

## Genetic Approaches to Heart Disease

Aron Geurts, PhD

Cardiovascular Research Center  
Genome Sciences and Precision Medicine Center  
Department of Physiology



## Objectives

- Learn how unique (and resilient) humans really are
- Learn how gene editing is applied in research to understand gene function
- Understand the link between basic research discoveries and precision medicine



Studies on populations have given us part of the answers

From last time: ~30% of American adults are Hypertensive



~300 common genetic sequence variants have been associated with Blood Pressure

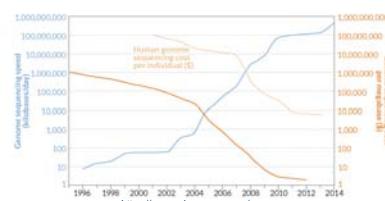
...but their cumulative effect on blood pressure is smaller than we expected.

Probably it is the combination of common and rare genetic variants, along with environment and lifestyle, that determine our blood pressure destiny

<https://www.genome.gov>



## Rate of DNA sequencing and Cost



2001 cost to sequence the first human genome:  
**\$95,263,072**  
October 2015 cost:  
**\$1,245**  
<https://www.genome.gov>

Slide from George Weinstock  
MCW Advancing a Healthier Wisconsin Endowment

## Every genome is unique



...and full of common and private mutations, polymorphisms, copy number variations, and chemical modifications ... and dark matter

*"There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know."*

Donald Rumsfeld



MCW  
ADVANCING A HEALTHIER WISCONSIN ENDOWMENT

## I've got bad news...

You are only 0.1% different than the person sitting next to you (less if you are related), and...

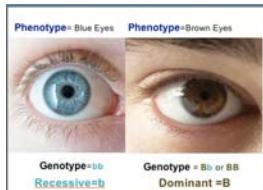
- You have about 400 defects in genes found in every cell of your body, including at least a couple that are associated with disease
- You inherited about 10 new ones from your parents when you were born
- Every single one of your 6 billion nucleotides has been mutated in your brain... many times over.

But, hey, you made it this far, right?!



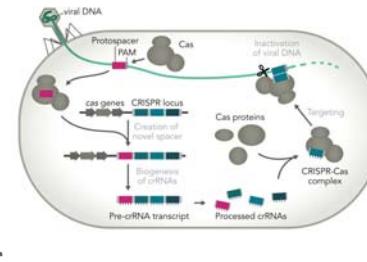
How do we attribute a new genetic variation (genotype) to a health outcome (phenotype)?

