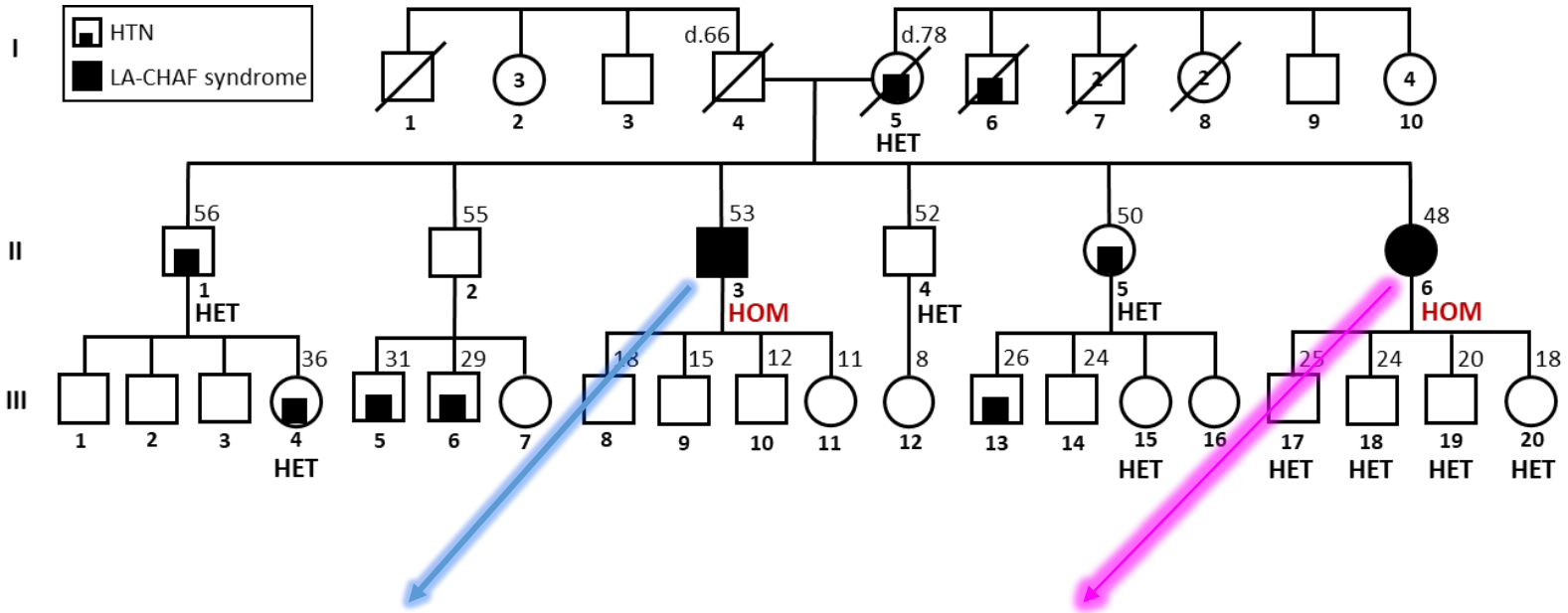
Corin-deficiency
AKA
CHAF-LA syndrome

Chofit Chai Gadot, PhD
The Translational Genetics and Genomics Research lab

May 2024



CHAF-LA syndrome

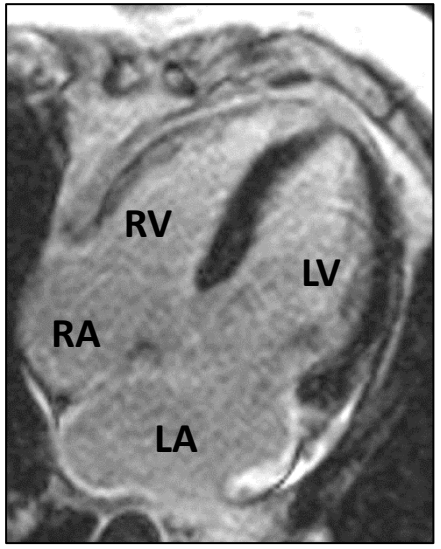
Cardiomyopathy (dilation and hypertrophy)

Hypertension

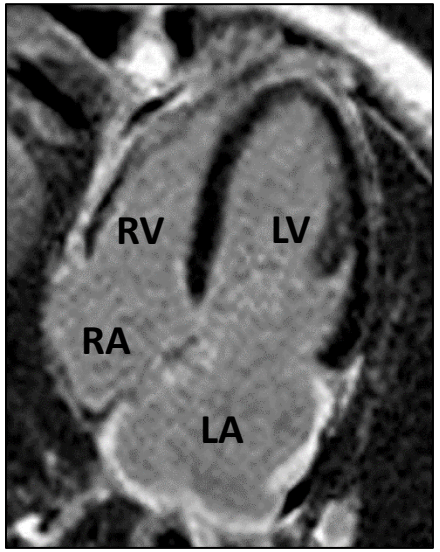
Arrhythmia (AFib in II-6; AFL in II-3)

