Genetic Variation in the *SIM1* Locus is Associated with Erectile Dysfunction

Eric Jorgenson, PhD
Kaiser Permanente Division of Research
February 26th, 2019

What Is the Public Health Relevance of the Study?

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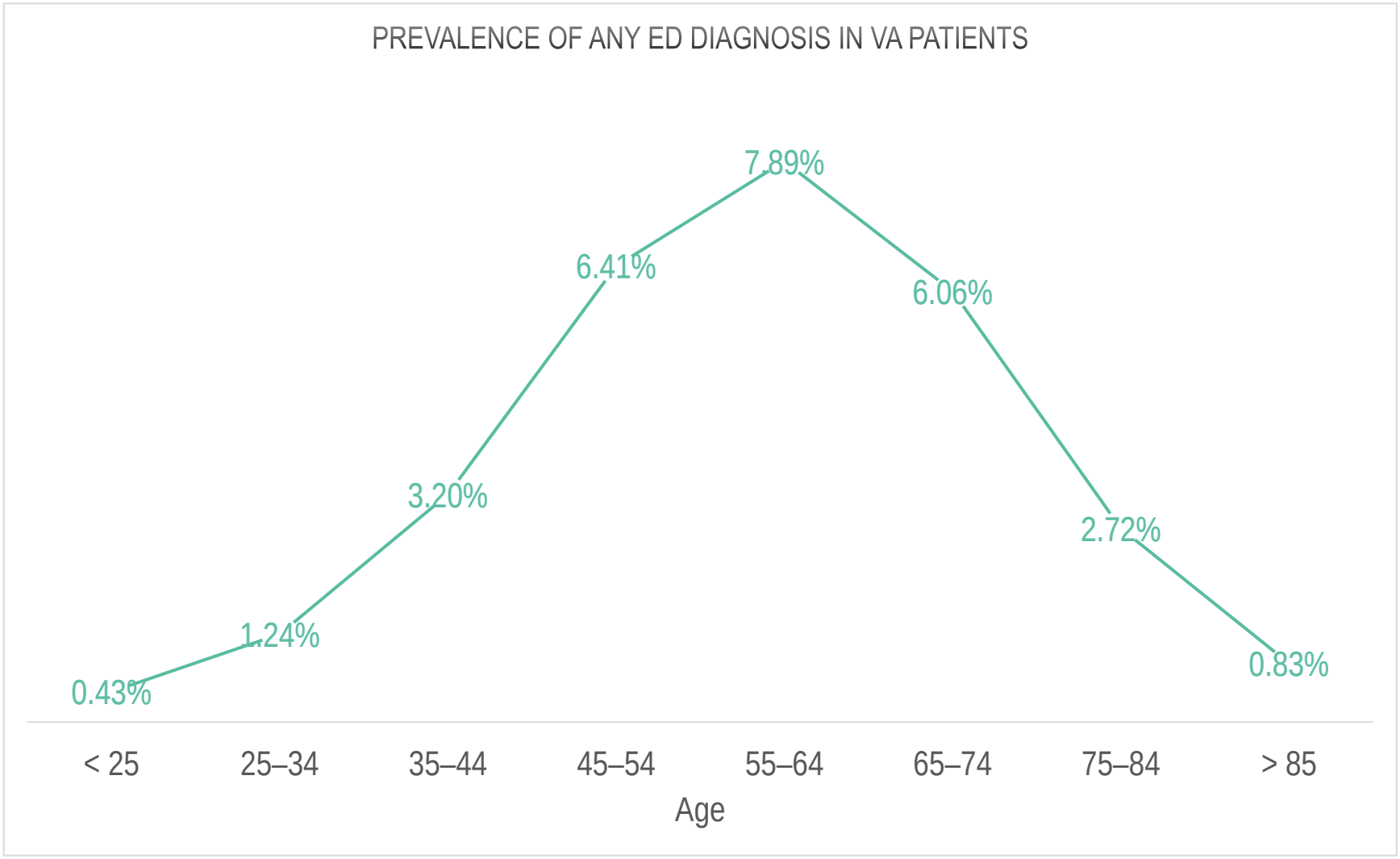
The Prevalence of Erectile Dysfunction Increases with Age



Adapted from Reference 2: Wessells *et al*. Journal of Urology 2007

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There are Different Types of ED and Risk Factors for ED

Category of Erectile Dysfunction	Common Disorders	Pathophysiology
Psychogenic	Performance anxiety Relationship problems Psychological stress Depression	Loss of libido, overinhibition, or impaired nitric oxide release
Neurogenic	Stroke or Alzheimer's disease Spinal cord injury Radical pelvic surgery Diabetic neuropathy Pelvic injury	Failure to initiate nerve impulse or interrupted neural transmission
Hormonal	Hypogonadism Hyperprolactinemia	Loss of libido and inadequate nitric oxide release
Vasculogenic (arterial or cavernosal)	Atherosclerosis Hypertension Diabetes mellitus Trauma Peyronie's disease	Inadequate arterial flow or impaired veno-occlusion
Drug-induced	Antihypertensive and antidepressant drugs Antiandrogens Alcohol abuse Cigarette smoking	Central suppression Decreased libido Alcoholic neuropathy Vascular insufficiency
Caused by other systemic diseases and aging	Old age Diabetes mellitus Chronic renal failure Coronary heart disease	Usually multifactorial, resulting in neural and vascular dysfunction

Reference 3: Lue. New England Journal of Medicine 2000

What Is the Study Setting?

