



“When thinking about diseases, I never think about how to cure them, but instead I think about how to prevent them.”  
-- Louis Pasteur

上医医未病之病  
中医医将病之病  
下医医已病之病

~黃帝內經~

“Superior Doctors Prevent the Disease.  
Mediocre Doctors Treat the Disease Before Evident.  
Inferior Doctors Treat the Full Blown Disease.”  
*-Huang Dee: Nai - Ching (2600 B.C. 1st Chinese Medical Text)*

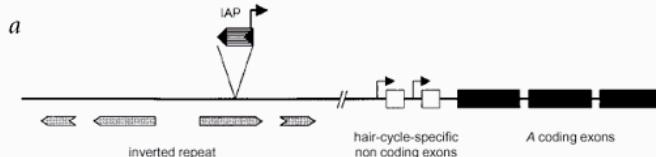
## An example: A tale of two mice



Yellow mouse  
•High risk of cancer,  
diabetes, obesity;  
•Reduced lifespan

Agouti mouse  
•Low risk of cancer,  
diabetes, obesity;  
•Prolonged lifespan

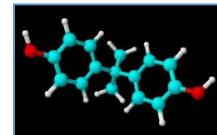
Maternal supplements  
with Zinc, methionine,  
betaine, choline, folate,  
 $B_{12}$



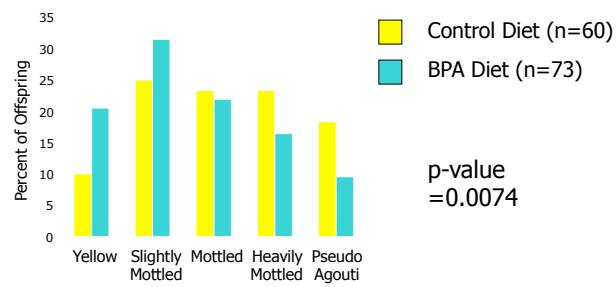
Morgan, Whitelaw,  
1999  
Waterland, Jirtle,  
2004

## Maternal Bisphenol A (BPA) Exposure

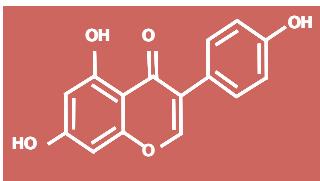
- Monomer that makes up polycarbonate plastic
- Endocrine active compound
- Found in commonly used products
- Present in 95% of humans tested
- Some animal studies reveal negative health outcomes