Fibrosis

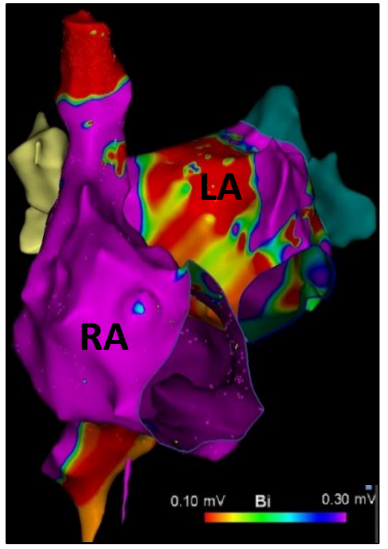
of the **L**eft **A**trium



Cardiac MRI

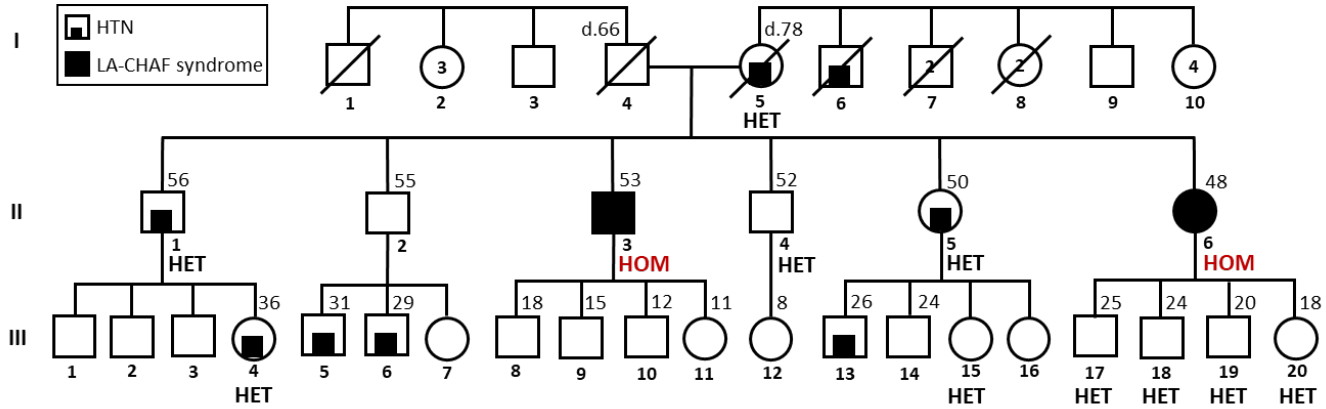


Cardiac MRI



CARTO mapping

Exome sequencing



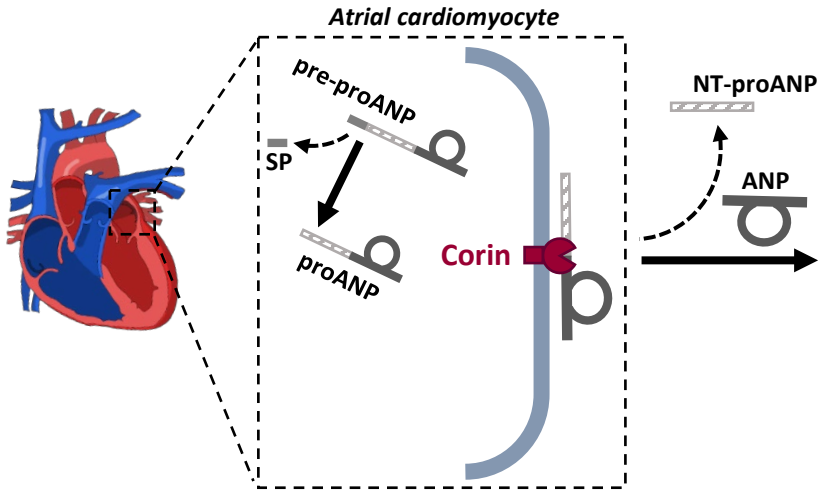
- Both siblings were sequenced

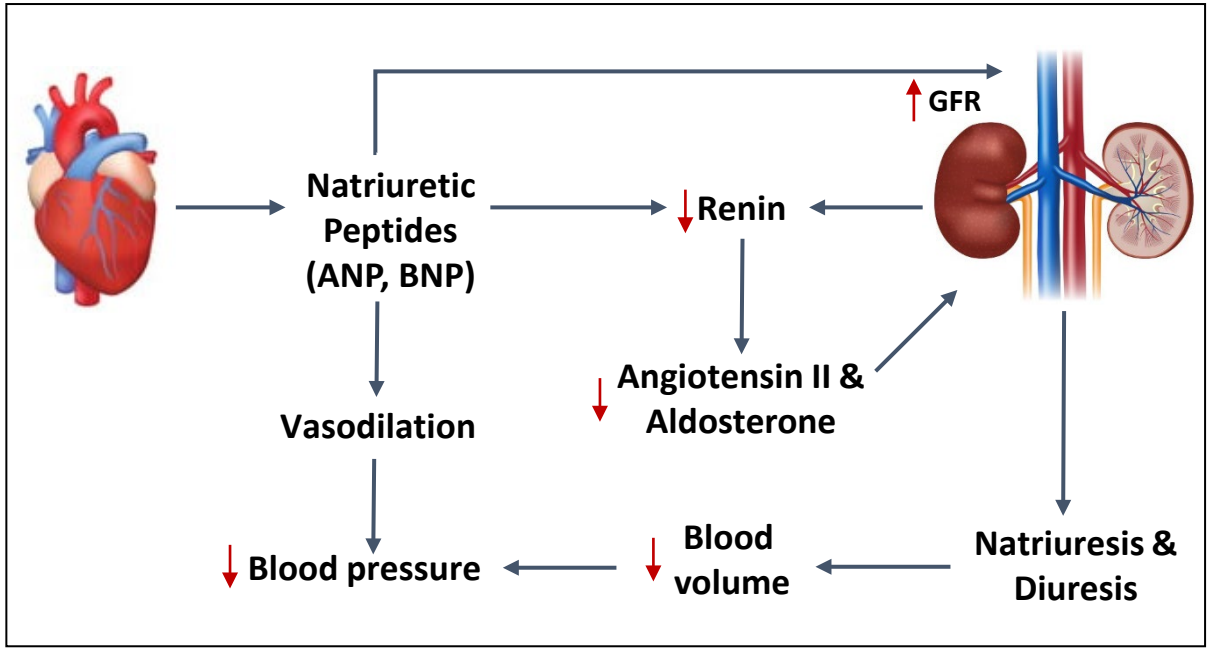
- ***CORIN* (NM_006587.4): c.684dupG; p.Met229Aspfs*16**
  - Homozygous in both
  - gnomAD MAF=0.000092 (0.001304 in East Asians)
  - Homozygous LOF variants were never described in humans