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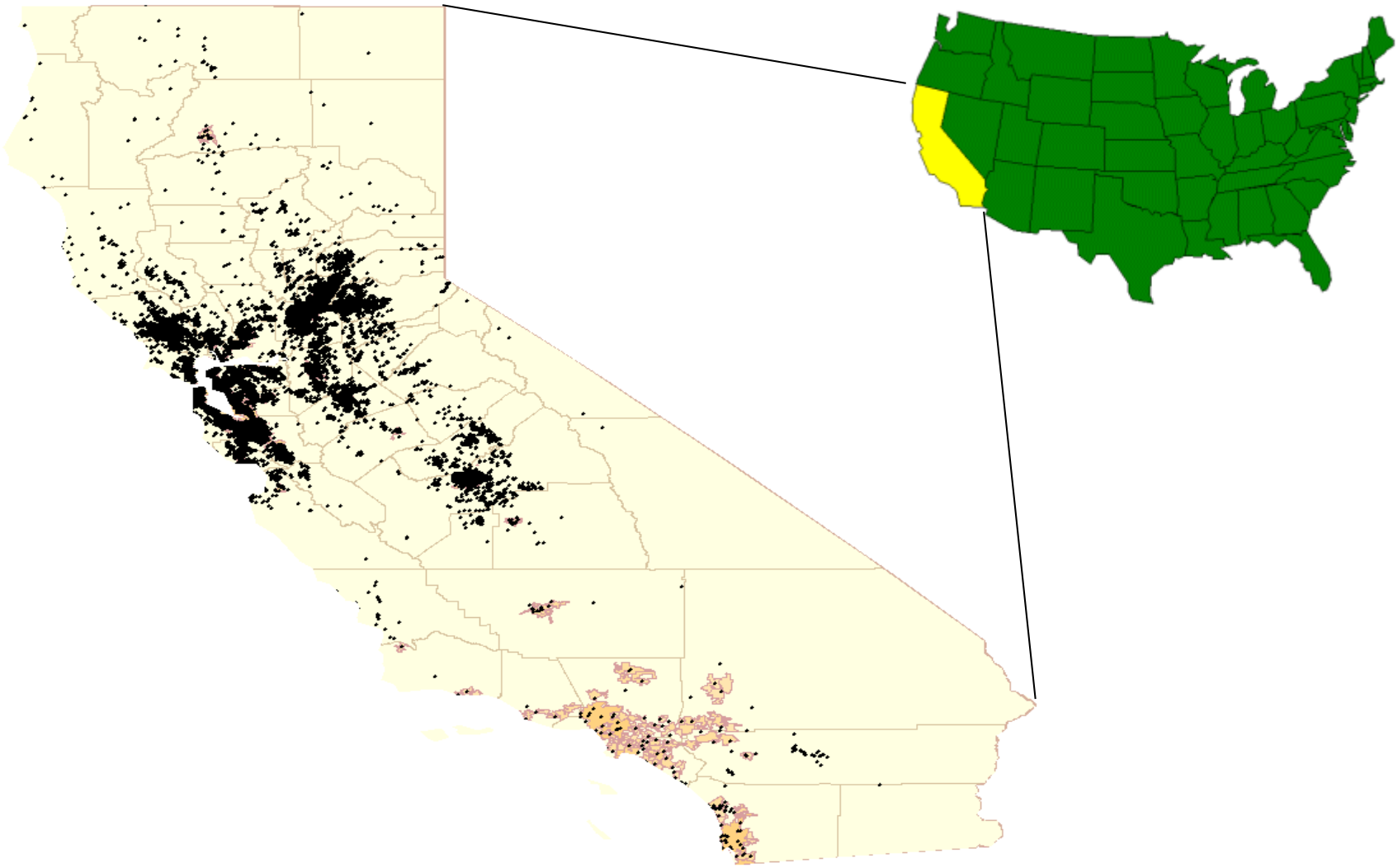
Kaiser Permanente Northern California Members



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GERA Cohort Characteristics

	Number of Subjects	%
Age at Specimen Donation		
18-39	7,025	6.3
40-59	33,344	30.2
60-79	57,856	52.4
80+	12,041	10.9
Sex		
Women	63,883	57.9
Men	46,383	42.1
Race/Ethnicity		
African American	3,765	3.4
Asian	8,512	7.7
Hispanic	7,917	7.2
Non-Hispanic White	89,259	81.0
Total	110,266	100.0

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How Are Cases and Controls Defined?

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Erectile Dysfunction: Self-report

The Independent

How Are Cases and Controls Defined?

36. Many men have difficulty getting and keeping an erection (or hard-on) that is rigid enough for satisfactory sexual activity. How would you describe your experience during the past year?

(Without the use of a medication like Viagra, Cialis, Levitra, injectable drugs or penis implant or pump device.)

- ○ Always able to get and keep an erection good enough for sexual activity
- ○ Usually able to get and keep an erection good enough for sexual activity
- ○ Sometimes able to get and keep an erection good enough for sexual activity
- ○ Never able to get and keep an erection good enough for sexual activity

How Are Cases and Controls Defined?

Characteristic		Always (n = 13,753)	Usually (n = 8,681)	Sometimes (n = 7,136)	Never (n = 7,079)	Total (n = 36,649)
Race/Ethnicity — no. (%)	Non-Hispanic white	11,090 (80.6)	6,905 (79.5)	5,704 (79.9)	6,160 (87.0)	29,859 (81.5)
	Hispanic/Latino	1,214 (8.8)	740 (8.5)	579 (8.1)	437 (6.2)	2,970 (8.1)
	East Asian	1,061 (7.7)	738 (8.5)	579 (8.1)	359 (5.1)	2,737 (7.5)
	African American	388 (2.8)	298 (3.4)	274 (3.8)	123 (1.7)	1,083 (3.0)
Age — yrs		54.1 ± 11.4	59.3 ± 10.7	64.9 ± 10.2	72.9 ± 9.8	61.1 ± 12.8

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How Was the Genetic Data Produced?

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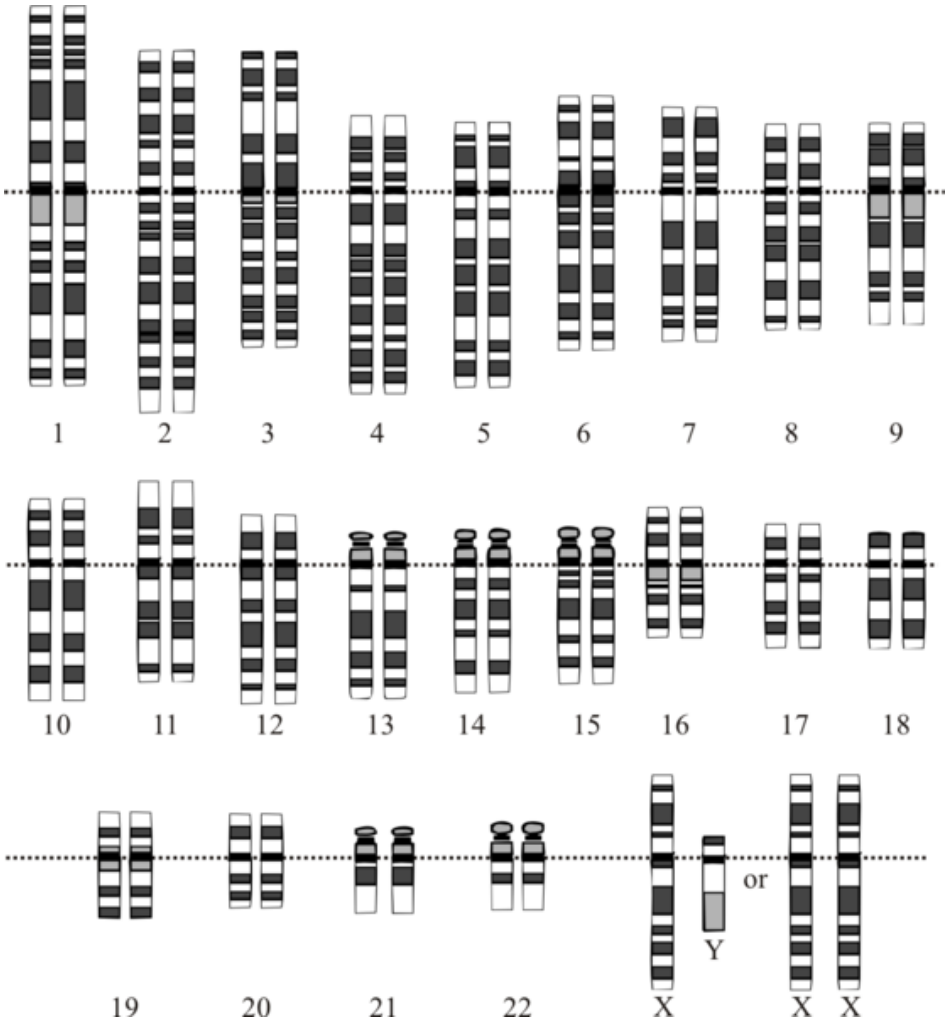
The Human Genome Is 3.2 Billion Basepairs Long