## Maternal BPA Exposure Results: Coat Color Distribution

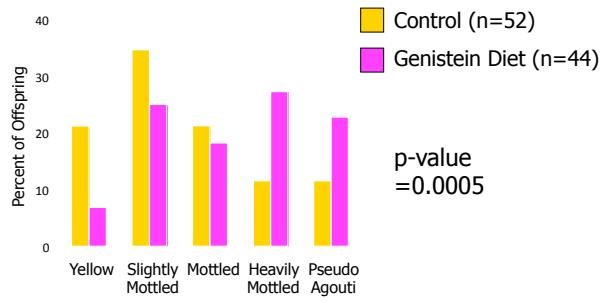


## Maternal Genistein Supplementation

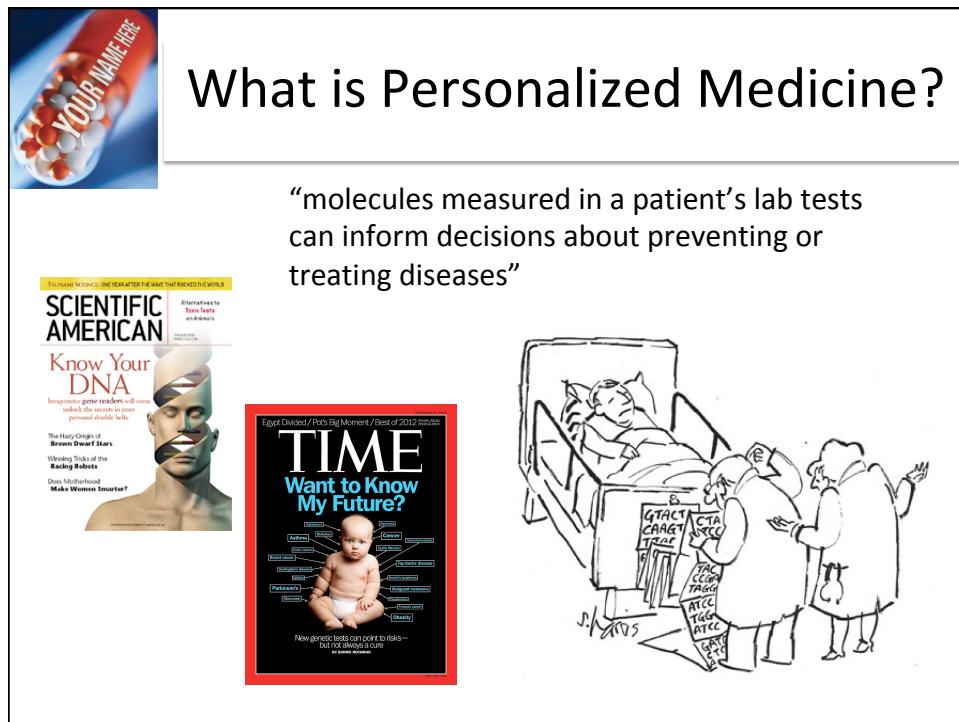
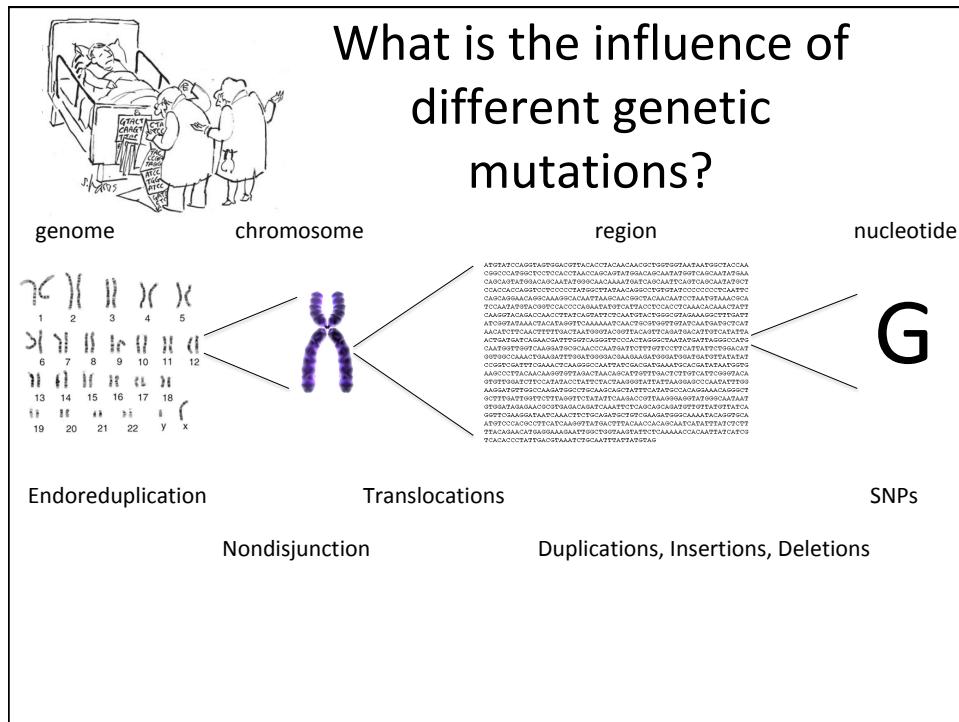


- Plant phytoestrogen
- Found in soy and soy products
- Selective estrogen receptor modulator
- Worldwide exposure varies by diet
- Chemoprevention and decreased adipocyte deposition