- Sister also het for ***PKP2*: c.1843T>A; p.Ser615Thr**
  - Arrhythmogenic right ventricular dysplasia 9, AD (nonsense variants)

- Segregation in available family members 

Corin and the natriuretic peptide system



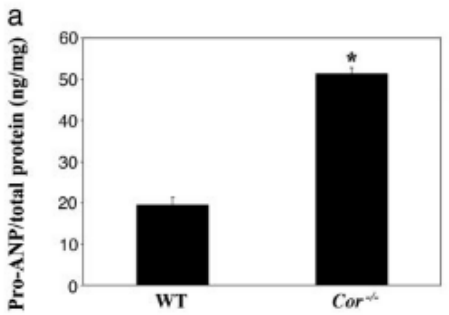


Chan et al. *PNAS* 2005

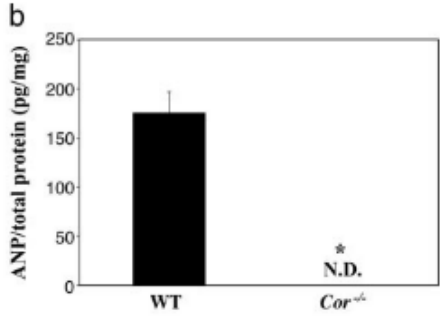
Hypertension in mice lacking the proatrial natriuretic peptide convertase corin

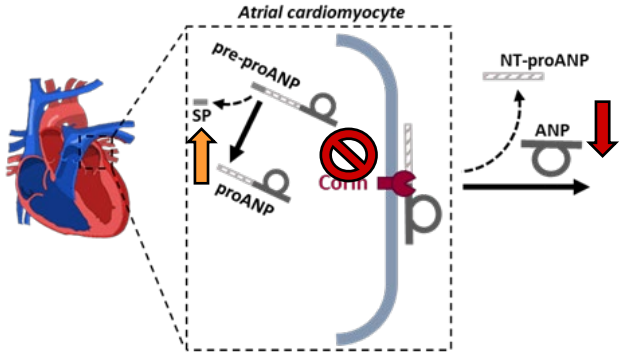
Joyce C. Y. Chan*, Ole Knudson, Faye Wu, John Morser, William P. Dole, and Qingyu Wu*

