G T C A

Seeing the Bigger Picture

T G G A

Through Billions of Bases

C

A

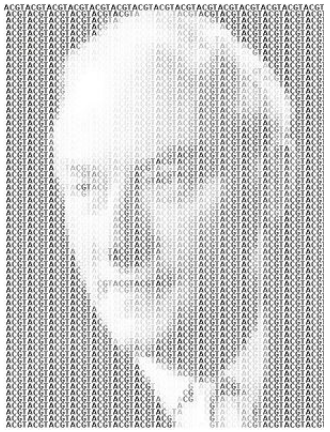
Nancy J. Cox, Ph.D.

The University of Chicago

http://genemed.uchospitals.edu

G T C A

Seeing the Bigger



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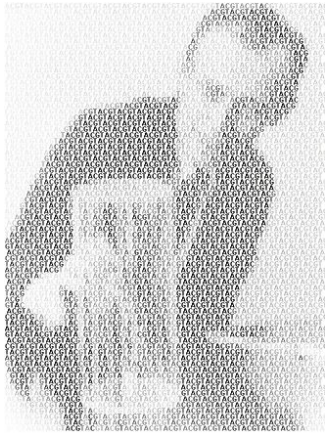

T G G

Through Billions of Bases

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Pictures and Art

- **Association studies via high-throughput genotyping – Cave painting?**
- **Insights from exome and whole-genome sequencing – Minimalism?**
- **Omics beyond DNA sequence – Abstraction?**
- **Prediction, causality – Impressionism?**
- **A more complete synthesis – post-modernism?**

Relating Genotype to Phenotype

Genotyping **Sequencing**

Relating Genotype to Phenotype

Genotyping

+

Sequencing

=

Genome Interrogation

GWAS Has …

Given us 1000-fold more discovery of loci associated with common human diseases and related quantitative traits

GWAS Has Not …

Given us much novel biological understanding; highly significant and reproducible signals tend to be non-coding and we are often unsure even what gene is implicated

Picking the Cherries …

Orchards of Cherry Trees to Pick

Ellsworth Kelly

Whole Genome and Exome Sequencing Has...

Given us an unprecedented understanding of human variation and drawn attention to how recent demography has shaped our genome

Enabled a successful assault on the remainder of Mendelian disorders not yet ascribed to genes

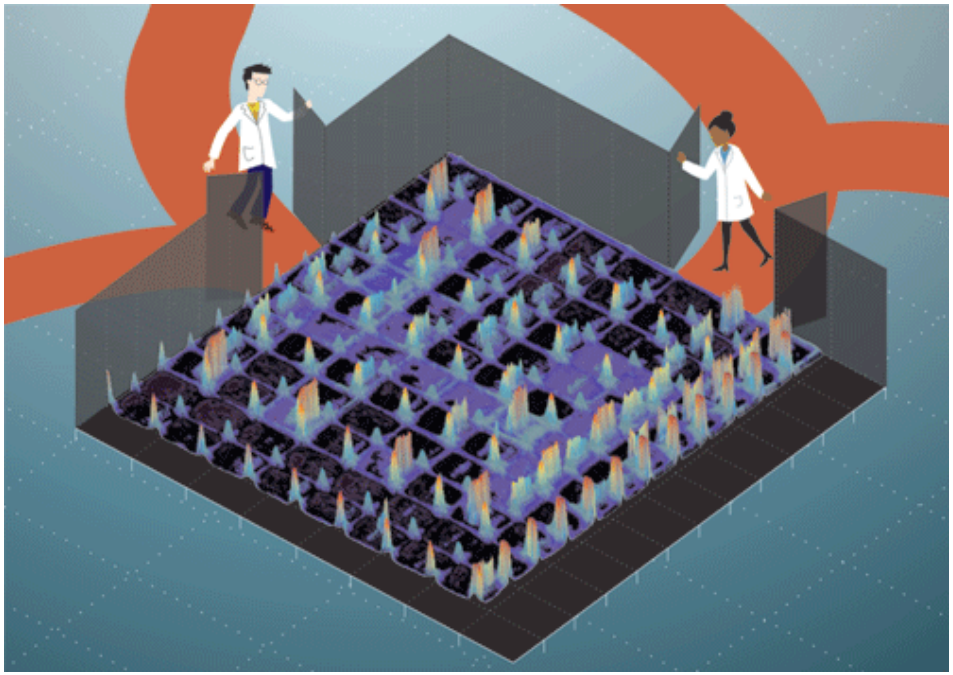
Taught us lessons we have not been keen to learn about effect sizes for rare variants in common diseases and quantitative traits

Frank Stella

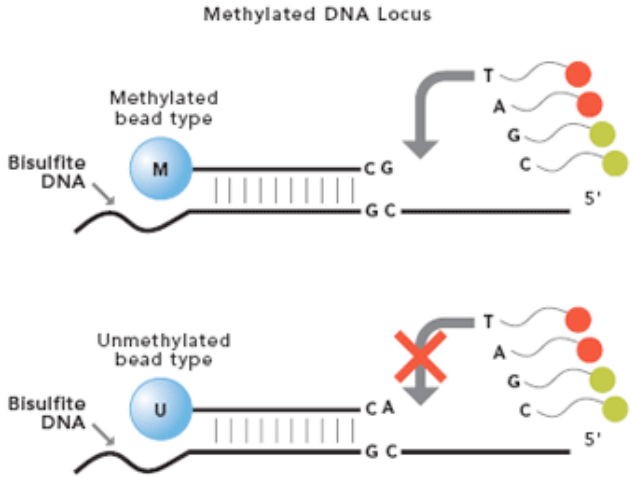
Exome Sequencing Has Not …

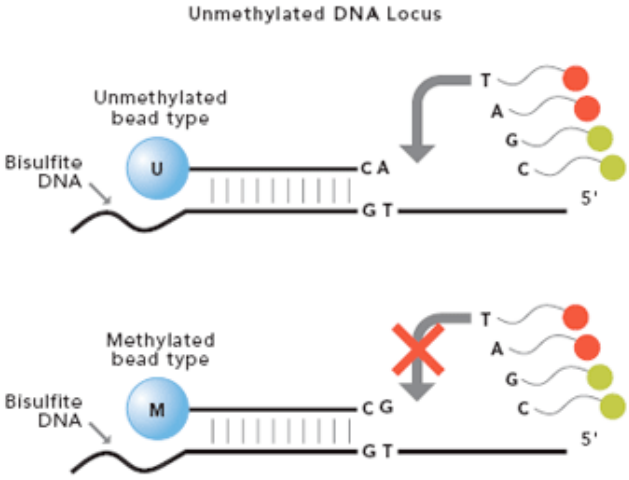
Enabled gene discovery for all “Mendelian” phenotypes or pedigrees attempted

Been adequately powered to enable discovery of novel contributing genes in applications to complex disorders at 10K + cases and controls



Protein-omics





Methylome

GTEx: Genotype Tissue Exchange

WE ACCELERATE DISCOVERY

HOME PROGRAMS RESEARCH FUNDING NEWS & EVENTS MULTIMEDIA HIGHLIGHTS ABOUT CONTACTS

Genotype-Tissue Expression (GTEx)

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OVERVIEW WORKING GROUP MEMBERS FUNDING PROGRAM RESOURCES PUBLICATIONS/NEWS MEETING/ACTIVITIES

Common Fund Home > Programs > Genotype-Tissue Expression (GTEx)

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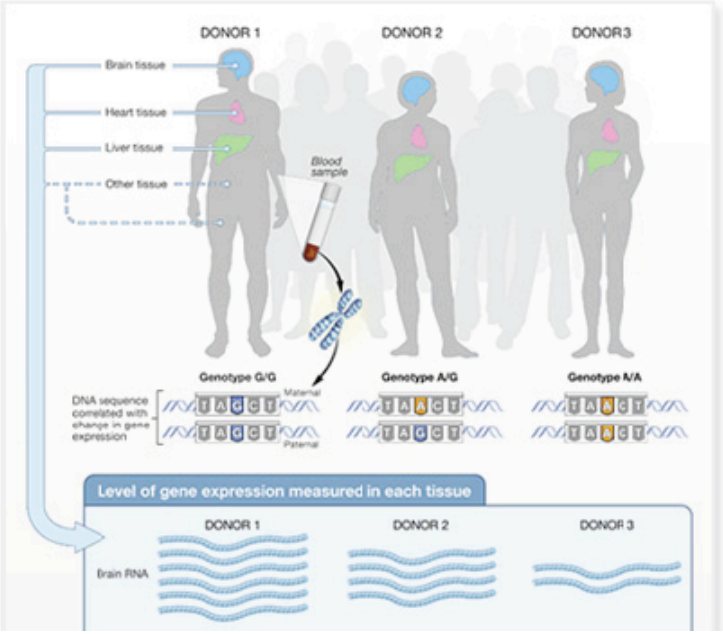
Program Snapshot