## Maternal Genistein Supplementation Results: Coat Color Distribution



Dolinoy, D et al (2006) *Environ Health Perspect*

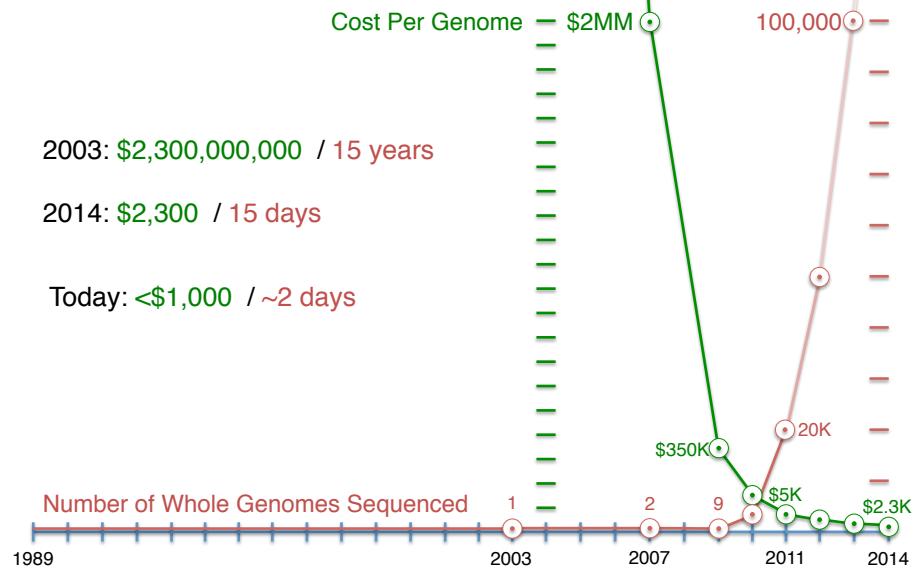


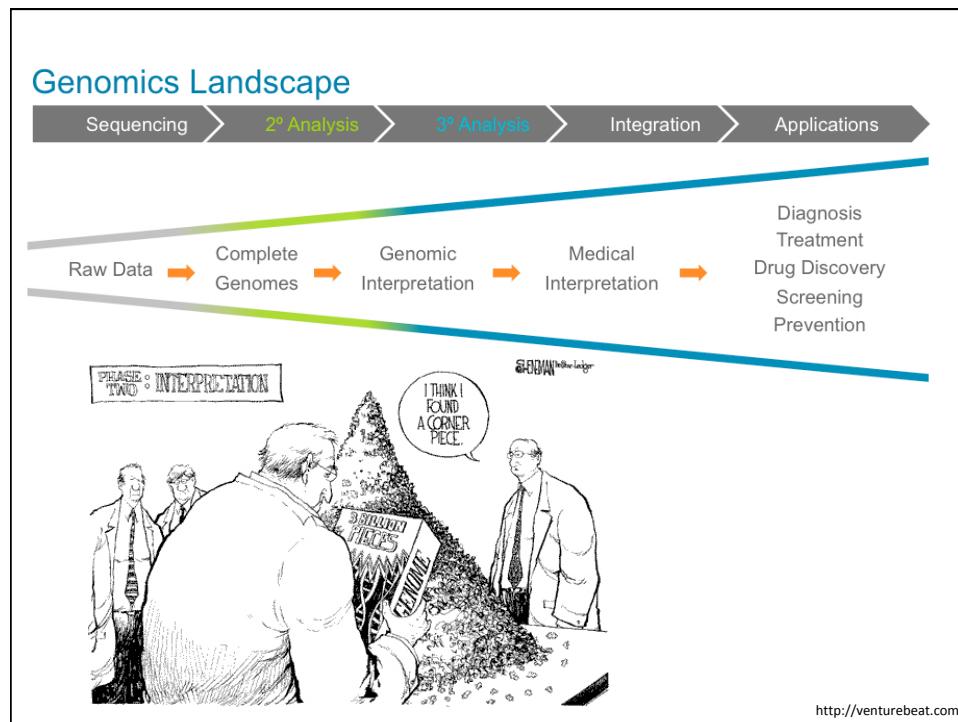
## Newborn screening for PKU

Screen for newborn for elevated phenylalanine  
 ↓  
 Identify affected newborns  
 ↓  
 Diet to prevent mental retardation