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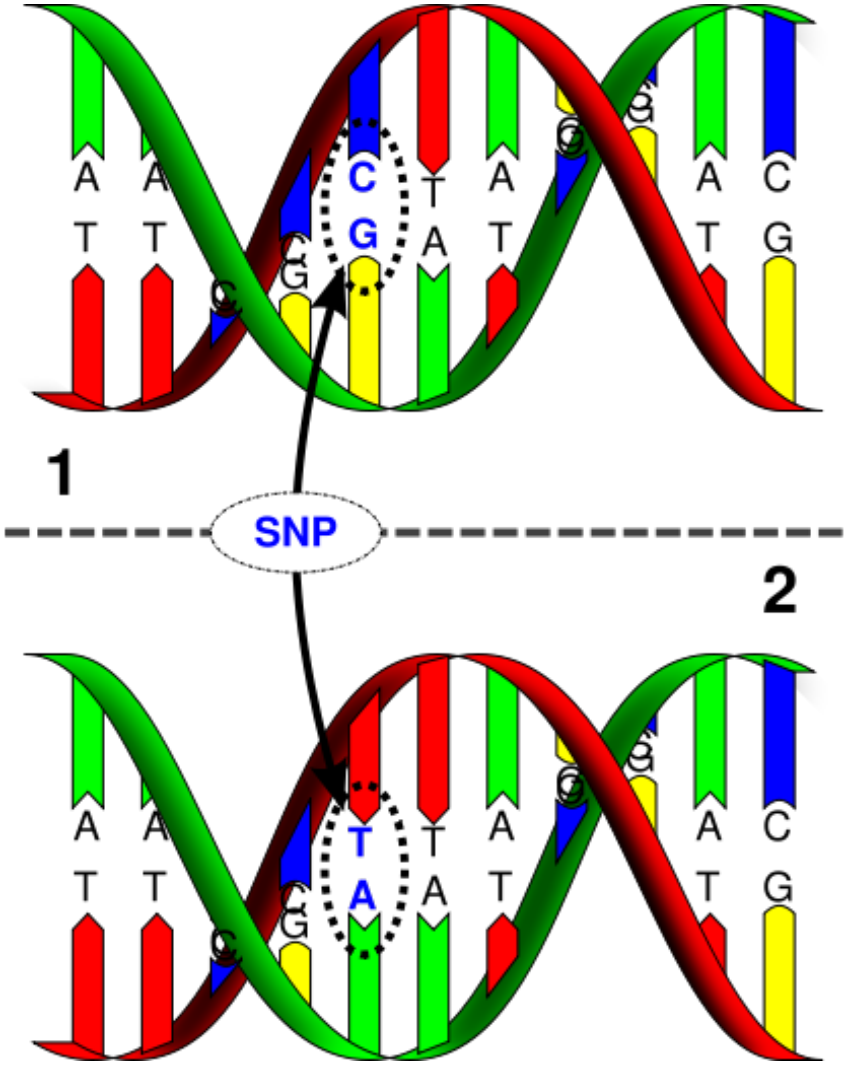
Single Nucleotide Polymorphism (SNP)



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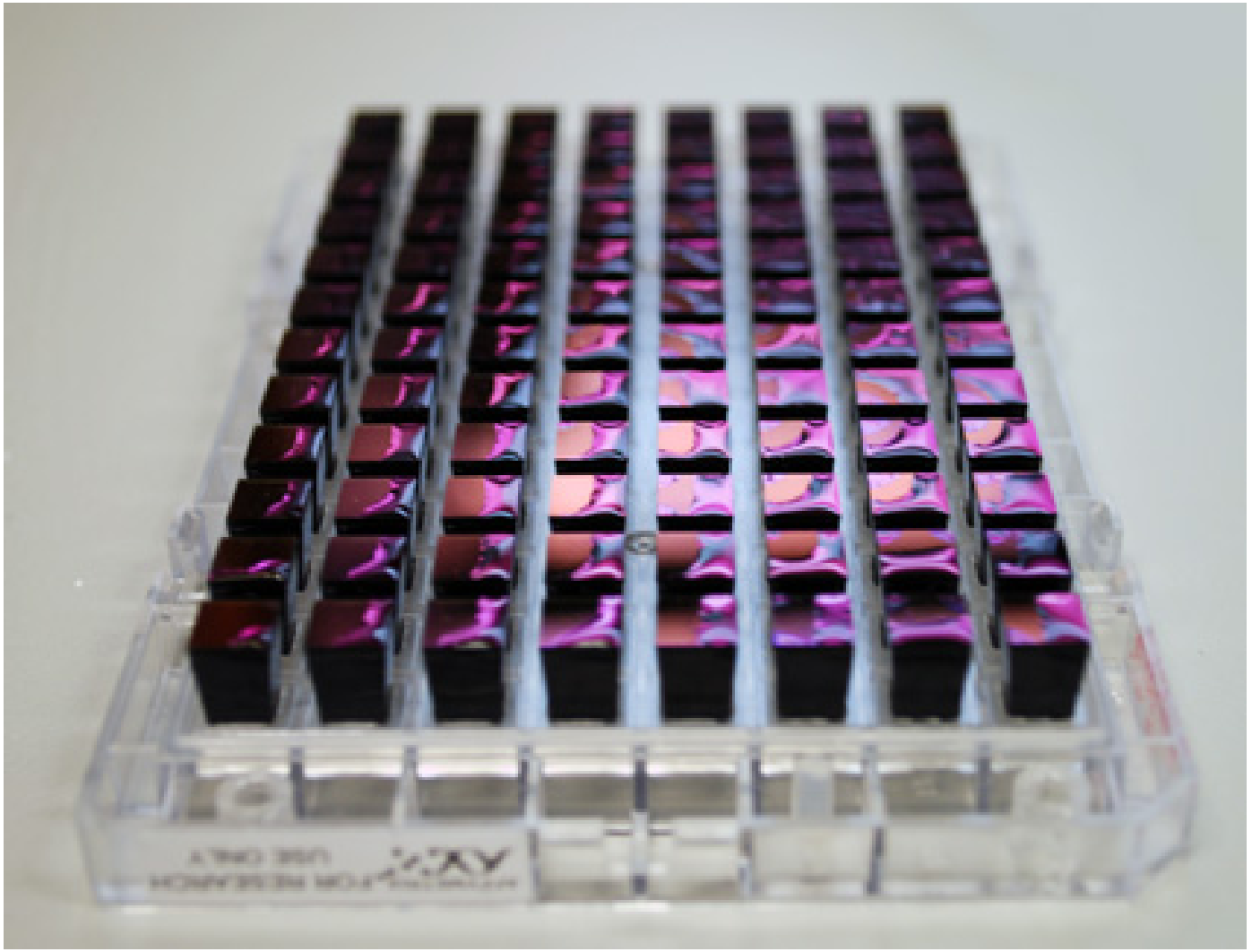
Genotyping Arrays Measure Millions of SNPs in Parallel