Pro-ANP

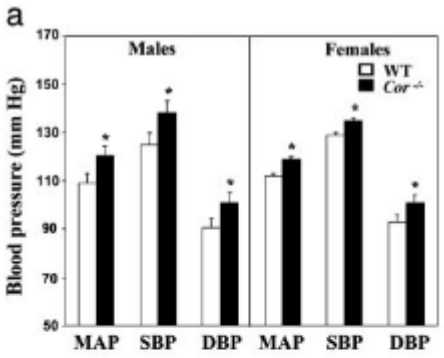


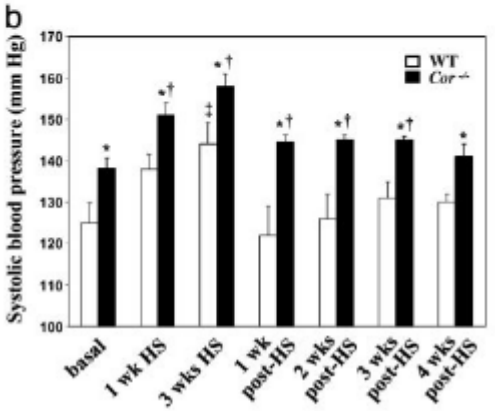
ANP



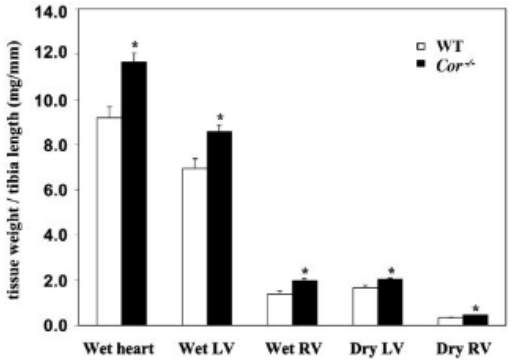


Hypertension

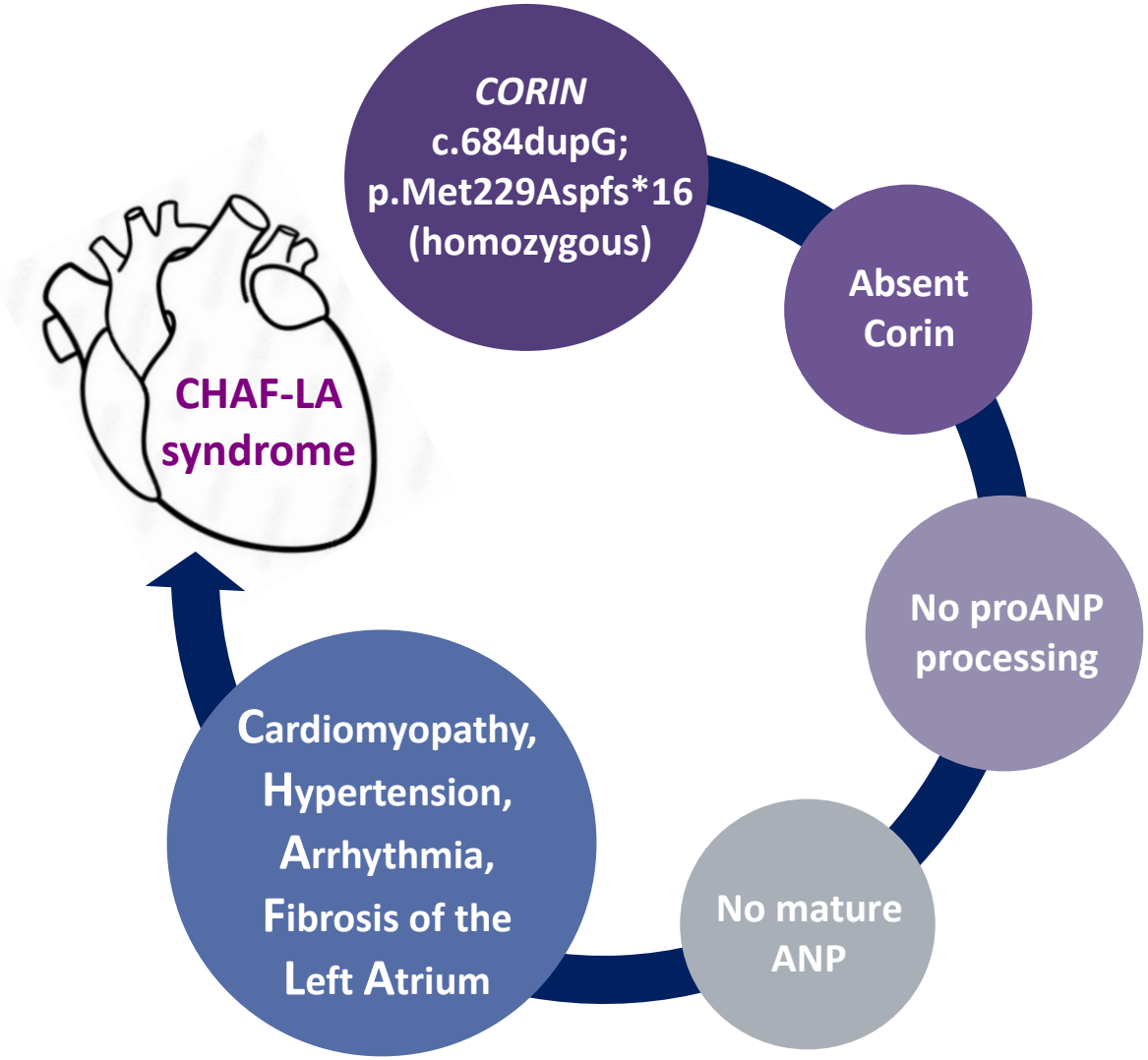




Cardiac hypertrophy



Our hypothesis

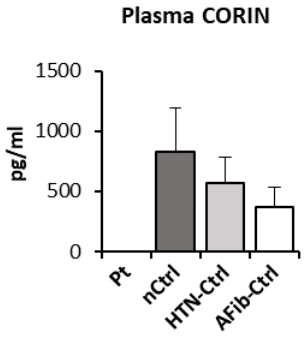


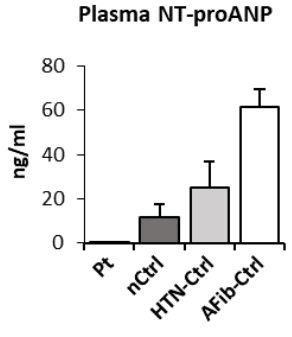
Corin expression → Soluble **Corin** levels in plasma

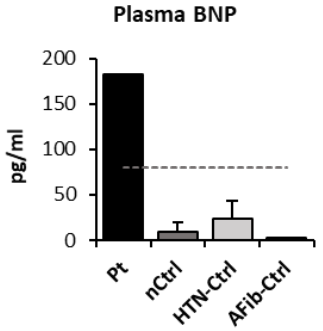
Corin function → **NT-proANP** levels in plasma