Natalie ATA TGA TCA ACA CTT  
Steven ATA TGA TCA ACA GTT



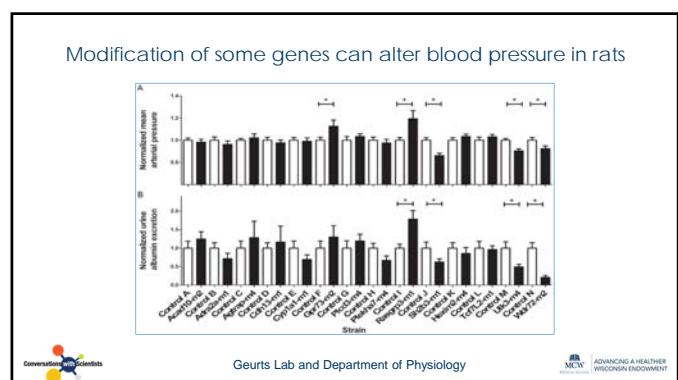
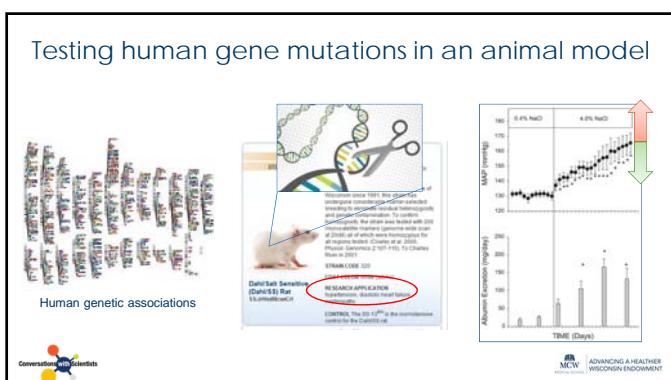
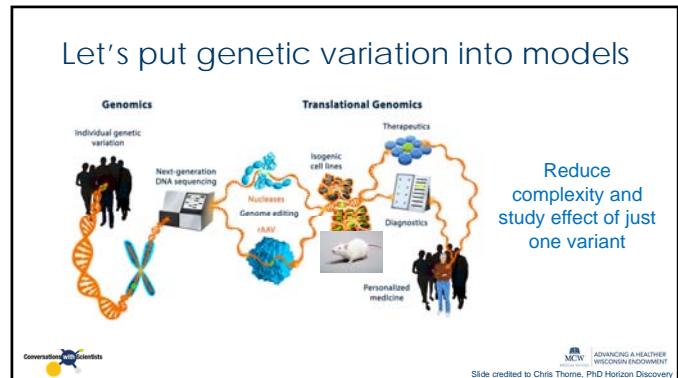
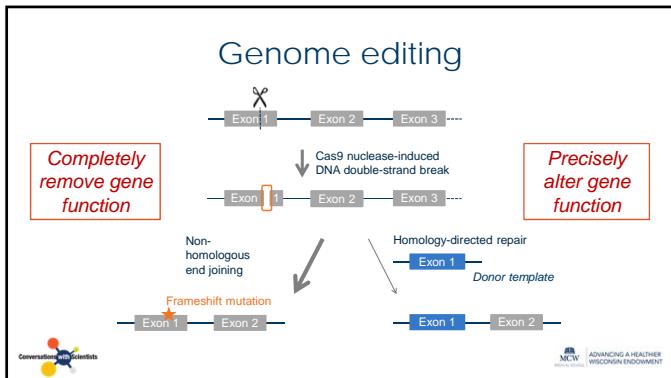
MCW  
ADVANCING A HEALTHIER WISCONSIN ENDOWMENT

Hijack a bacterial adaptive immunity system for understanding our genomes?



**CRISPR**  
Clustered  
Regularly  
InterSpaced  
Palindromic  
Repeats





## Combining cutting edge tools

**IPS Cells**

Method of turning adult cells in to stem cells  
-> then back into adult cells

NOBEL Prize 2012

Geurts lab

**CRISPR/Cas9**

Method of "Gene Editing" which enables very precise modification of genes

The CRISPR Craze

NOBEL Prize pending

Advancing A Healthier Wisconsin Endowment

## Dilated Cardiomyopathy (DCM)

- Heart muscle disorder resulting from cardiomyocyte dysfunction
- Characterized by chamber dilation and diminished ability to contract
- Most prevalent form of cardiomyopathy not resulting from a blocked artery
- Common cause of heart failure
- Strong heritability

Normal heart

Heart with dilated cardiomyopathy

A genome-wide association study identifies four loci associated with heart failure due to dilated cardiomyopathy

Comparative Studies of Copy Number Variation and Insertion/Deletion Polymorphism Variants in Human and Mouse

BAG3: a new player in the heart failure paradigm

Only some mutations in BAG3 can cause disease. Which ones?

Advancing A Healthier Wisconsin Endowment

### BAG3-R477H iPS-Cardiomyocytes exhibit impaired intracellular organization

WT

BAG3-<sup>-/-</sup> p.R477H<sup>+/+</sup>

WT

BAG3-<sup>-/-</sup> p.R477H<sup>+/+</sup>

Isoproterenol

Treatment	WT	BAG3- <sup>-/-</sup> p.R477H <sup>+/+</sup>
Untreated	~65	~75
Isoproterenol	~105	~115

Contraction in nm<sup>-1</sup>

Christopher McDermott-Roe, Geurts Lab

Advancing A Healthier Wisconsin Endowment

### Precision Medicine is dependent on basic researchers filling in the knowledge gaps

WT

BAG3-<sup>-/-</sup> p.R477H<sup>+/+</sup>

Evidence

Understanding  
+ ENVIRONMENT + LIFESTYLE

Precision Medicine

1 million leaves....

Advancing A Healthier Wisconsin Endowment

## Take aways

- Genetic studies in populations have gotten us part of the way there and sequencing individual patients is giving us new insights into genetic variation contributing to disease
- We use gene editing in model systems to attribute health outcomes to genetic variation
- Armed with this knowledge, Precision Medicine will take your biology, genome, environment and lifestyle and tailor the best care for YOU