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Sample QC Workflow

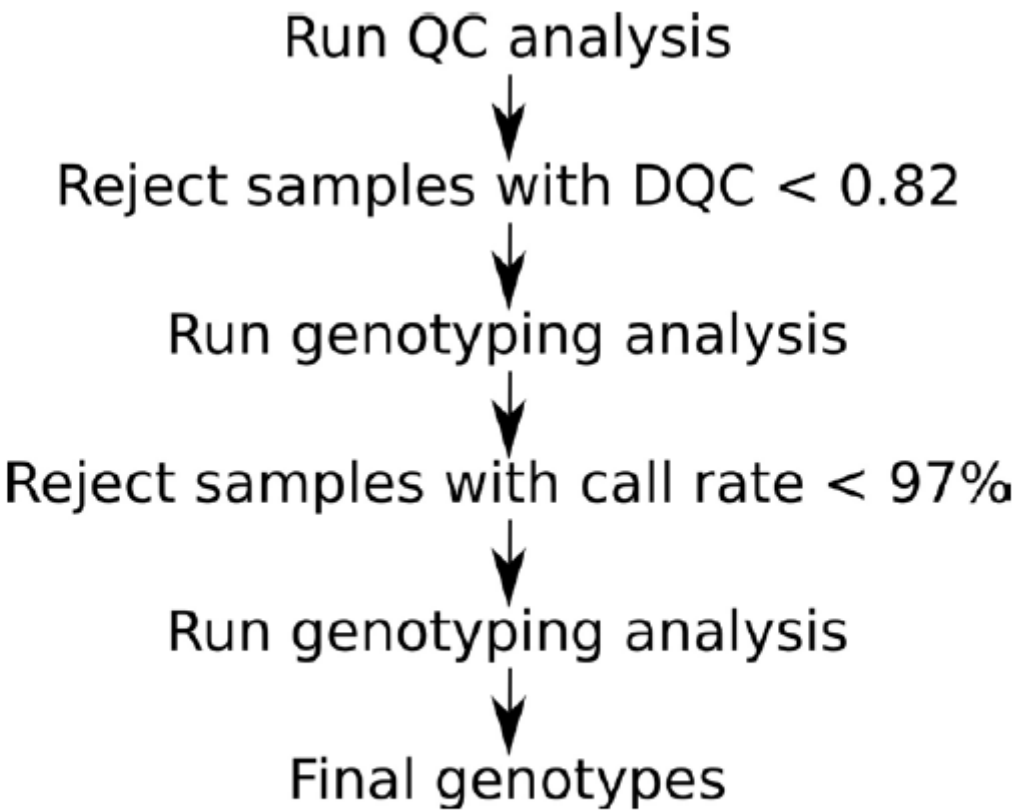

Figure 1 Standard Affymetrix Axiom Genotyping Analysis Workflow.

Reference 25: Kvale *et al*. Genetics 2015

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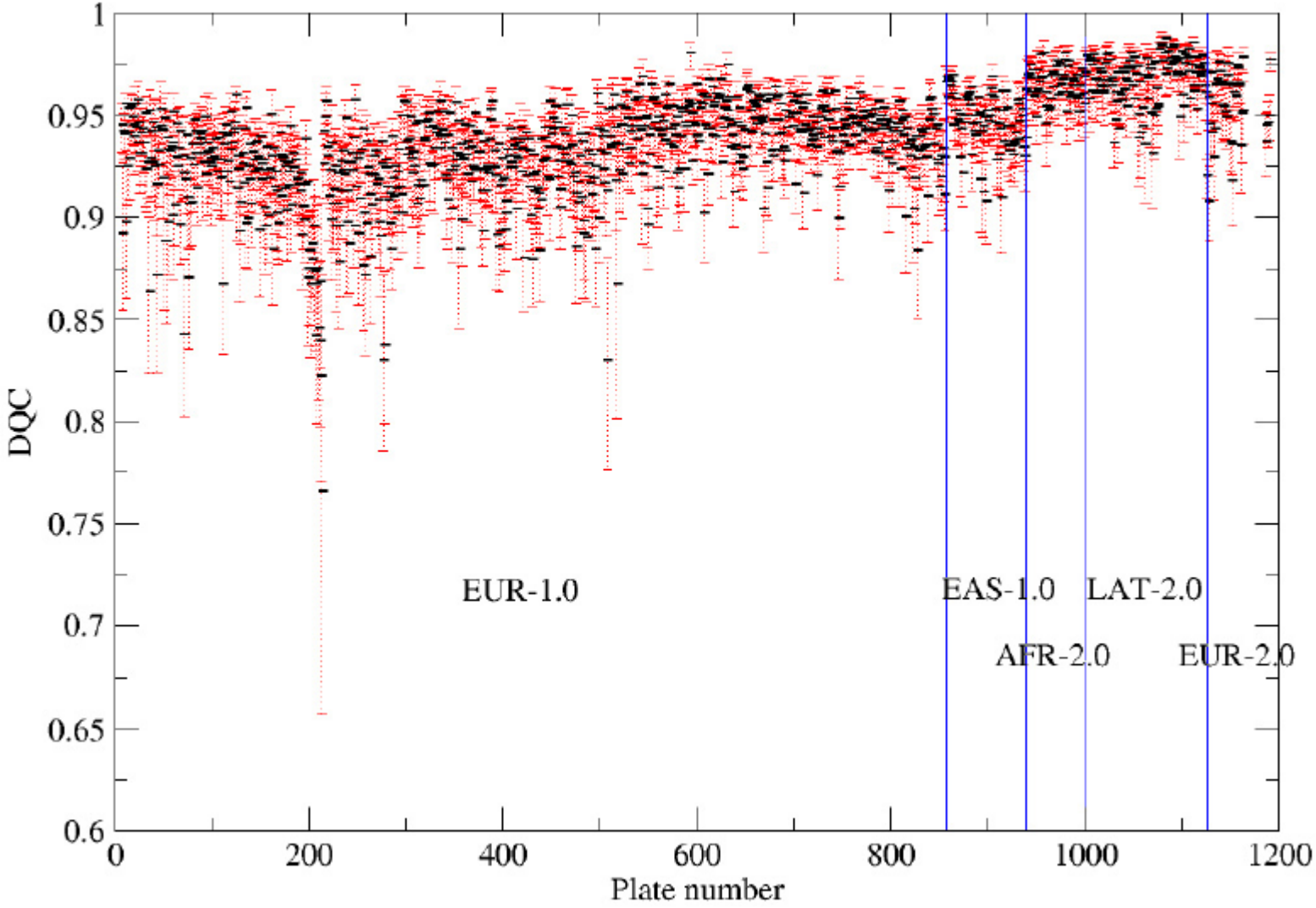
Genotyping Performance Was Tracked in Real Time