## Economics of Genome Sequencing





## What's The Right Nail For Sequencing Technology?

- As a diagnostic tool in enigmatic patients
- As a public health tool to identify those apparently well individuals with dramatically increased risk of preventable disease



## Challenges to Harnessing NGS in Clinical Medicine & Public Health

- Accuracy
  - 99.99% accuracy x 3 billion nucleotides
  - = 300,000 errors *per patient*
- Interpretation of the variants we find
- Storage and access in the medical record
- Education of patients and public
- Issues of consent and reporting
- Education of providers

## Case Study I: Exome sequencing

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### Targeted capture and massively parallel sequencing of 12 human exomes

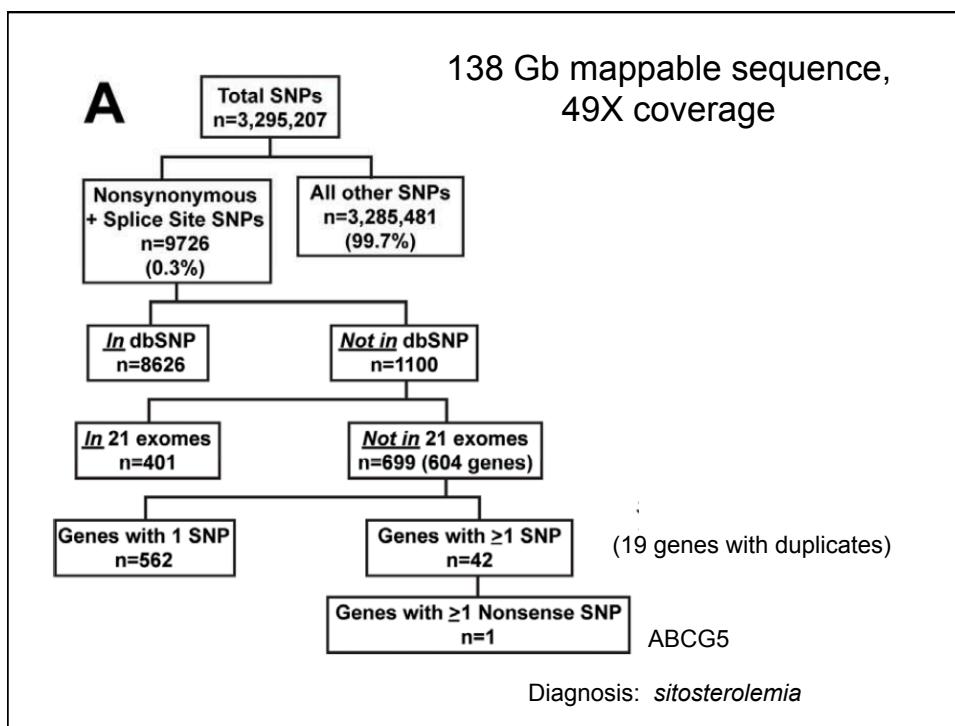
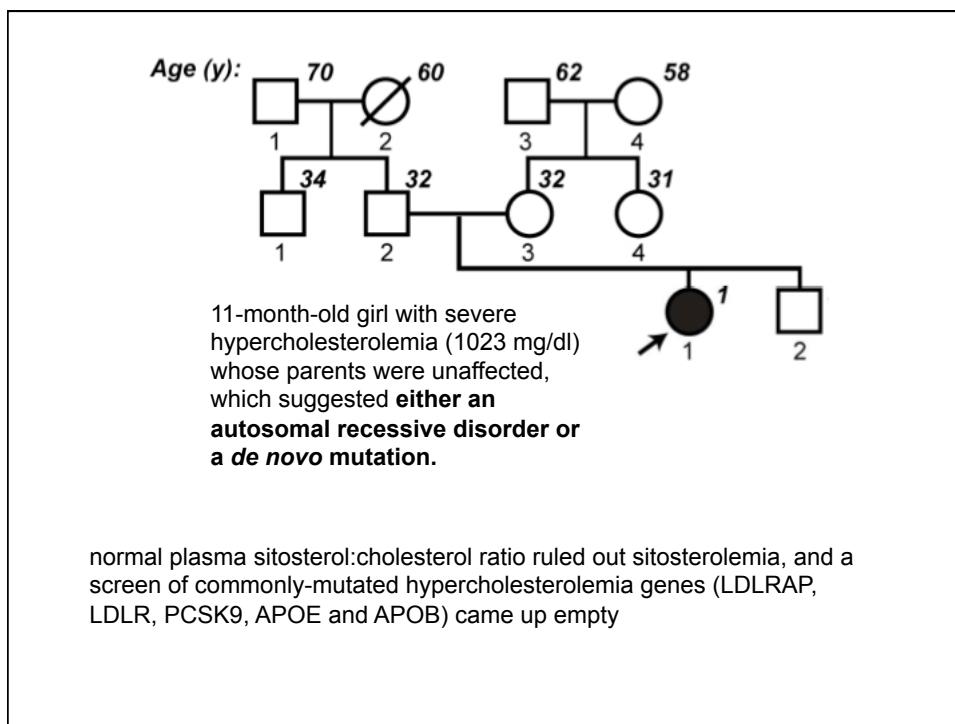
Sarah B. Ng<sup>1</sup>, Emily H. Turner<sup>1</sup>, Peggy D. Robertson<sup>1</sup>, Steven D. Flygare<sup>1</sup>, Abigail W. Bigham<sup>2</sup>, Choli Lee<sup>1</sup>,  
Tristan Shaffer<sup>1</sup>, Michelle Wong<sup>1</sup>, Arindam Bhattacharjee<sup>4</sup>, Evan E. Eichler<sup>1,3</sup>, Michael Bamshad<sup>2</sup>,  
Deborah A. Nickerson<sup>1</sup> & Jay Shendure<sup>1</sup>