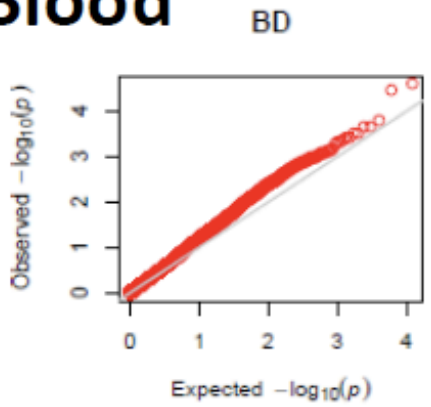
The Common Fund's **Genotype-Tissue Expression (GTEx)** program aims to study human gene expression and regulation in multiple tissues, providing valuable insights into the mechanisms of gene regulation and, in the future, its disease-related perturbations. Genetic variation between individuals will be examined for correlation with differences in gene expression level to identify regions of the genome that influence whether and how much a gene is expressed. The GTEx project includes the following initiatives:

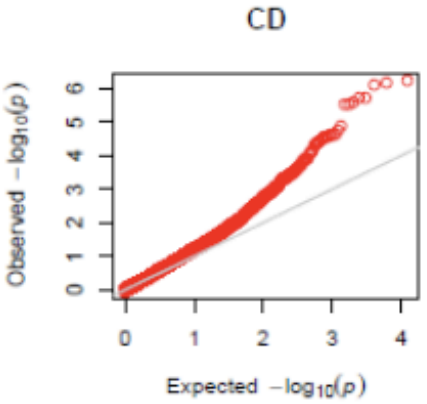
- Novel Statistical Methods for Human Gene Expression Quantitative Trait Loci (eQTL) Analysis
- Laboratory, Data Analysis, and Coordinating Center (LDACC)
- caHUB Acquisition of Normal Tissues in Support of the GTEx Project

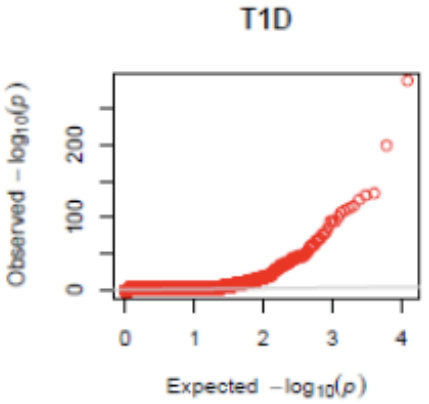
Read more...