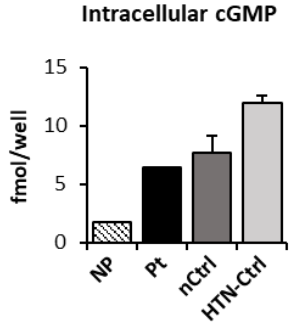
BNP → **BNP** levels in plasma

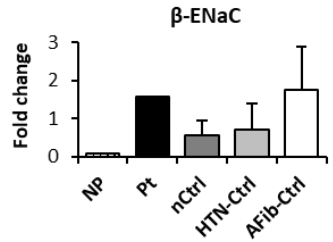
ANP function → **cGMP** levels in HEK293 following incubation with human plasma; **ENaC** subunit levels in HEK293 following incubation with human plasma

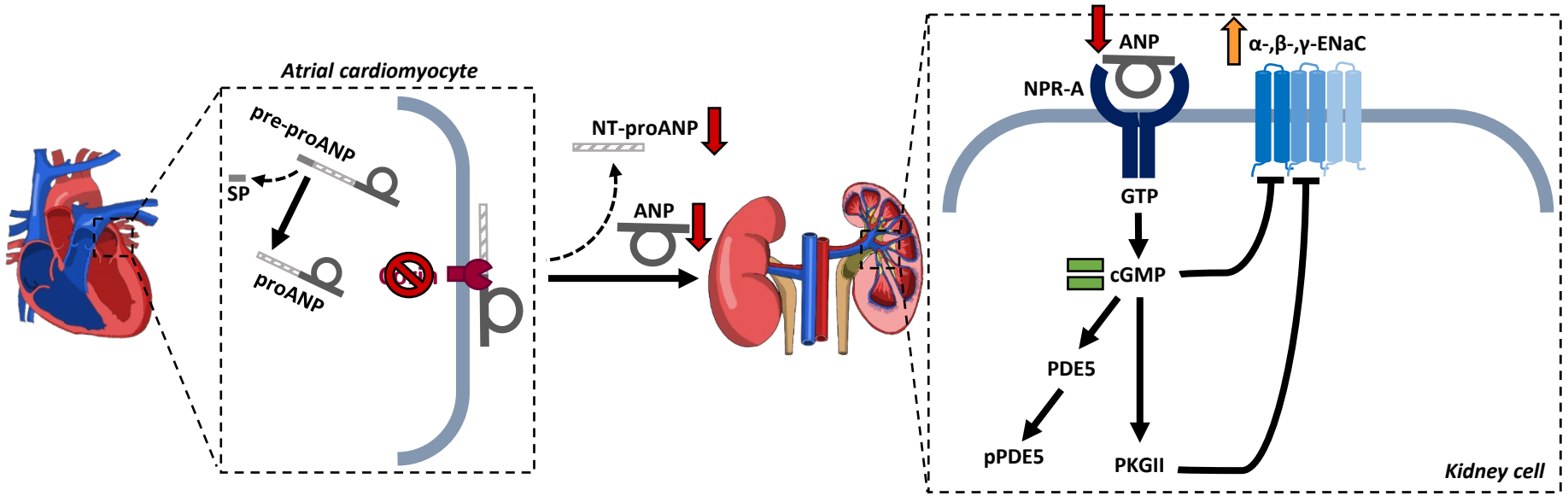










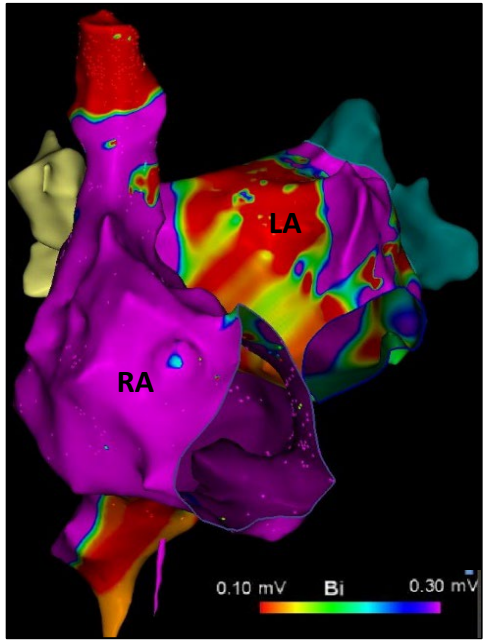


c.684dupG; p.Met229Aspfs*16

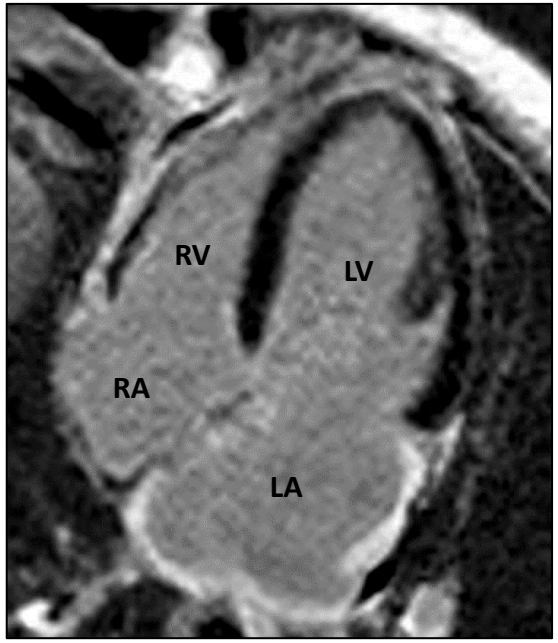
NP = no plasma

Fibrosis

Patient 1 (II-6)