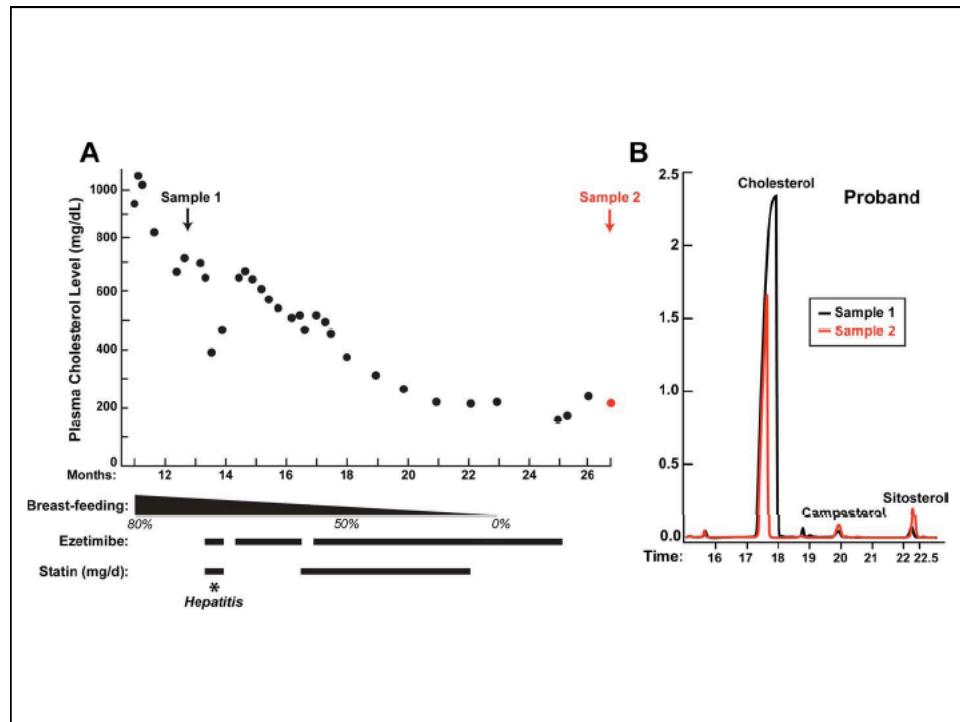
Can we map a Mendelian Disease by Next-Gen Sequencing?