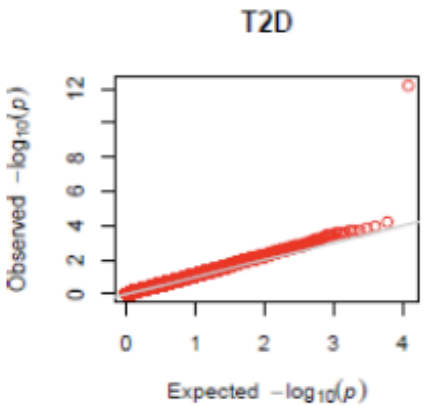


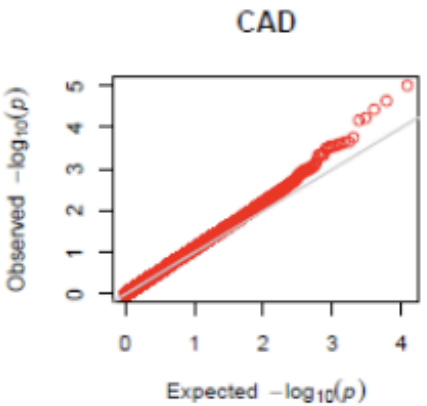
Whole Blood

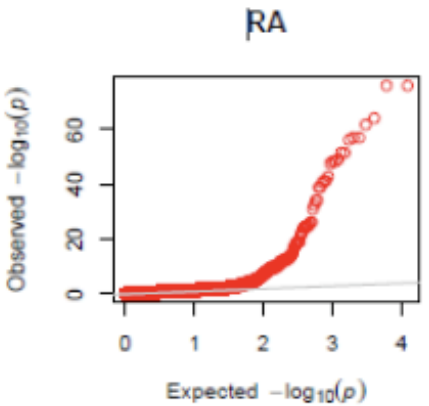


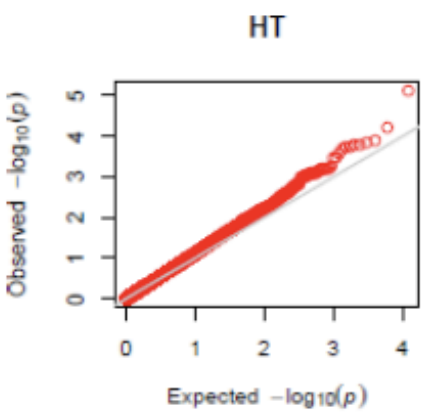






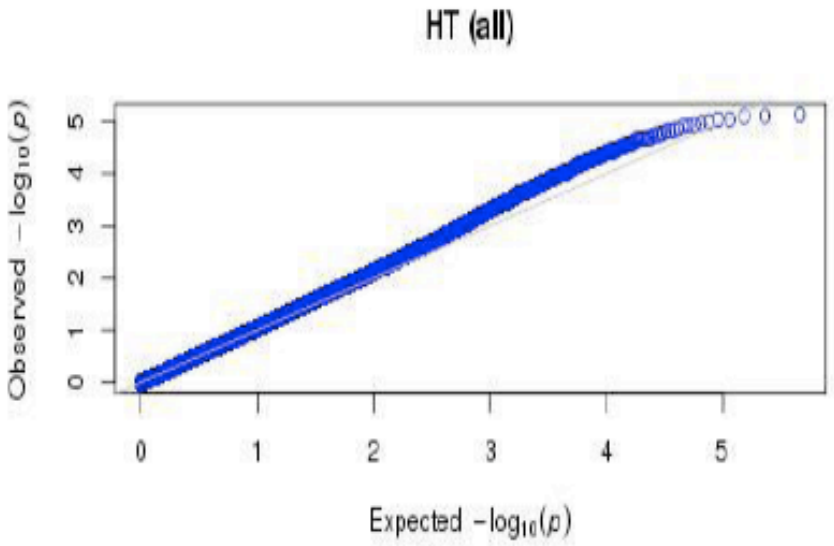


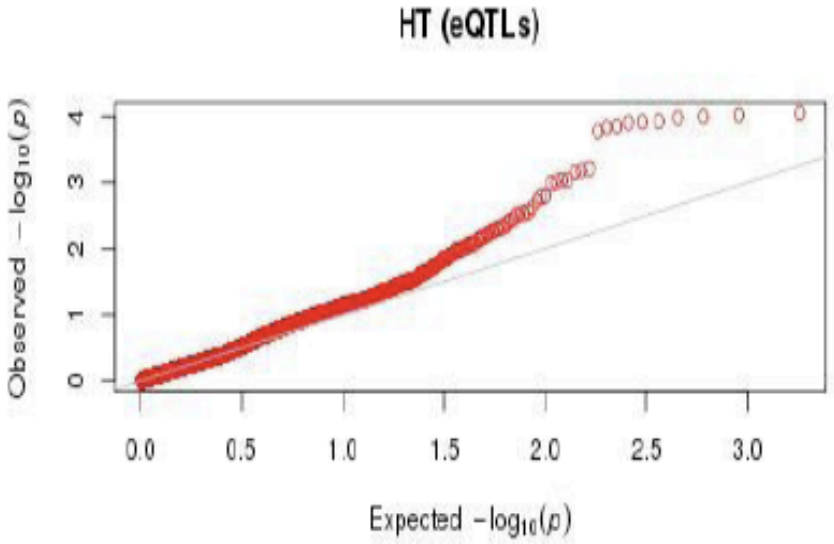




Autoimmune Disorders

Hypertension and Adipose eQTLs





Polygenic Modeling and Prediction

REPORT

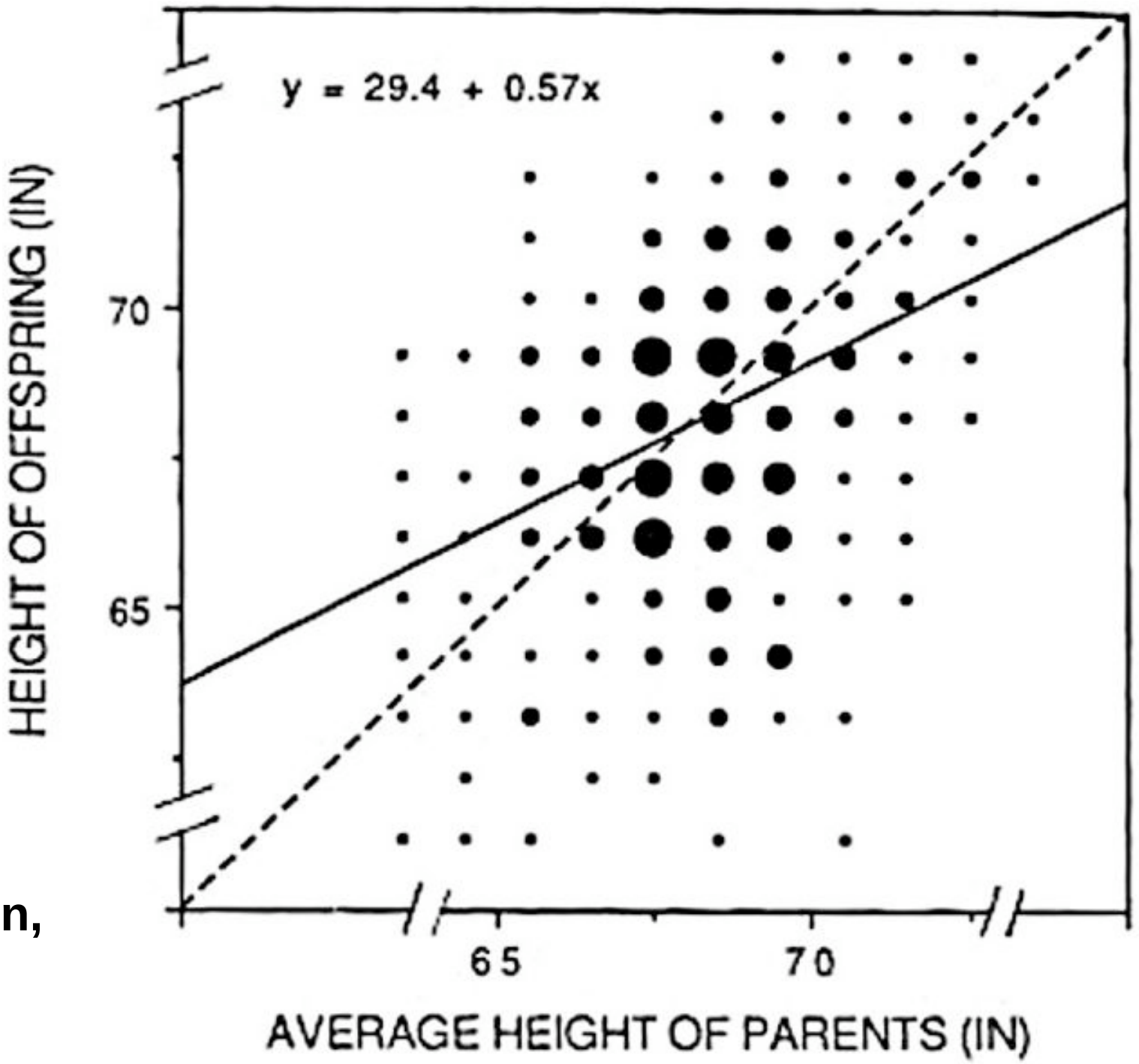
GCTA: A Tool for Genome-wide Complex Trait Analysis

Jian Yang,[1,*] S. Hong Lee,[1] Michael E. Goddard,[2,3] and Peter M. Visscher[1]

ARTICLE

Estimating Missing Heritability for Disease from Genome-wide Association Studies

Sang Hong Lee,[1] Naomi R. Wray,[1] Michael E. Goddard,[2,3] and Peter M. Visscher[1,*]


y = 29.4 + 0.57x
HEIGHT OF OFFSPRING (IN)
70
65
65
70
AVERAGE HEIGHT OF PARENTS (IN)

Galton, 1889

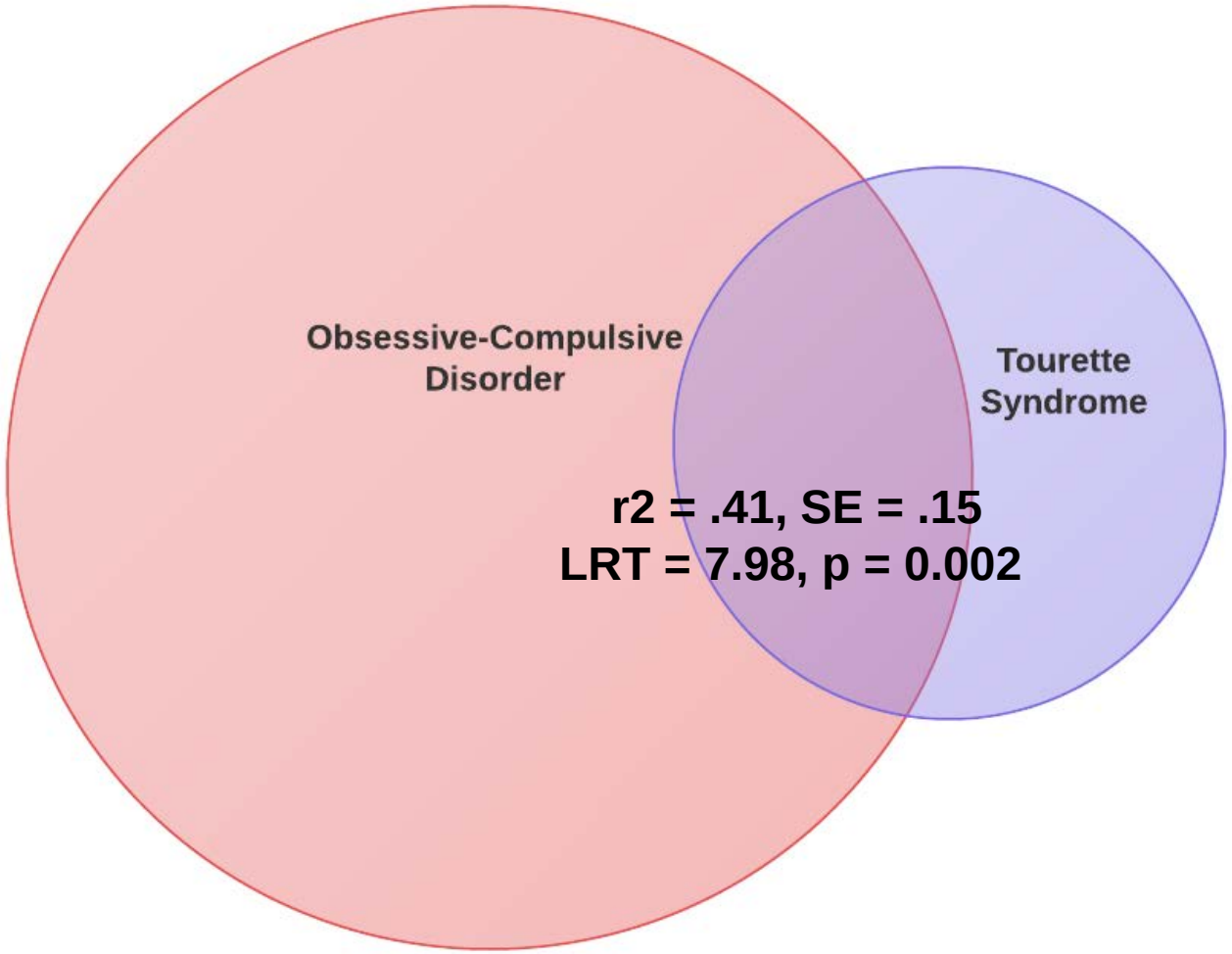
By Minor Allele Frequency

	Tourette Syndrome		Obsessive-Compulsive Disorder	
MAF	Number of SNPs	h2 (s.e.)	Number of SNPs	h2 (s.e.)
> 0.001 – 0.05	20,316	0.13 (0.04)	19,605	0 (0.03)
> 0.05 – 0.1	49,445	0.02 (0.05)	47,976	0.04 (0.05)
> 0.1 -0.2	96,398	0.11 (0.07)	91,661	0.08 (0.08)
> 0.2-0.3	81,924	0.12 (0.07)	77,641	0.01 (0.01)
> 0.3-0.4	74,393	0.16 (0.07)	70,193	0.11 (0.05)
> 0.4 -0.5	70,911	0.07 (0.06)	66,770	0.11 (0.05)