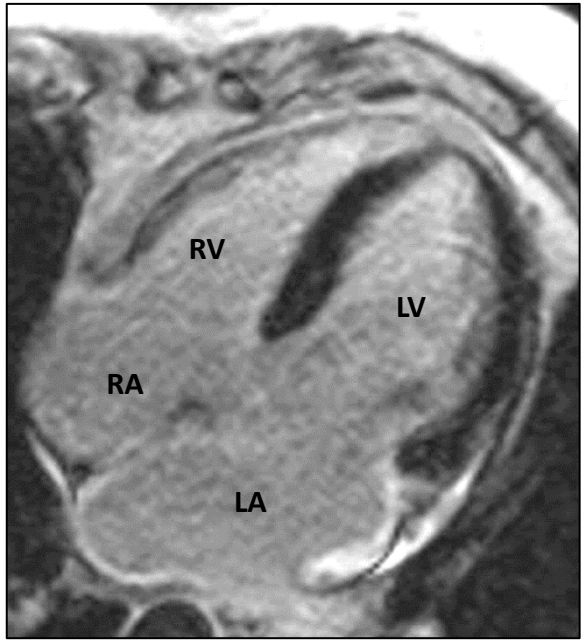


CARTO mapping



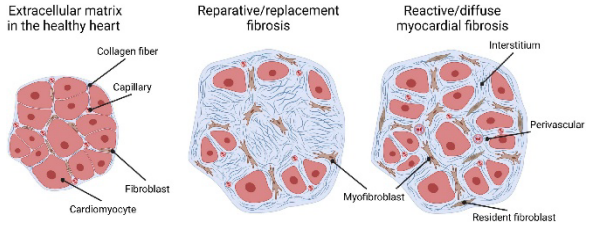
Cardiac MRI

Patient 2 (II-3)

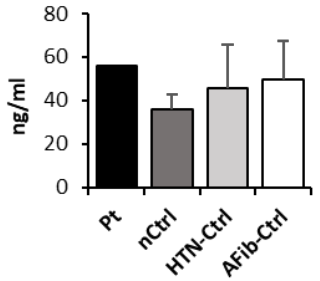


Cardiac MRI

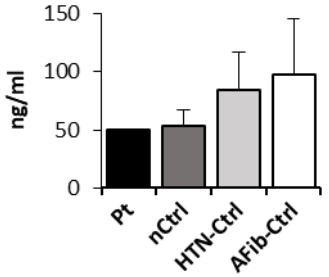
Myocardial fibrosis



Plasma PICP



Plasma TIMP-1



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Corin and Left Atrial Cardiomyopathy, Hypertension, Arrhythmia, and Fibrosis

Hagit Baris Feldman, M.D., Chofit Chai Gadot, Ph.D., David Zahler, M.D., Adi Mory, Ph.D., Galit Aviram, M.D., Emil Elhanan, M.D., Gabi Shefer, Ph.D., Ilana Goldiner, Ph.D., Yam Amir, M.Sc., Alina Kurolap, R.N., Ph.D., and Jacob N. Ablin, M.D.

SUMMARY

Two siblings presented with cardiomyopathy, hypertension, arrhythmia, and fibrosis of the left atrium. Each had a homozygous null variant in *CORIN*, the gene encoding atrial natriuretic peptide (ANP)–converting enzyme. A plasma sample obtained from one of the siblings had no detectable levels of corin or N-terminal pro-ANP but had elevated levels of B-type natriuretic peptide (BNP) and one of the two protein markers of fibrosis that we tested. These and other findings support the hypothesis that BNP cannot fully compensate for a lack of activation of the ANP pathway and that corin is critical to normal ANP activity, left atrial function, and cardiovascular homeostasis.

Since then…

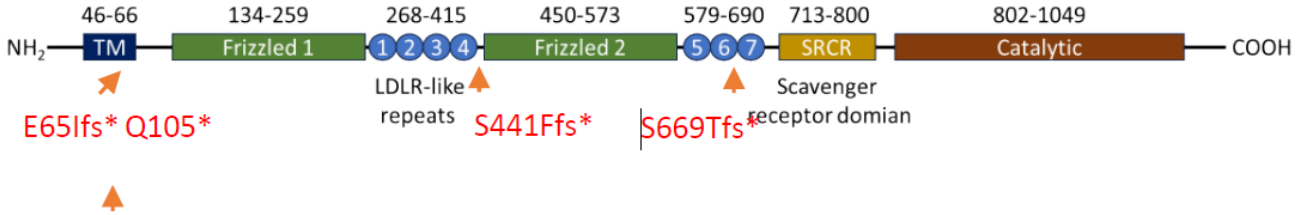
The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

100,000 Pakistani exomes (Dominy et al. 2024)

A.

Variants identified by whole exome sequencing and used in recall by genotype studies



B.