Reference 25: Kvale *et al*. Genetics 2015

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SNP Quality Control

Array	SNPs Assayed	Autosomal	X-linked	Y-Chrom	mtDNA	Passing QC	% of SNPs Passing
EUR	674,518	660,990	13,123	289	116	670,572	99.42%
EAS	712,950	699,324	13,385	158	83	708,373	99.36%
AFR	893,631	867,035	26,264	234	98	878,176	98.27%
LAT	817,810	792,056	25,397	234	123	802,186	98.09%

Reference 25: Kvale *et al*. Genetics 2015

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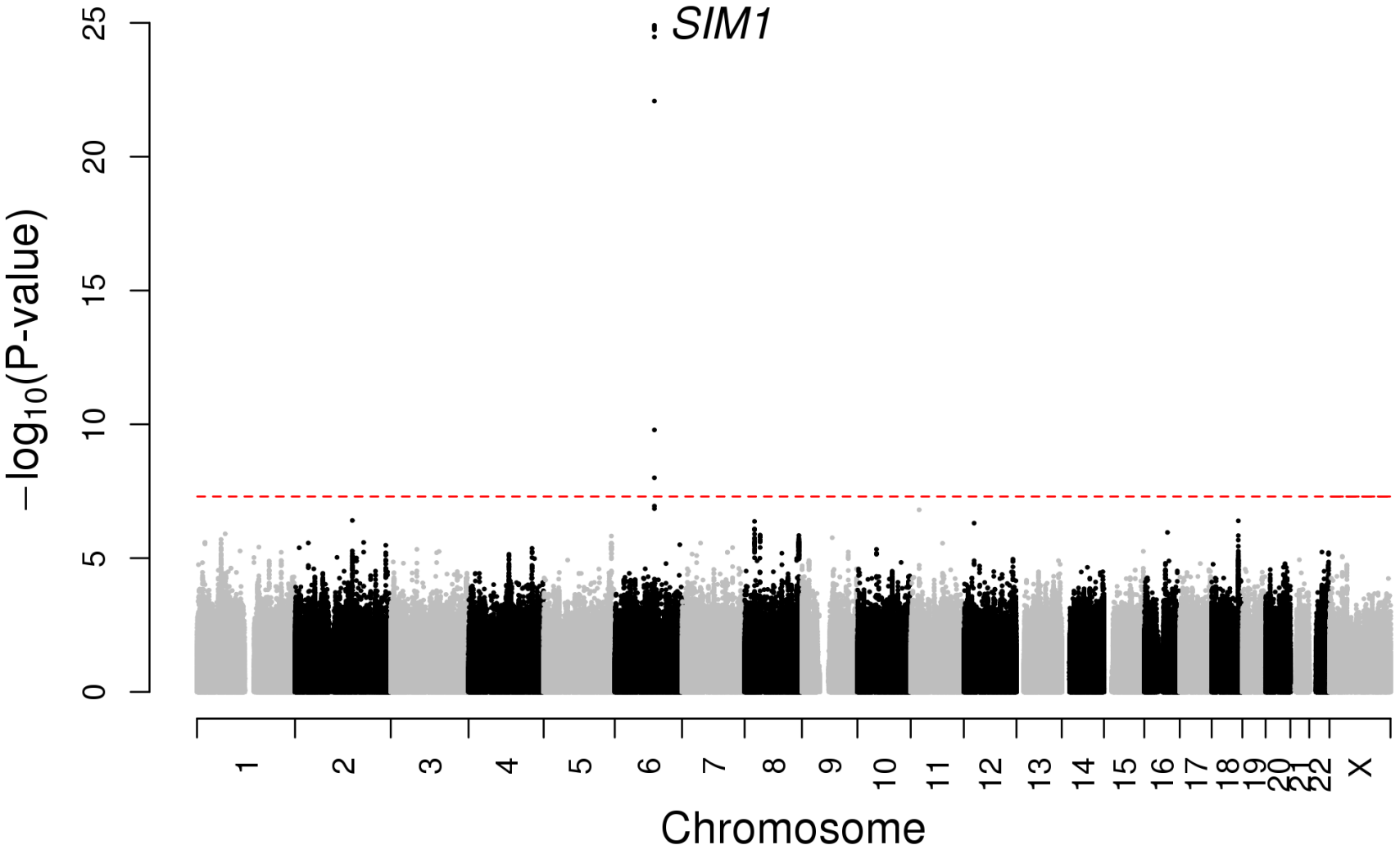
What Are the Main Association Findings?

Manhattan Plot of Erectile Dysfunction GWAS Results



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Are the Findings Affected by Phenotype Definition?

Erectile Dysfunction: Prescription Information

The Independent

The Irish Examiner

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Erectile Dysfunction: Artistic Interpretation

The Independent

The Irish Examiner

Inverse.com

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How Similar are the EHR and Prescription Definitions?

Table 1. Characteristics of GERA men

Characteristic	Control, $n = 22,434$	Case, $n = 14,215$	Total, $n = 36,649$
Race/ethnicity, no. participants (%)			
Non-Hispanic whites	17,995 (80.2)	11,864 (83.5)	29,859 (81.5)
Hispanic/Latinos	1,954 (8.7)	1,016 (7.1)	2,970 (8.1)
East Asian	1,799 (8.0)	938 (6.6)	2,737 (7.5)
African American	686 (3.1)	397 (2.8)	1,083 (3.0)
Age, y*	56.1 ± 11.4	68.9 ± 10.8	61.1 ± 12.8
BMI*	26.9 ± 4.3	27.7 ± 4.7	27.2 ± 4.5
Diabetes, no. participants (%)			
Yes	3,265 (14.6)	4,240 (29.8)	7,505 (20.5)
No	19,169 (85.4)	9,975 (70.2)	29,144 (79.5)
Smoking history, no. participants (%)†			
Never	12,586 (57.2)	5,545 (40.7)	18,131 (50.9)
Former	8,181 (37.2)	7,235 (53.1)	15,416 (43.3)
Current	1,220 (5.5)	841 (6.2)	2,061 (5.8)
EHR diagnosis, no. participants (%)			
Yes	5,237 (23.3)	5,591 (39.3)	10,828 (29.5)
No	17,197 (76.7)	8,624 (60.7)	25,821 (70.5)
PDE5i prescription, no. participants (%)			
Yes	6,513 (29.0)	8,422 (59.2)	14,935 (40.8)
No	15,921 (71.0)	5,793 (40.8)	21,714 (59.2)

Self-Report vs. Electronic Health Record (EHR)