Heritability by MAF (Imputed)

	Tourette Syndrome		Obsessive-Compulsive Disorder	
MAF	Number of SNPs	h2 (s.e.)	Number of SNPs	h2 (s.e.)
> 0.001 – 0.05	2,243,744	0.15 (0.09)	2,357,568	0.000001 (0.06)
> 0.05 – 0.5	5,538,943	0.34 (0.10)	5,492,973	0.32 (0.12)

Genetic Correlation



Bipolar Disorder

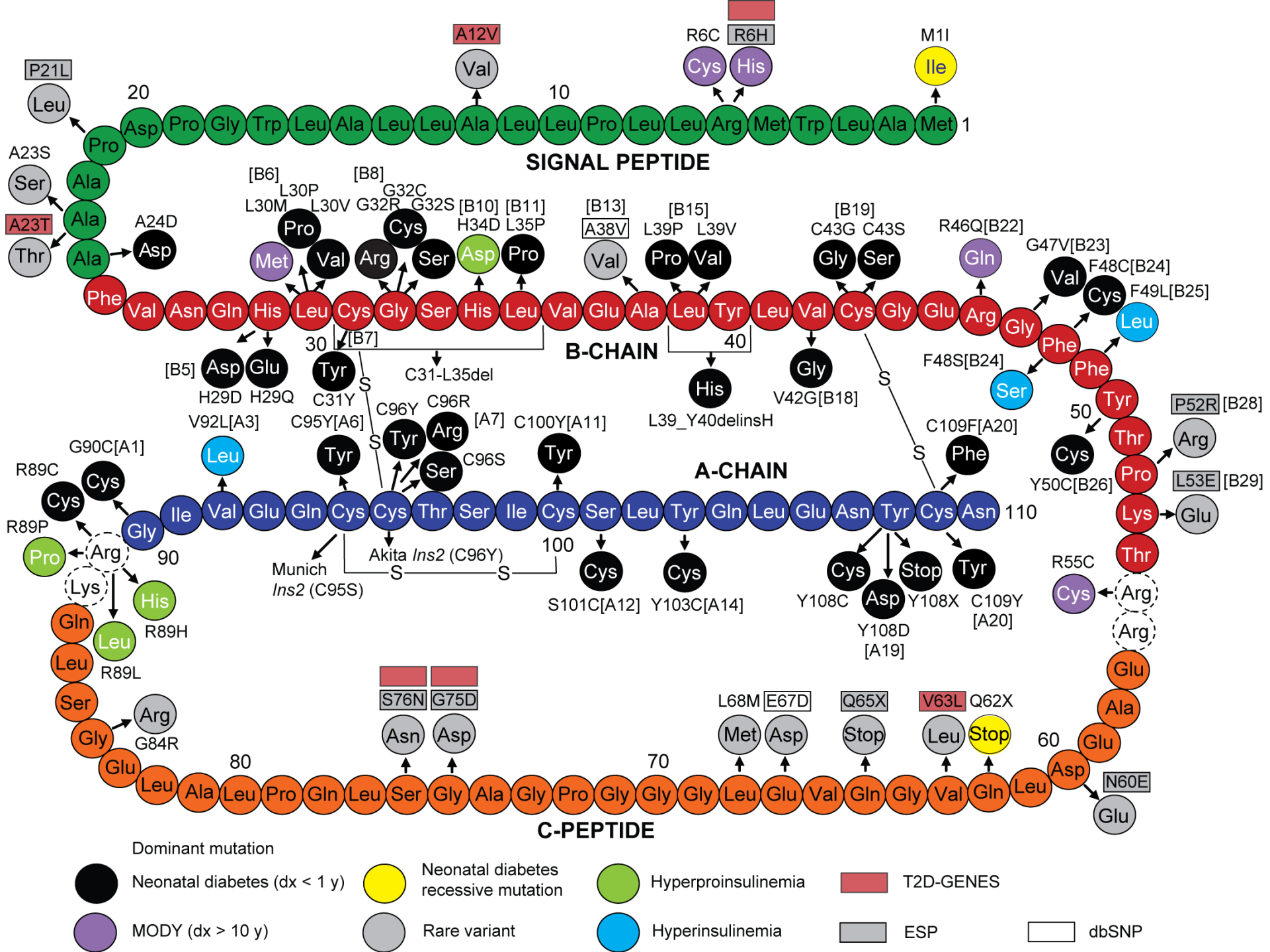
- **Heritability estimated from previous twin and family studies ~ 0.7**
- **Heritability estimated from (GAIN + Bipolar Genome Study) ~ 0.35 (600K SNPs)**
- **Heritability estimated for same samples using 27K cis-eQTLs from brain ~ 0.2**
- **Heritability estimated for same samples using 27K cis-eQTLs from LCLs < 0.01**

Causality …

Remains hugely challenging for rare variant discoveries in Mendelian diseases and for common and rare variant discoveries in complex disorders

Cannot be assessed through knock-outs and knock-ins in every situation

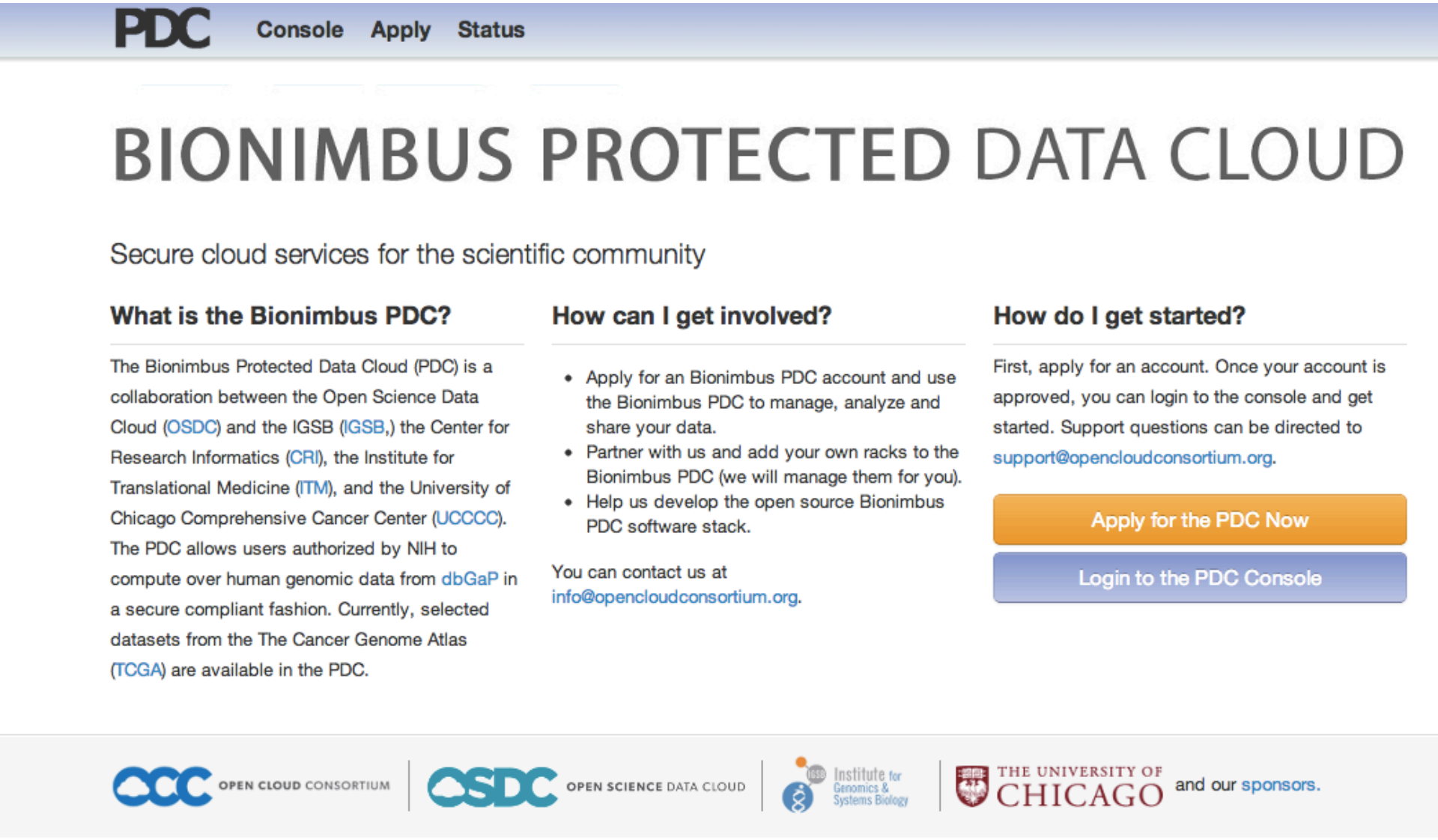
Is particularly hard to prove when you have a single family (or individual) with a rare phenotype