CORIN LoF is associated with increased risk of hypertension

CORIN Zygosity	Hypertension / Total (%)*
Wild type	3/53 (5.7%)
Heterozygous LoF	7/24 (29.2%)
Homozygous LoF	1/2 (50%)

***p=5.6e-3, OR=5.4 [1.6, 17.8]**
(Logistic regression with age and gender as covariates)

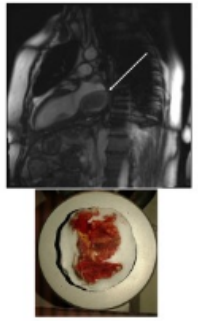
ESHG 2024
EUROPEAN SOCIETY OF HUMAN GENETICS

Atrial amyloidosis caused by bialelic mutations in CORIN

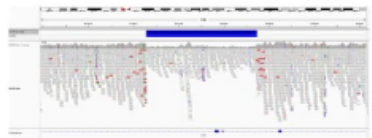
Piherová L.[1], Melenovská P.[1],Hnízda A.[1], Mušálková D.[1], Vrbacká A.[1], Steiner-Mrázová L.[1], Trešlová H.[1], Stránecký V.[1], Kubánek M.[2], Krebsová A.[2], Melenovský V.[2]
1 – Resesarch unit for Rare Disorders, KPDPM, 1.LF UK Prague, CZ
2 - Institute for Clinical and Experimental Medicine (IKEM), Prague, CZ

Background/Objectives:
Middle-aged woman with hypertension, AFib and an incidental LA mass with a rim of late gadolinium-enhancing tissue. Upon surgery, an intraumal hematoma was found within entirely diffusely thickened LA wall, extensively infiltrated by ANP-containing amyloid (confirmed by immunohistochemistry and mass spectrometry). ANP gene sequence was normal, but western-blot of LA tissue showed predominance of proANP, consistent with defective CORIN processing. ANP precursor contains amyloid aggregation-prone segment.

Clinical Information:
2013 - **ECHO** examination revealed a mass in the left atrium - suspected myxoma.
MRI - in the dilated left atrium there was a mass filling half of the left atrium and extending into the lower pulmonary veins bilaterally -> assessed as a thrombus of different age with a fresher component -> indications for the dissection.
Macroscopically: the character of the older coagulum.
Histologically: solid partially organizing left atrial hematoma superimposed on myocardium permeated by massive amyloid deposits - typed as ANP.
Further follow-up by echocardiography only; MRI March 2024 - control with no recurrence of the left atrial mass and no pathological saturation with no pathological gadolinium saturation.



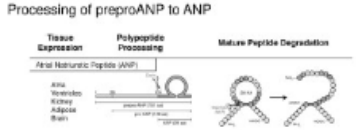
Methods:
ANP a CORIN exons were sequenced by Sanger method. By this method we found missense variant in exon 16. A large part of the gene was sequenced on a MiniON sequencer. Large deletion was detected by genome sequencing on Illumina platform.



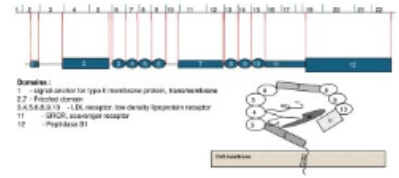
Conclusion:
Due to biallelic variants in CORIN, protease enzymatic activity is affected. It is therefore likely that defects in proANP processing may lead to more extensive LA wall infiltration by ANP amyloid, mimicking tissue fibrosis on MR imaging, and contributing per se to arrhythmogenesis and LA dysfunction.

Acknowledgement:
The project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, Project No. LX22NPO5104) - Funded by the European Union – Next Generation EU.

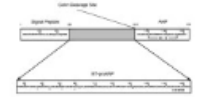
Processing of preproANP to ANP



Schema of CORIN – serine protease; Pro-ANP-Convertase



Results:
We found biallelic variant in *CORIN*, which is serine protease cleaving proANP to ANP.



Rare missense variant is in scavenger receptor domain and second variant is a large deletion, found by genome sequencing.
Deletion boundaries are localized in repetitive LINE/L1 segments. This variant leads to production of neo-protein, where are scavenger receptor domain and peptidase S1 domain affected.

Missense variant: NM_006587.4c.2186A>C (p.Gln729Pro);
ACMG classification VUS
Deletion: In frame deletion of exons 18 and 19;
chr4:47622559-47627471 (hg 19); size - 4912bp

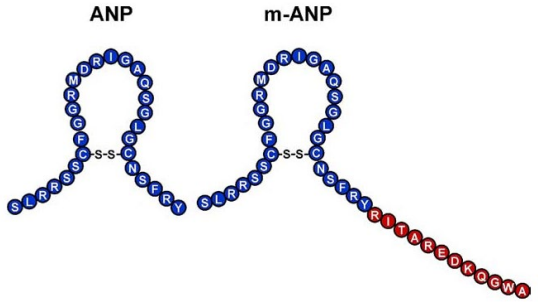
Mutations on protein level:
Protein lacks enzyme activity due to absence of critical regions for catalysis

Mutation leads to structural instability caused by a loss of polar contacts with Y1035 and H766 and by sterical distortions induced by prolyl residue.