- 4 Individuals with Freeman-Sheldon Syndrome
- 8 Hapmap Individuals

		FSS24895	FSS10208	FSS10066	FSS22194	Any 3 of 4
		FSS24895	FSS10208	FSS10066	FSS22194	FSS24895 FSS10208 FSS10066 FSS22194
Number of genes in which each affected has at least one...	Non-synonymous cSNP, splice site variant or coding indel (NS/SS/I)	4,510	3,284	2,765	2,479	3,768
	NS/SS/I not in dbSNP	513	128	71	53	119
	NS/SS/I not in eight HapMap exomes	799	168	53	21	160
	NS/SS/I neither in dbSNP nor eight HapMap exomes	360	38	8	1 ( <i>MYH3</i> )	22
	...And predicted to be damaging	160	10	2	1 ( <i>MYH3</i> )	3

Case Study II: a single individual						
<b>Identification by Whole Genome Resequencing of Gene Defect Responsible for Severe Hypercholesterolemia</b>						
Jonathan Rios <sup>1</sup> , Evan Stein <sup>2</sup> , Jay Shendure <sup>3</sup> , Helen H. Hobbs <sup>1,4*</sup> , Jonathan C. Cohen <sup>1**</sup>						





## Case Study III: Whole genome

Highly recommended reading:

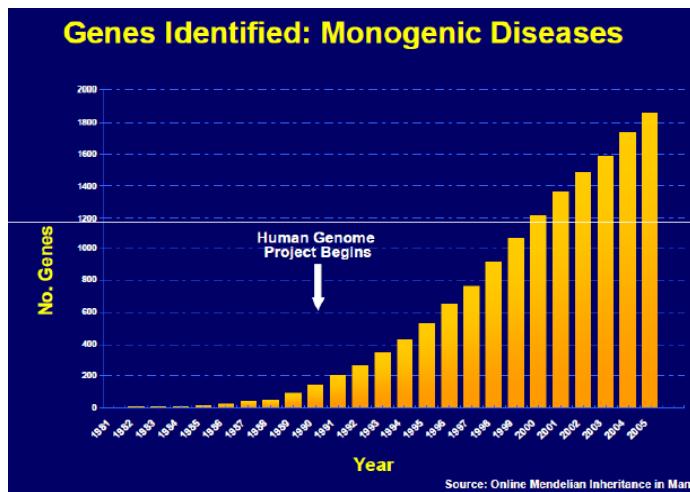
[\*\*"We Gained Hope." The Story of Lilly Grossman's Genome\*\*](#)



National Geographic's Blog  
"PHENOMENA: Not exactly rocket science"  
Posted: Monday March 11, 2013

<http://phenomena.nationalgeographic.com/2013/03/11/we-gained-hope-the-story-of-lilly-grossmans-genome/>

## Monogenic Disorders: Success stories



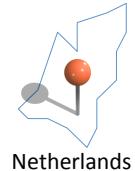
## Intellectual Disability: RUNMC



Netherlands

- Prof. Han Brunner, Prof. Joris Veltman
- Severe ID usually due to de novo variation
- Diagnostic Yield of WGS vs. exome
- Previous exome study published in NEJM
- Current study 50 exome negative trios
- Variants in exome & regulatory regions
- Focus on de novo events