SIGNAL PEPTIDE
B-CHAIN
A-CHAIN
C-PEPTIDE
P21L
A23S
A23T
A24D
A12V
R6C
R6H
M1I
[B6] L30P L30M L30V
[B8] G32C G32R G32S
[B10] H34D
[B11] L35P
[B13] A38V
[B15] L39P L39V
[B19] C43G C43S
R46Q[B22]
G47V[B23]
F48C[B24]
F49L[B25]
F48S[B24]
P52R [B28]
L53E [B29]
[B5] H29D H29Q
[B7]
C31-L35del
C31Y
C95Y[A6]
V92L[A3]
C96Y
C96R
[A7]
C96S
C100Y[A11]
L39_Y40delinsH
V42G[B18]
C109F[A20]
Y50C[B26]
G90C[A1]
R89C
R89P
R89H
R89L
Munich Ins2 (C95S)
Akita Ins2 (C96Y)
S101C[A12]
Y103C[A14]
Y108C
Y108X
Y108D [A19]
C109Y [A20]
R55C
G84R
S76N
G75D
L68M
E67D
Q65X
V63L
Q62X
N60E
Dominant mutation
Neonatal diabetes (dx < 1 y)
Neonatal diabetes recessive mutation
Hyperproinsulinemia
T2D-GENES
MODY (dx > 10 y)
Rare variant
Hyperinsulinemia
ESP
dbSNP

Post-Modernism?

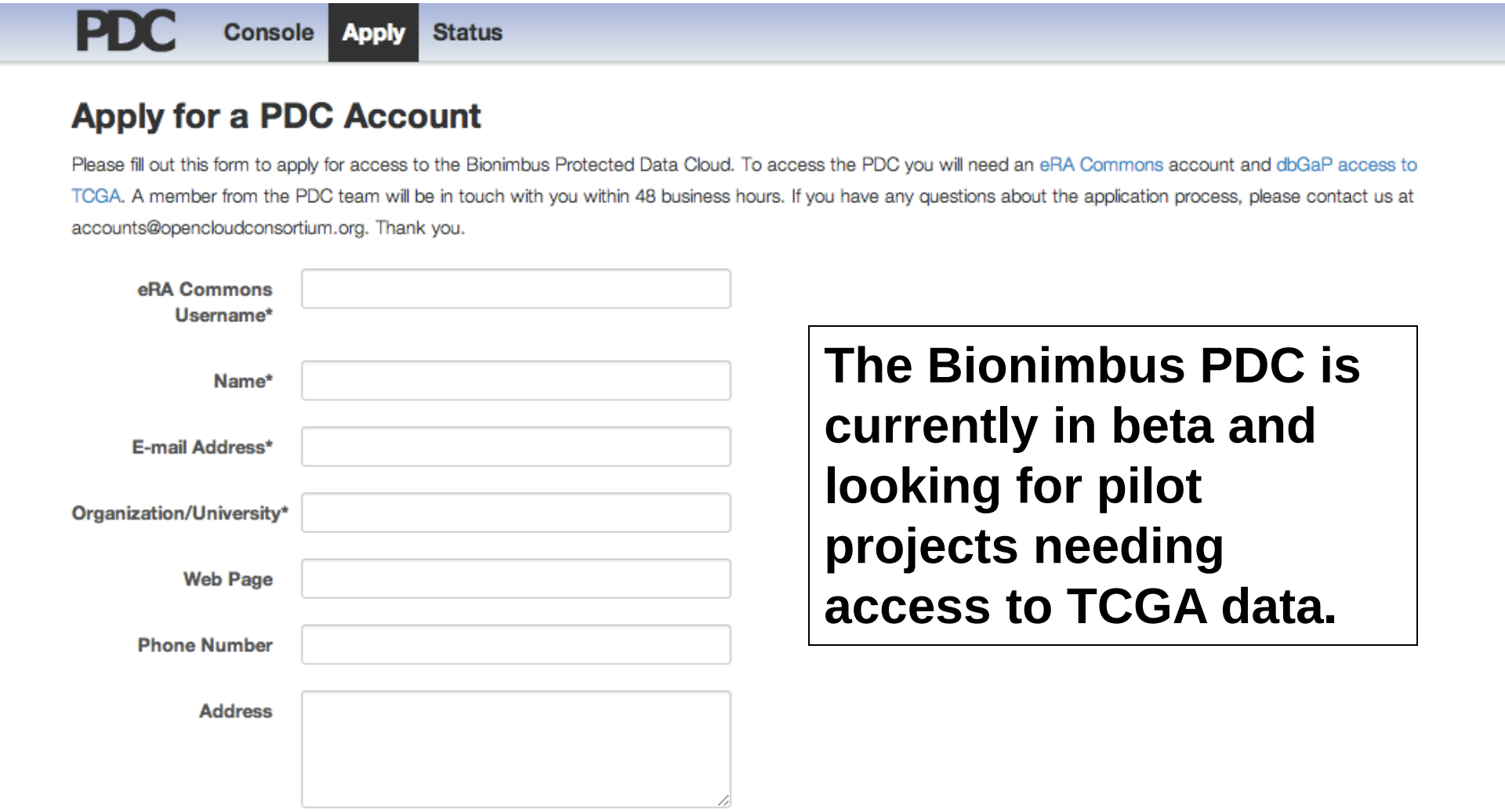
Whole genome interrogation – genes as well as other functional units

Using more – ideally all – available information simultaneously



bionimbus-pdc.opensciencedatacloud.org

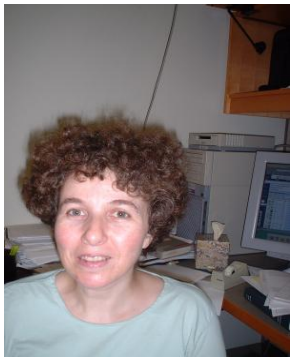
Apply For An Account



The Bionimbus PDC is currently in beta and looking for pilot projects needing access to TCGA data.

bionimbus-pdc.opensciencedatacloud.org

Cox Lab



Anna Pluzhnikov

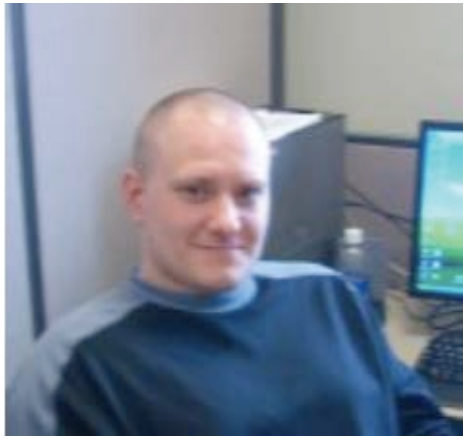
Steven Zhang

Jason Torres

Lea Davis (Bridget)