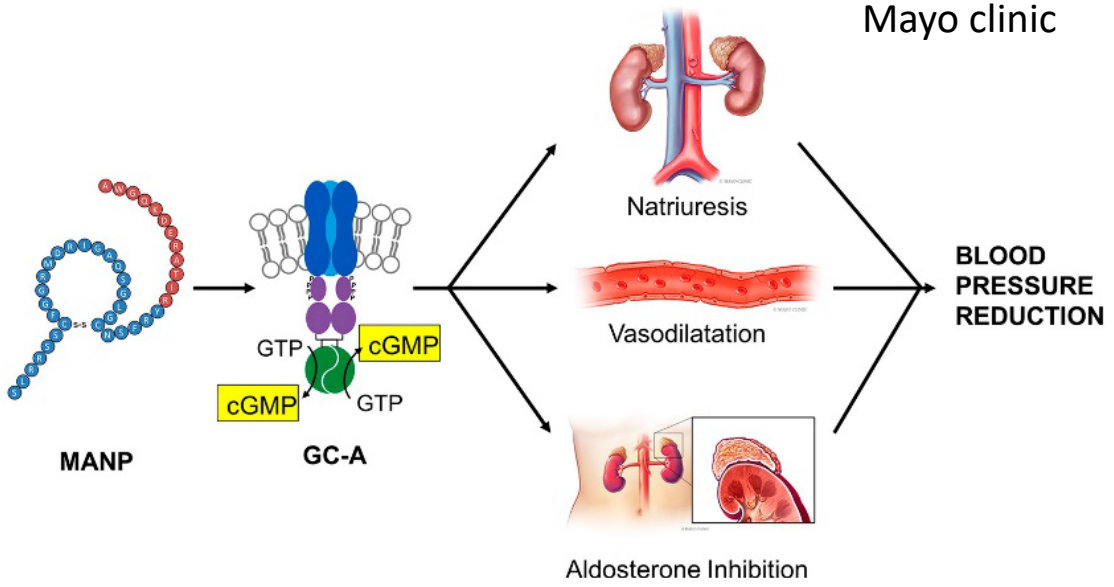
Literature:
Potter LR, Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handb Exp Pharmacol. 2009;(191):341-66.
Baris Feldman H., Corin and Left Atrial Cardiomyopathy, Hypertension, Arrhythmia, and Fibrosis. N Engl J Med. 2023 Nov 2;389(18):1685-1692.

ANP therapeutics

- Atrial natriuretic peptide (ANP)
  - **Carperitide** - recombinant ANP
  - Half life ~2 min
  - Requires continuous IV at low doses
- Modified ANP
  - **M-atrial natriuretic peptide (MANP)** - ANP analog that was engineered to be more potent and long-lasting than native ANP



Prof. John Burnett
Mayo clinic



Hypertension

ORIGINAL ARTICLE

MANP (M-Atrial Natriuretic Peptide) Reduces Blood Pressure and Furosemide-Induced Increase in Aldosterone in Hypertension

Nina A. Dzhoyashvili, Seethalakshmi R. Iyer, Horng H. Chen, John C. Burnett Jr

Hypertension

NOVEL THERAPEUTIC

First-in-Human Study of MANP: A Novel ANP (Atrial Natriuretic Peptide) Analog in Human Hypertension

Horng H. Chen, Siu-Hin Wan, Seethalakshmi R. Iyer, Valentina Cannone, S. Jeson Sangaralingham, Joel Nuetel, John C. Burnett Jr

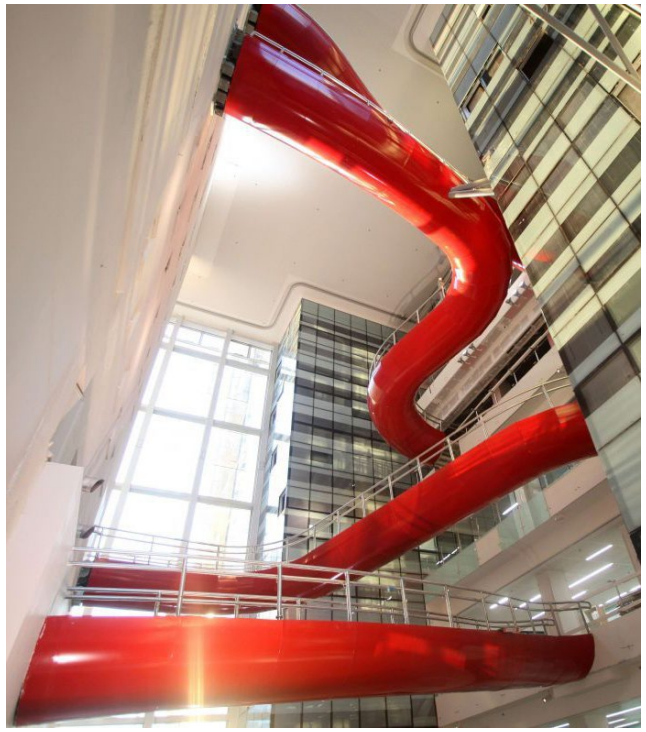
CLINICAL RESEARCH

MANP in Hypertension With Metabolic Syndrome

Proof-of-Concept Study of Natriuretic Peptide-Based Therapy for Cardiometabolic Disease

Xiao Ma, PhD,[a,b] Paul M. McKie, MD,[b] Seethalakshmi R. Iyer, MS,[a,b] Christopher Scott, MS,[c] Kent Bailey, PhD,[c] Bradley K. Johnson, BS,[c] Sherry L. Benike, RN,[b] Horng Chen, MD,[a,b] Wayne L. Miller, MD,[b] Aderville Cabassi, MD, PhD,[e] John C. Burnett, Jr, MD,[a,b,d] Valentina Cannone, MD, PhD[a,b,e]

Planned collaboration



המרכז הרפואי תל-אביב
ע"ש סוראסקי
איכילוב

TEL AVIV SOURASKY
MEDICAL CENTER
ICHILOV

Genetics
- Chofit Gadot
- Alina Kurolap
- Emil Elhanan
- Adi Mory
- Hagit Baris Feldman

Internal Medicine
- Jacob Ablin

Cardiology
- David Zahler

Clinical laboratories
- Gabi Shefer (endo)
- Ilana Goldiner (biochem)

Imaging
- Galit Aviram