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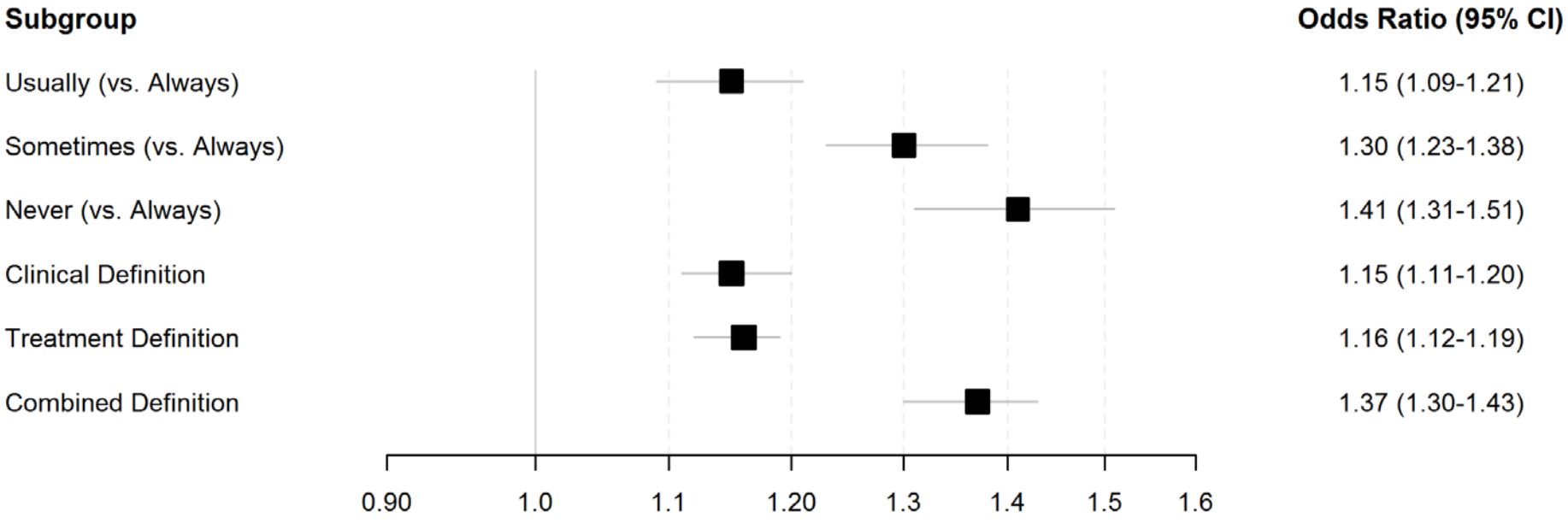
Sensitivity Analyses by Diagnostic Subgroup: rs17185536



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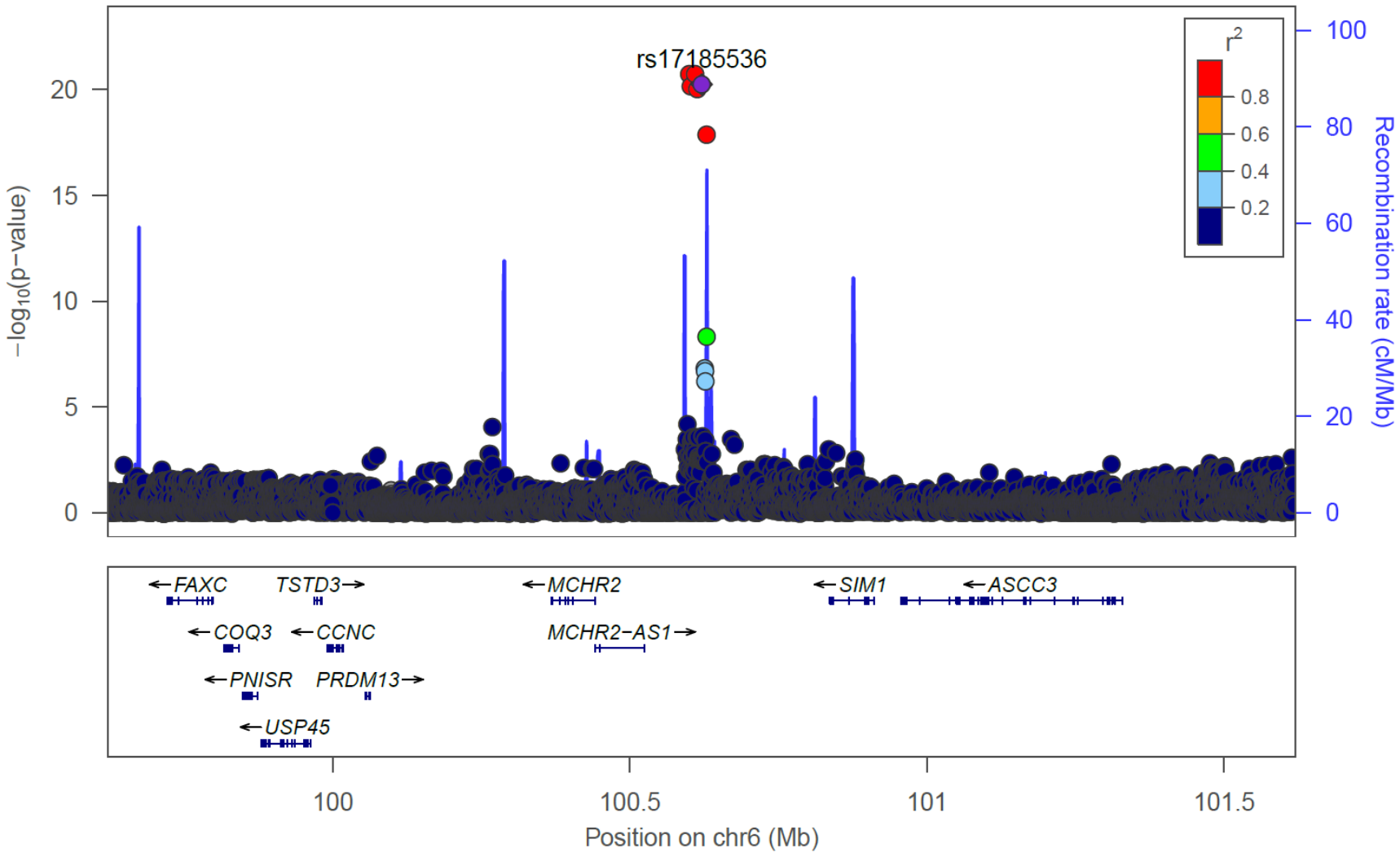
Multiple Associated SNPs in the *SIM1* Region



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95% Credible Set Identifies 5 SNPs in the *SIM1* Locus

Chromosome	Position	SNP	Posterior Inclusion Probability	Cumulative Inclusion Probability
6	100,610,044	rs78677597	0.298	0.298
6	100,600,097	rs17789218	0.296	0.595
6	100,620,931	rs17185536	0.151	0.745
6	100,602,753	rs9496567	0.137	0.882
6	100,613,551	rs9496614	0.112	0.995

CAVIAR: http://genetics.cs.ucla.edu/caviar/

U.K. Biobank Subject Characteristics

Case/Control Status	Race/Ethnicity	no. (%)	Age — yrs	Body Mass Index
Cases (n = 2,959)				
	European/White	2,783 (94.1)	61.2 ± 6.3	29.1 ± 4.6
	South Asian	70 (2.4)	59.3 ± 7.3	28.5 ± 5.0
	Mixed/other	36 (1.6)	58.2 ± 7.8	28.6 ± 4.4
	African British	68 (1.6)	58.8 ± 7.5	28.9 ± 3.9
	East Asian	2 (0.3)	61.0 ± 1.4	27.0 ± 5.1
Controls (n = 220,079)				
	European/White	206,975 (94.0)	57.4 ± 8.1	27.8 ± 4.2
	South Asian	5,234 (2.4)	53.8 ± 8.7	27.0 ± 3.9
	Mixed/other	3,626 (1.2)	54.3 ± 8.6	27.9 ± 4.3
	African British	3,566 (2.3)	52.0 ± 8.2	28.3 ± 4.3
	East Asian	678 (0.1)	52.3 ± 8.1	25.5 ± 3.2