Anna Tikhomirov

Anuar Konkashbaev

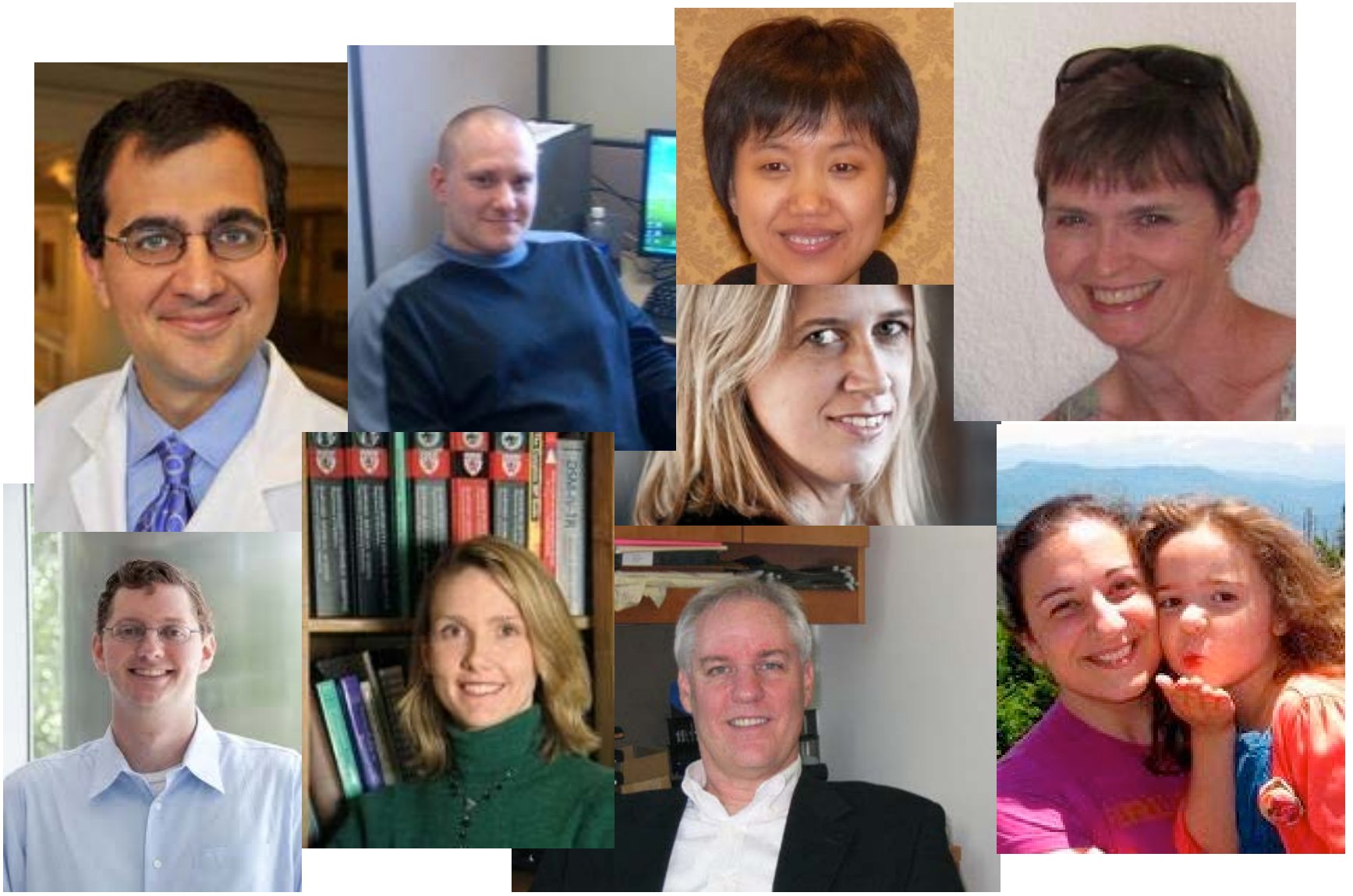


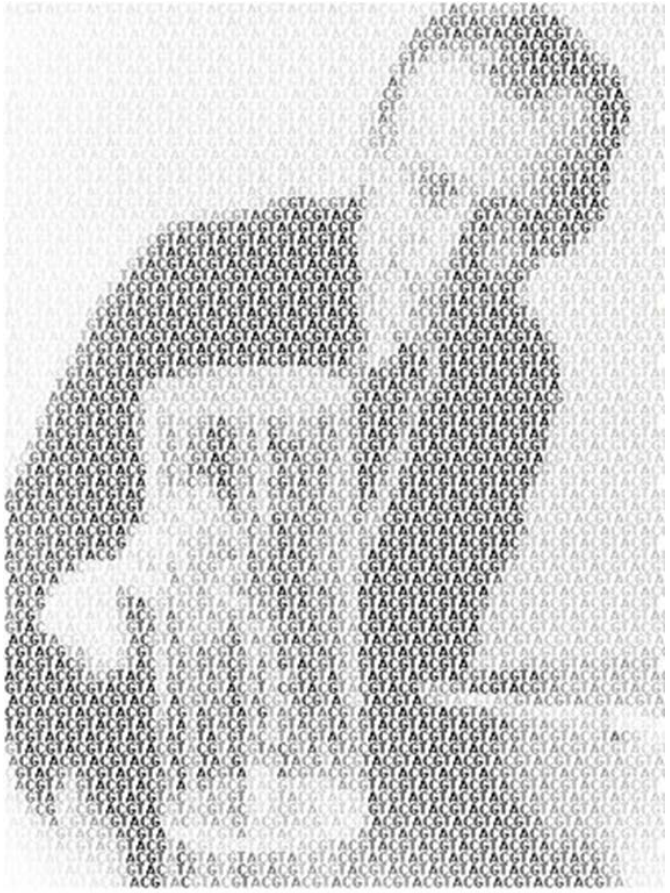
Pat Evans

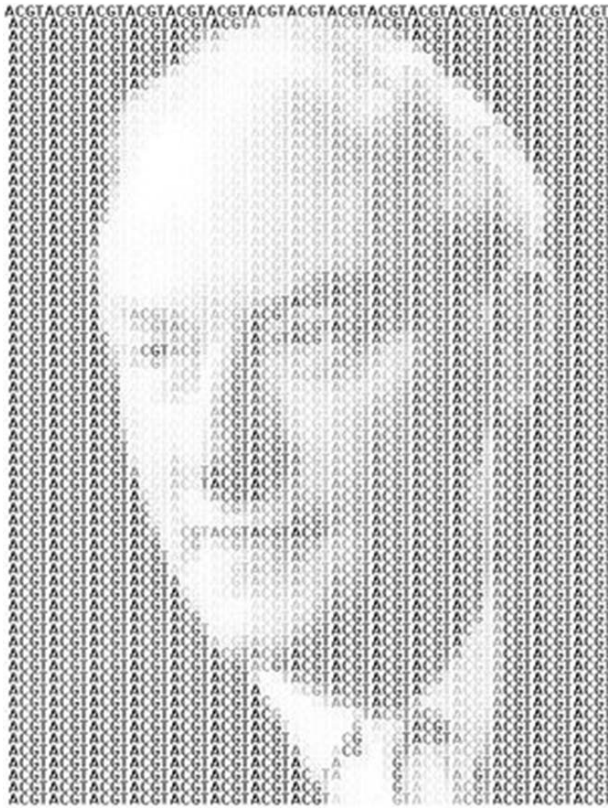
Vasily Trubetskoy

Eric Gamazon

The “nitty gritty” analysis group!



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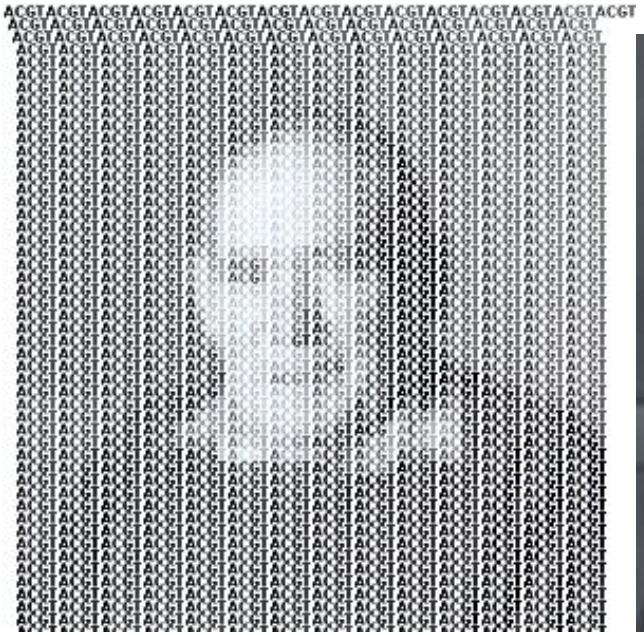