2012: Diagnostic Exome 100 ID Trios  
All negative by Sanger, Microarray

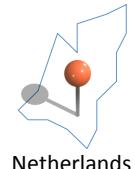


Netherlands

POSITIVE DIAGNOSIS	NUMBER OF PATIENTS (n=100)
All Mutations	16
De Novo Mutations	13
Autosomal Dominant	10
Autosomal Recessive	1
X-Linked	2
Inherited Mutations	3
Autosomal Dominant	0
Autosomal Recessive	0
X-Linked	3
Candidate Causal Variants	19
No Diagnosis	65

De Ligt, et al. New Engl J Med. Vol 367, November 2012

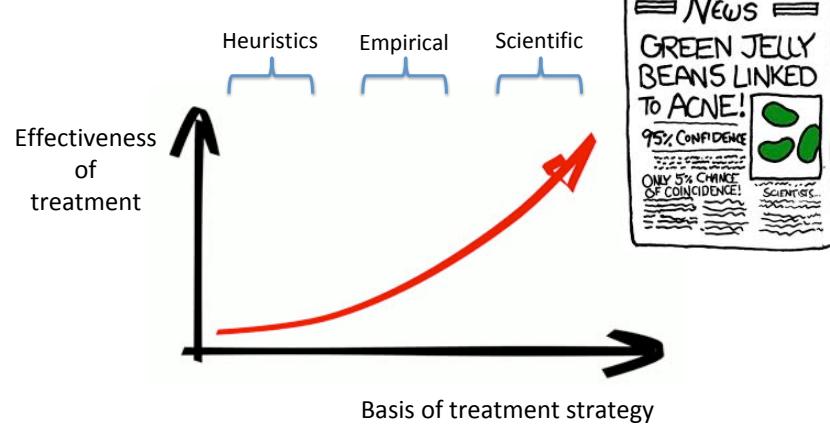
2013: Whole Genome 50 ID trios  
All negative by Sanger, Microarray, Exome



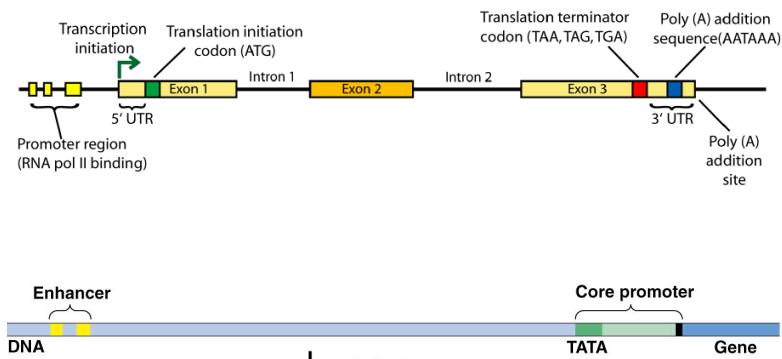
Netherlands

POSITIVE DIAGNOSIS	NUMBER OF PATIENTS (n=50)
All Mutations	19
De Novo Mutations	18
Autosomal Dominant	14
Autosomal Recessive	0
X-Linked	4
Inherited Mutations	1
Autosomal Dominant	0
Autosomal Recessive	1
X-Linked	0
Candidate Causal Variants	8
No Diagnosis	23

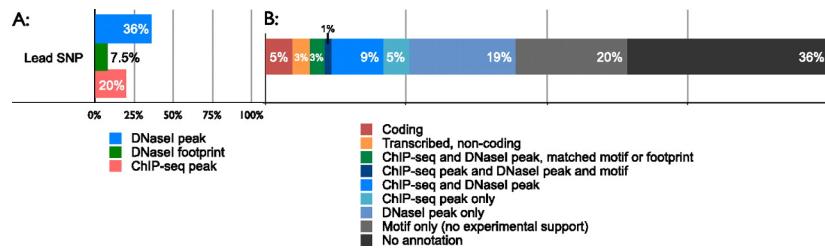
Efficacy of diagnosis/treatment is related to our understanding of disease!



Interpreting SNPs depends on annotation and how well we understand the feature.



## Most disease associations are NOT to protein coding regions



These are all markers of regulation !!!!

Schaub M A et al. Genome Res. 2012;22:1748-1759