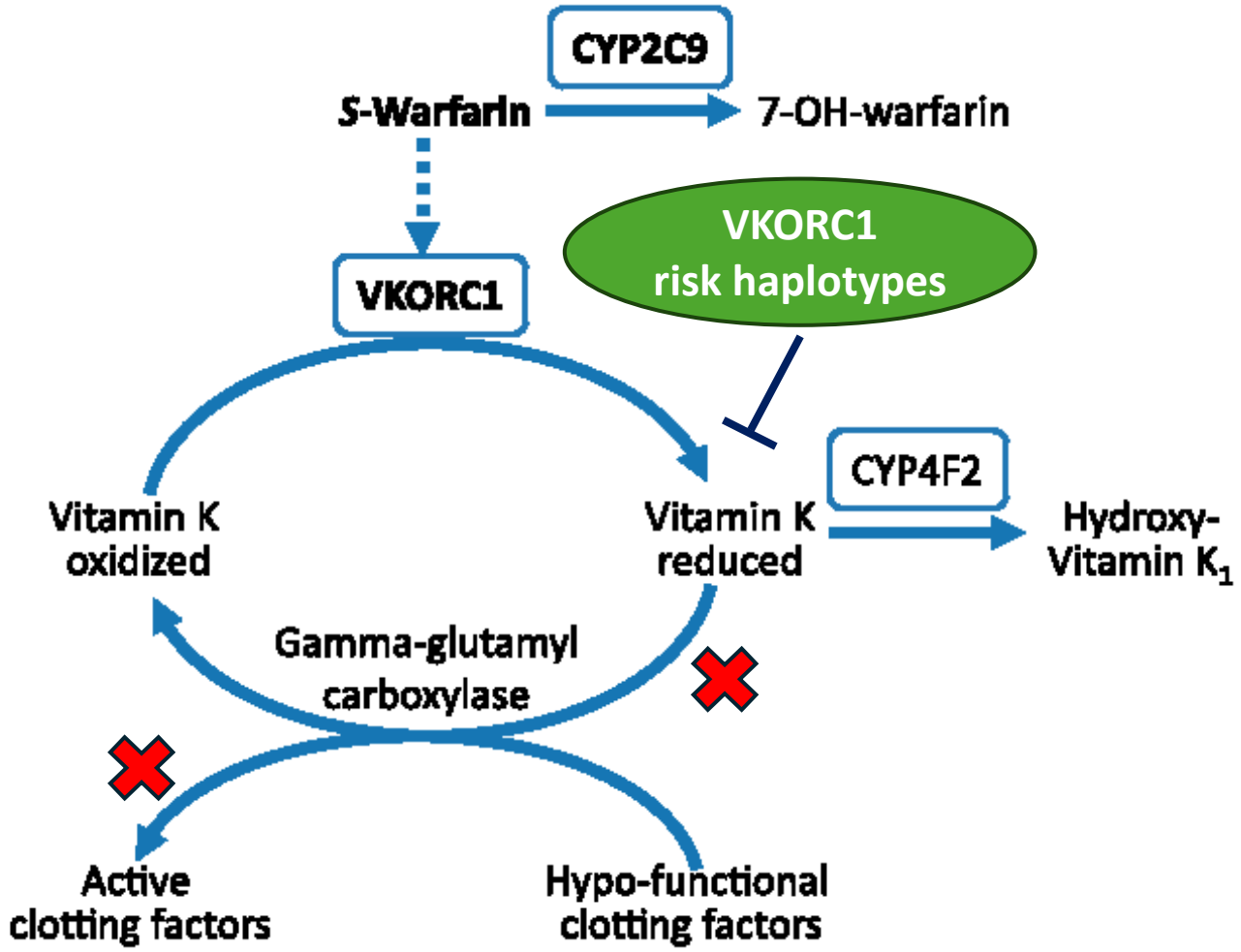


Ref: Curr Treat Options Oncol. 2024;25(11):1406-1427

VKORC1
(Vitamin K Epoxide Reductase Complex Subunit 1)

- Highly expressed in the heart
- Key element of vitamin K signaling and warfarin dosage
- The rs2884737 C allele is associated with increased sensitivity to warfarin dose compared to the wild-type A allele
- VKORC1 haplotypes are associated with arterial vascular diseases (e.g., stroke, coronary heart disease, and aortic dissection)
- Among 49 Brighton Level 1 myocarditis cases, 3 are homozygous for the risk allele (CC) and 24 are heterozygous (AC) for rs2884737