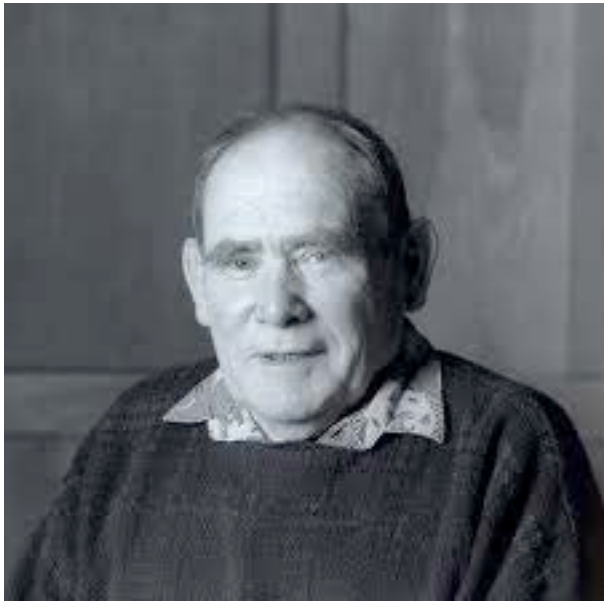

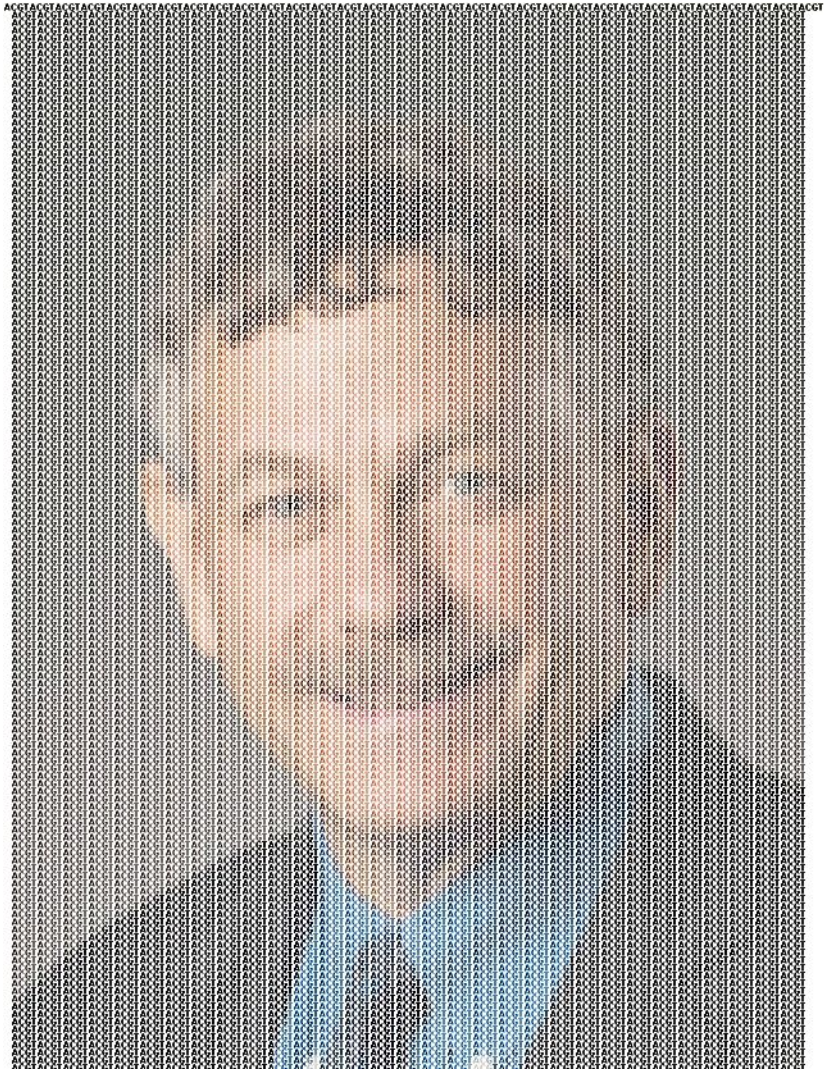

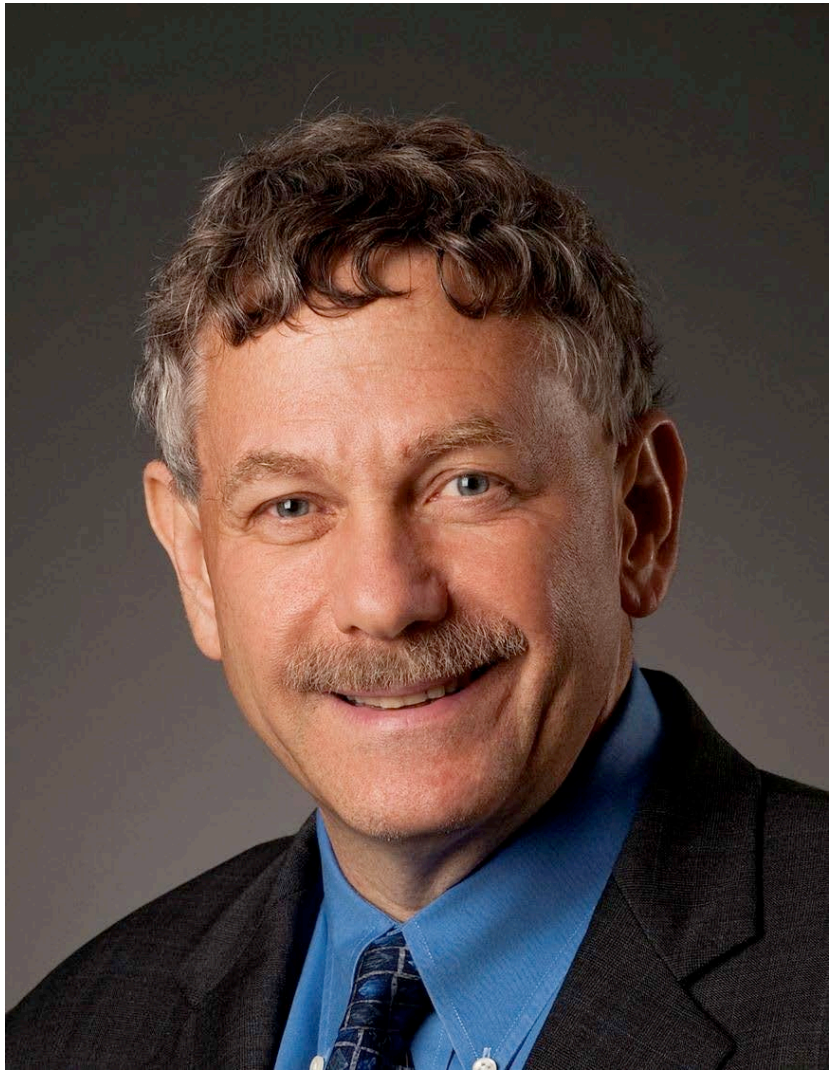

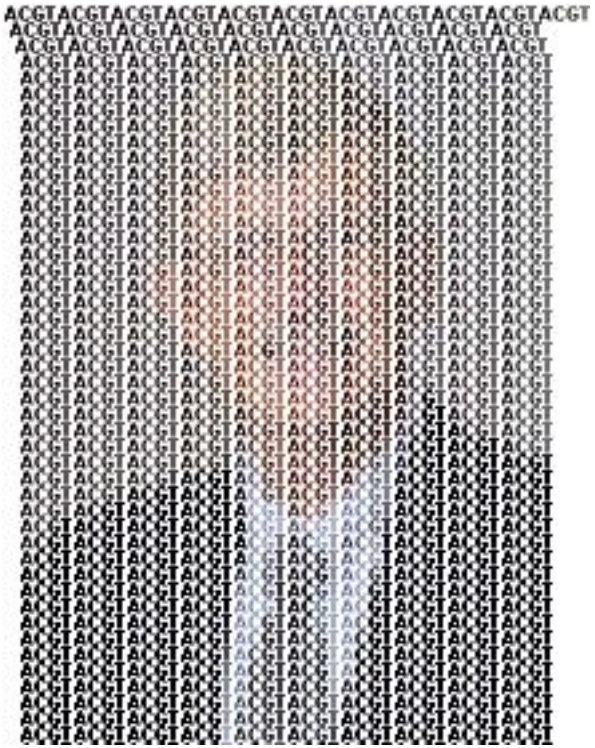

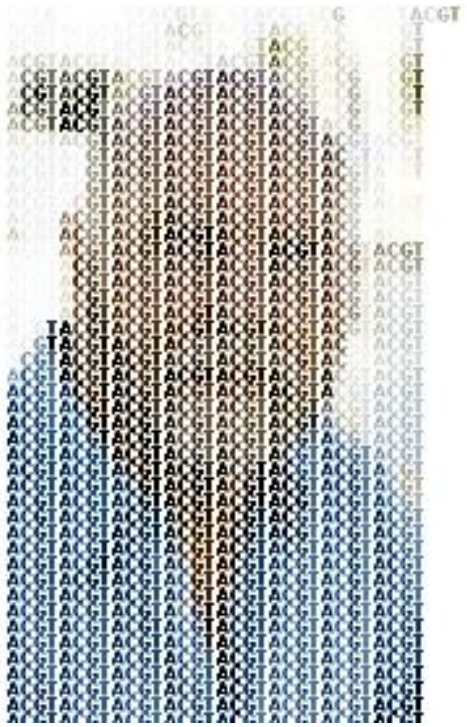

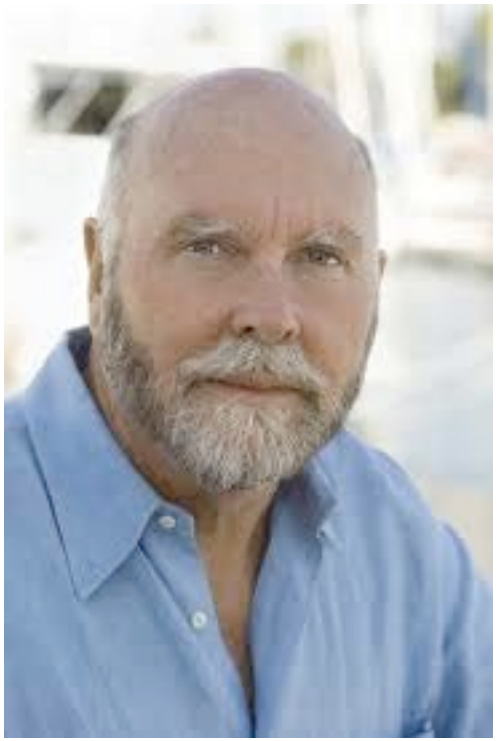