Age and Body Mass Index are presented as means ± standard deviation.

https://biobank.ctsu.ox.ac.uk/showcase

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Replication of Credible Set SNPs

				GERA		UKB		Combined	
Chromosome	Position	SNP	Risk Allele	OR	p	OR	p	OR	p
6	100,600,097	rs17789218	C	1.26	$1.40*10^{-25}$	1.15	$5.64*10^{-13}$	1.25	$7.02*10^{-37}$
6	100,602,753	rs9496567	A	1.26	$1.60*10^{-25}$	1.14	$1.73*10^{-13}$	1.25	$2.31*10^{-37}$
6	100,610,044	rs78677597	C	1.27	$1.23*10^{-25}$	1.16	$4.21*10^{-13}$	1.25	$4.61*10^{-37}$
6	100,613,551	rs9496614	C	1.26	$1.81*10^{-25}$	1.14	$3.83*10^{-13}$	1.25	$6.00*10^{-37}$
6	100,620,931	rs17185536	T	1.26	$3.36*10^{-25}$	1.20	$6.78*10^{-14}$	1.25	$1.84*10^{-37}$

Imputation Quality Control

			GERA					UKB		
Chromosome	Position	SNP	Non-Hispanic white	East Asian	African American	Hispanic /Latino	White	South Asian	Mixed	African British
6	100,600,097	rs17789218	1.00	1.00	0.87	0.93	1.00	1.00	1.00	1.00
6	100,602,753	rs9496567	0.99	0.97	1.00	1.00	0.99	0.99	0.99	0.99
6	100,610,044	rs78677597	0.99	0.99	0.88	0.94	1.00	1.00	1.00	1.00
6	100,613,551	rs9496614	0.99	0.98	0.99	0.99	0.99	0.99	0.99	0.99
6	100,620,931	rs17185536	0.97	0.91	0.94	0.97	0.99	0.99	0.99	0.99

What is the Evidence That the Locus Is Functional?

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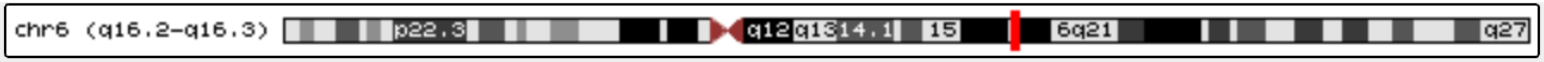
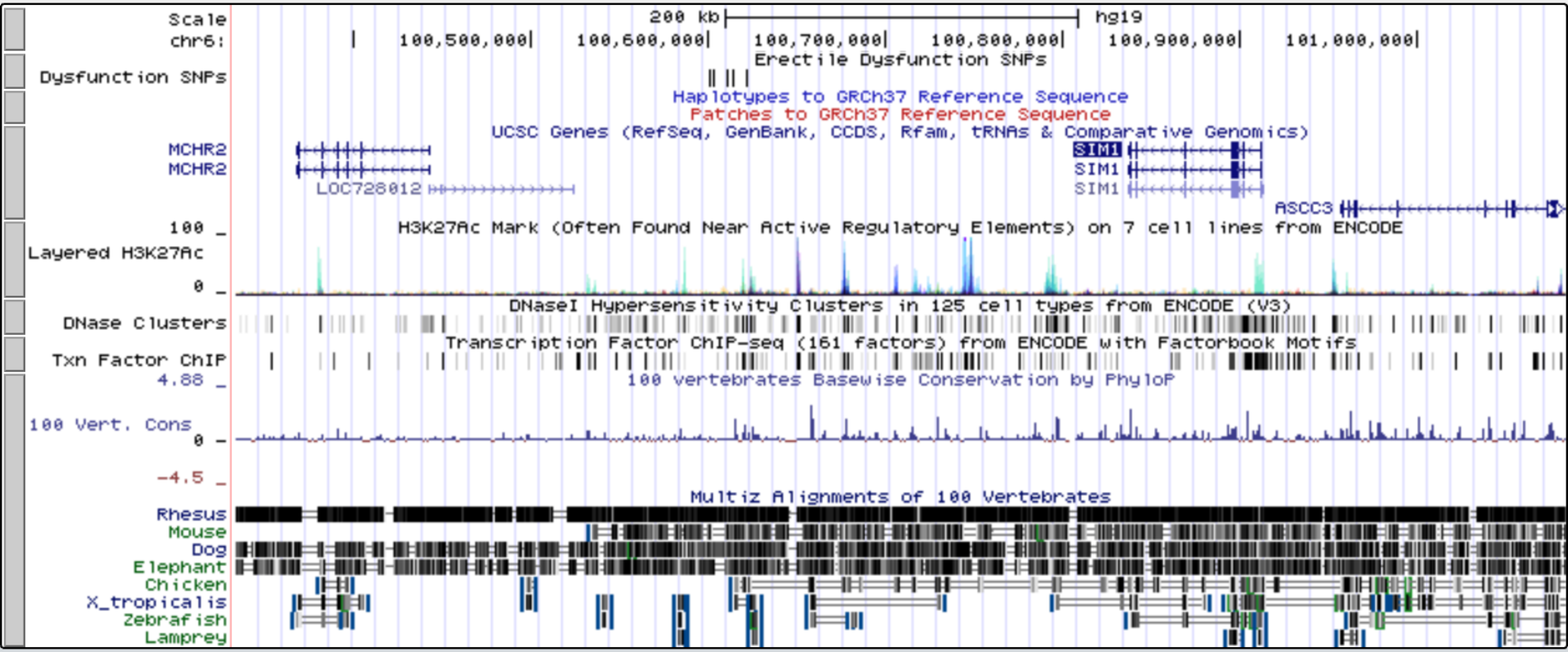
Genomic Context of Erectile Dysfunction Credible Set SNPs