VKORC1



Prevent vascular calcification
Prevent atherosclerosis

Ref: Pharmacol Rev. 2013;65(3):987-1009

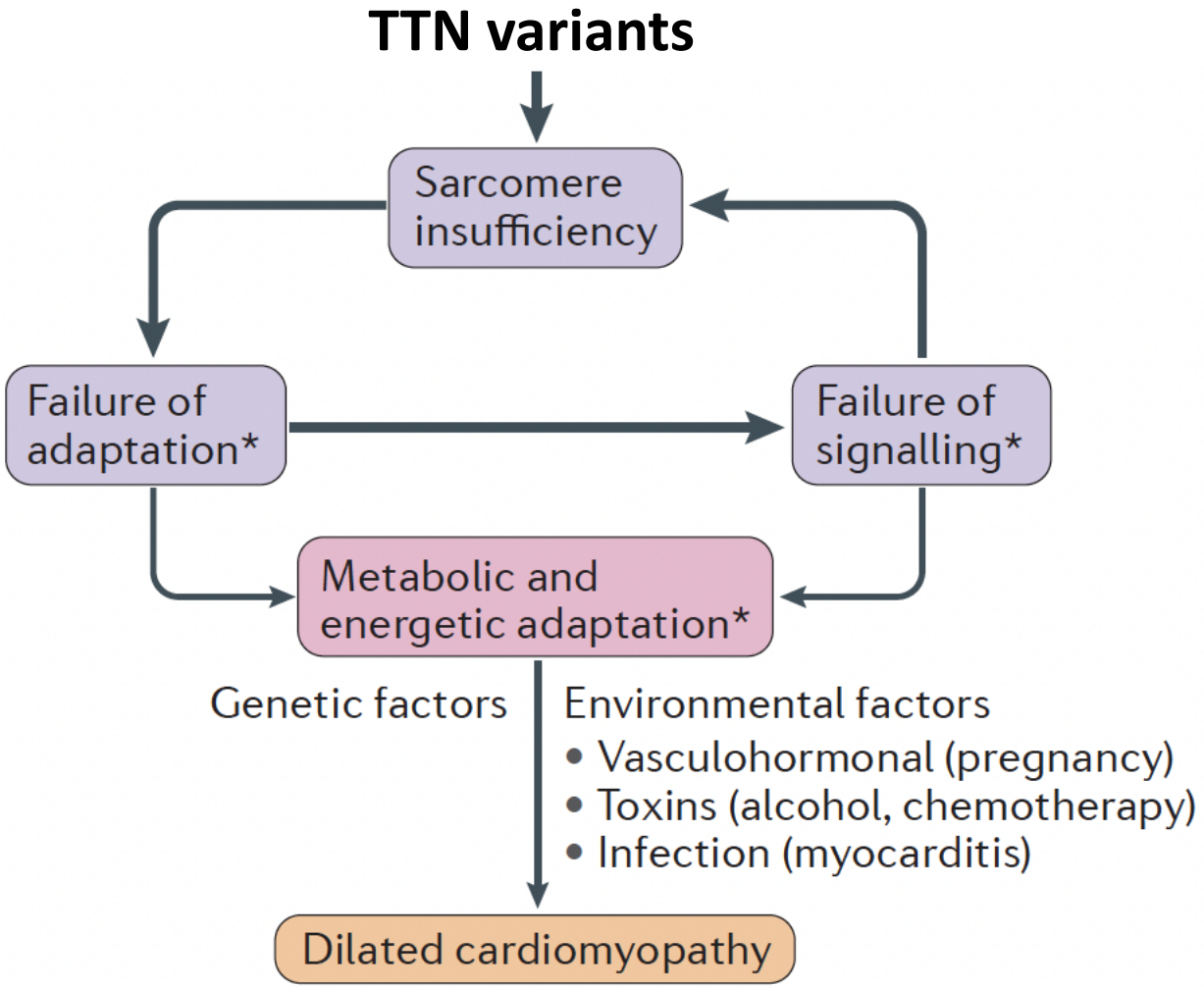
TTN (Titin)

- TTN variants are the most frequent cause of dilated cardiomyopathy and account for 25% of familial and 18% of idiopathic cases

- TTN is associated with acute myocarditis, with a higher variant prevalence in cases (6%) than in controls (1%-2.9%) (*P*=0.019).

- Among 49 Brighton Level 1 myocarditis cases, 3 are homozygous for all four variants, 2 are homozygous for three variants, and 21 are heterozygous for all four variants.

Consequences of TTN variants



Ref: Nat Rev Cardiol. 2018;15(4):241-252.

Planned Next Steps

- **Before the GVDN grant was cancelled**
  - Goal: **275** cases per each adverse event and **2,750** controls per vaccine platform (a total of **5,500** controls for both mRNA and adenoviral vector-based platforms)

Adverse event	Expected #	Enrolled #
Myocarditis	422	207 (195 mRNA)
Pericarditis	301	47 (39 mRNA)
Myopericarditis	273	36 (32 mRNA)
VITT	235	81 (51 AVV)
GBS	154	37 (27 AVV)
Control	4,960	1,967 (1,005 mRNA & 804 AVV)

- Further analysis and verification of the exome sequencing data
- Genome-wide analysis for the full cohort of myocarditis (+/- pericarditis and myopericarditis) will be conducted once the target enrollment is reached
- Exome analysis of vaccine-induced immune thrombotic thrombocytopenia (VITT) will be conducted in a subset of patients with the highest certainty of being vaccine-induced
- Genome-wide analysis for the full cohort of VITT will be conducted once the target enrollment is reached.

A final word about vaccine genomics

- Genomics studies of drugs have revolutionized drug therapy allowing for personalized approaches to treatment. More than 500 FDA-approved drugs have genetic information annotated in their labels.

- Identifying genetic markers of risk for vaccine adverse events would serve two purposes:
  - Facilitating a better understanding of the pathophysiology of events
  - Allow for personalized vaccine schedules that reduce the risk of AEFIs.