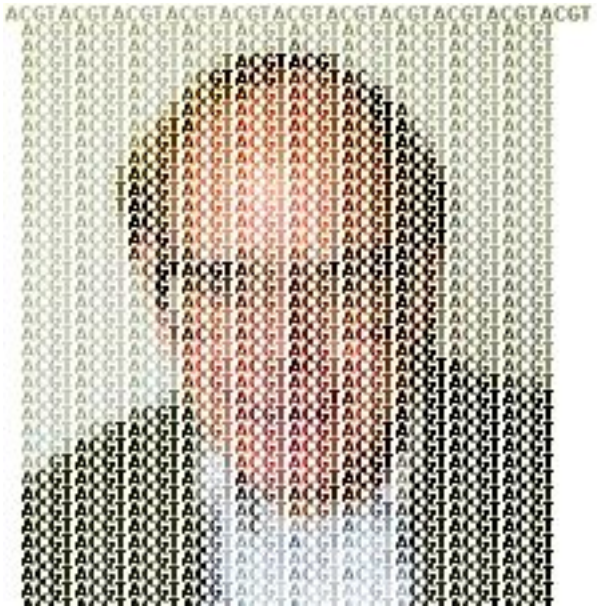

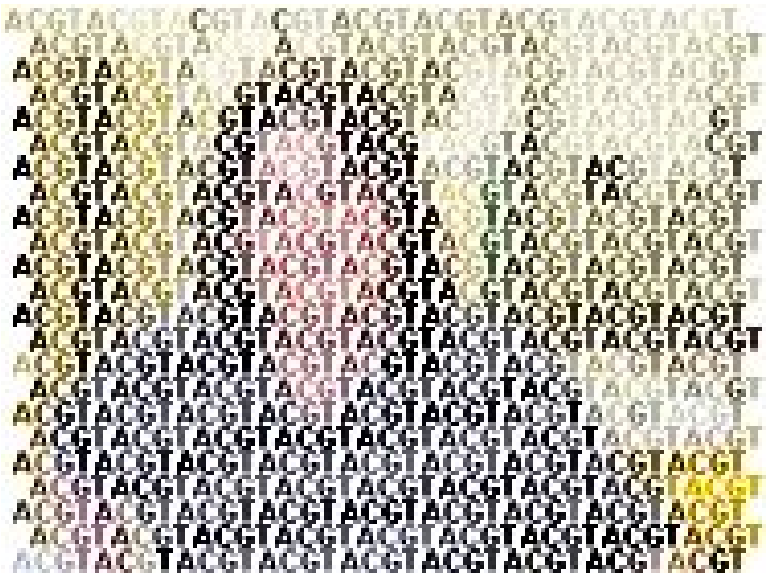

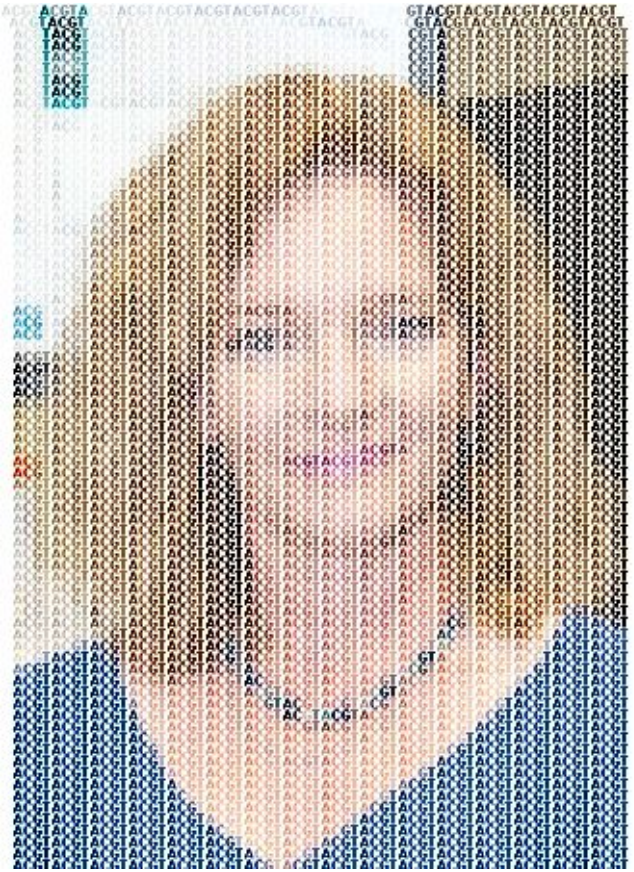


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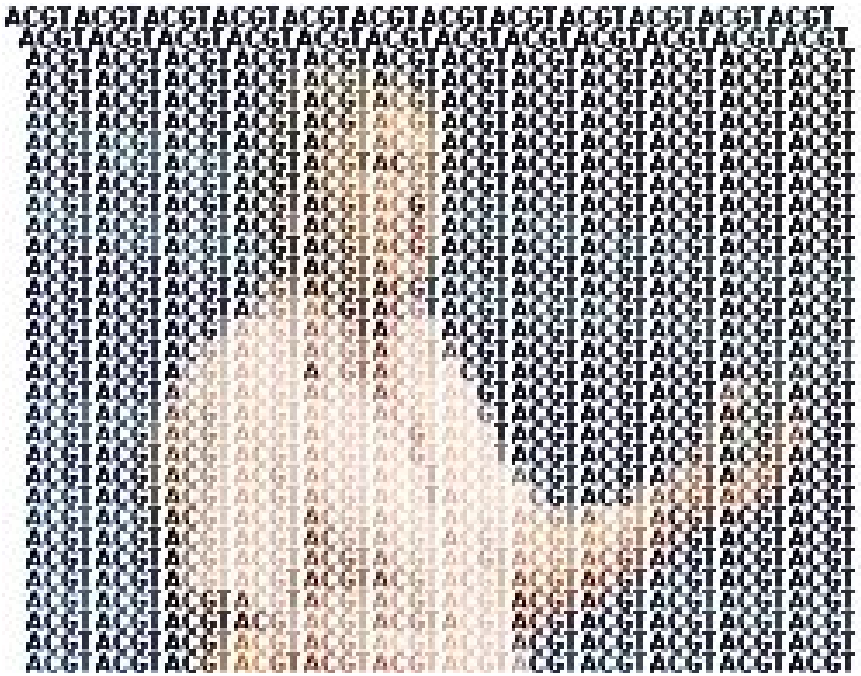


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