https://genome.ucsc.edu/cgi-bin/hgGateway

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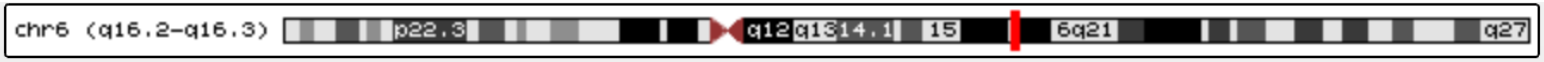
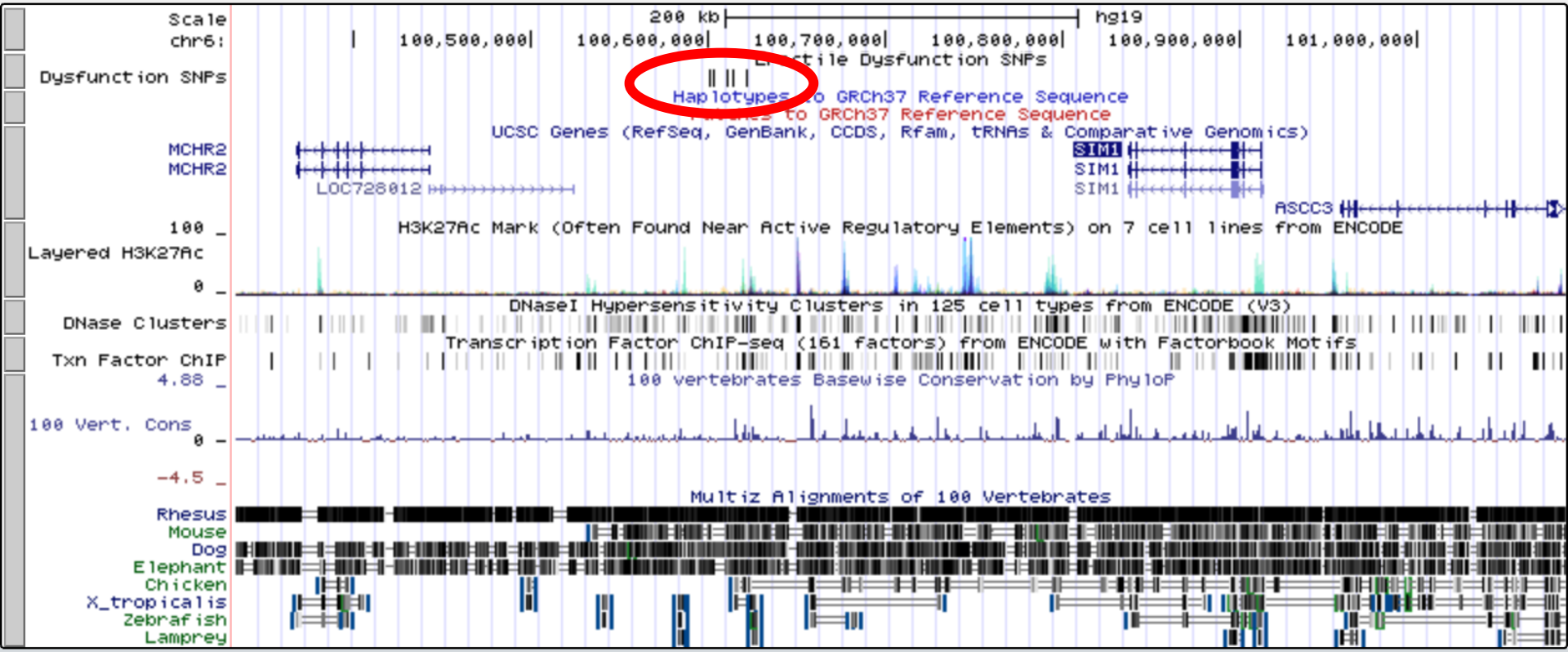
5 Credible Set SNPs





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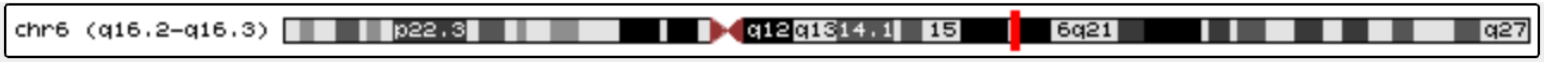
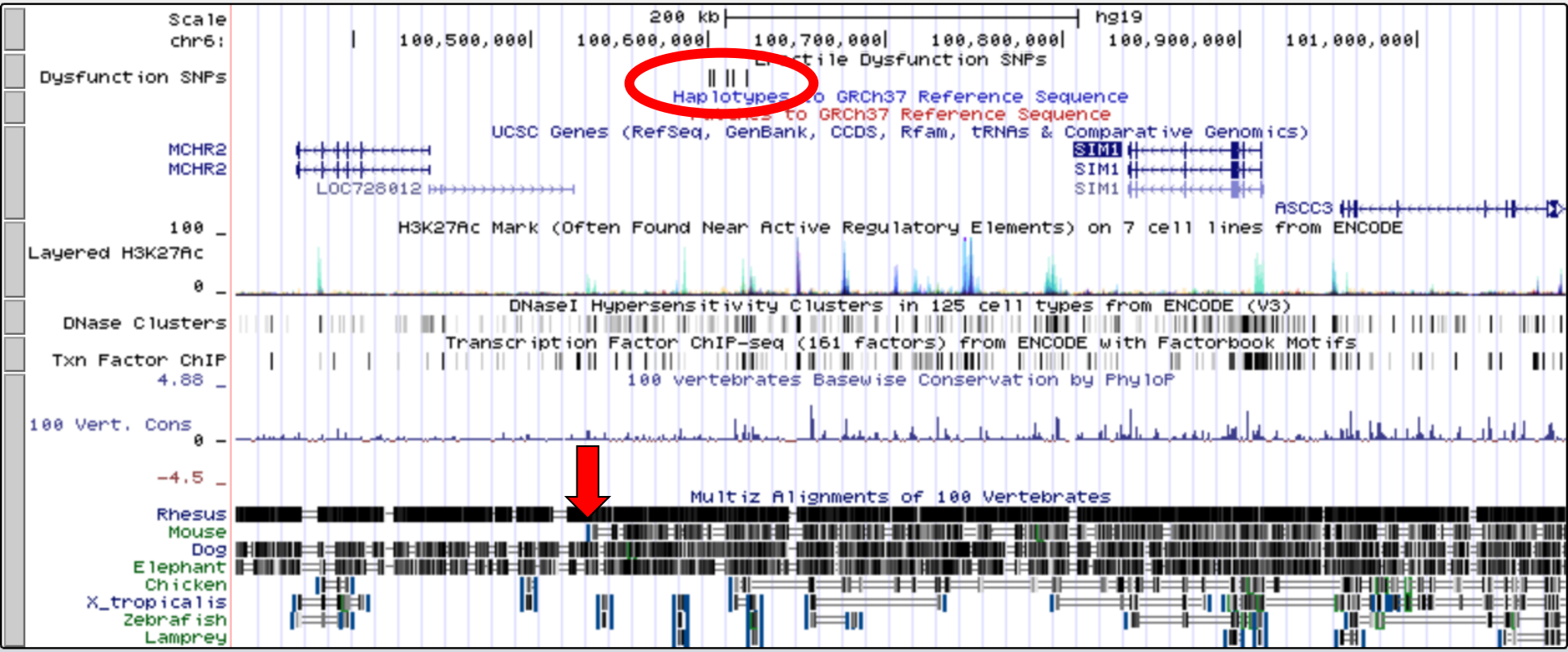
Human-Mouse Synteny Breakpoint





https://genome.ucsc.edu/cgi-bin/hgGateway

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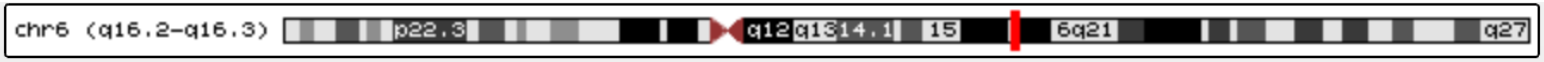
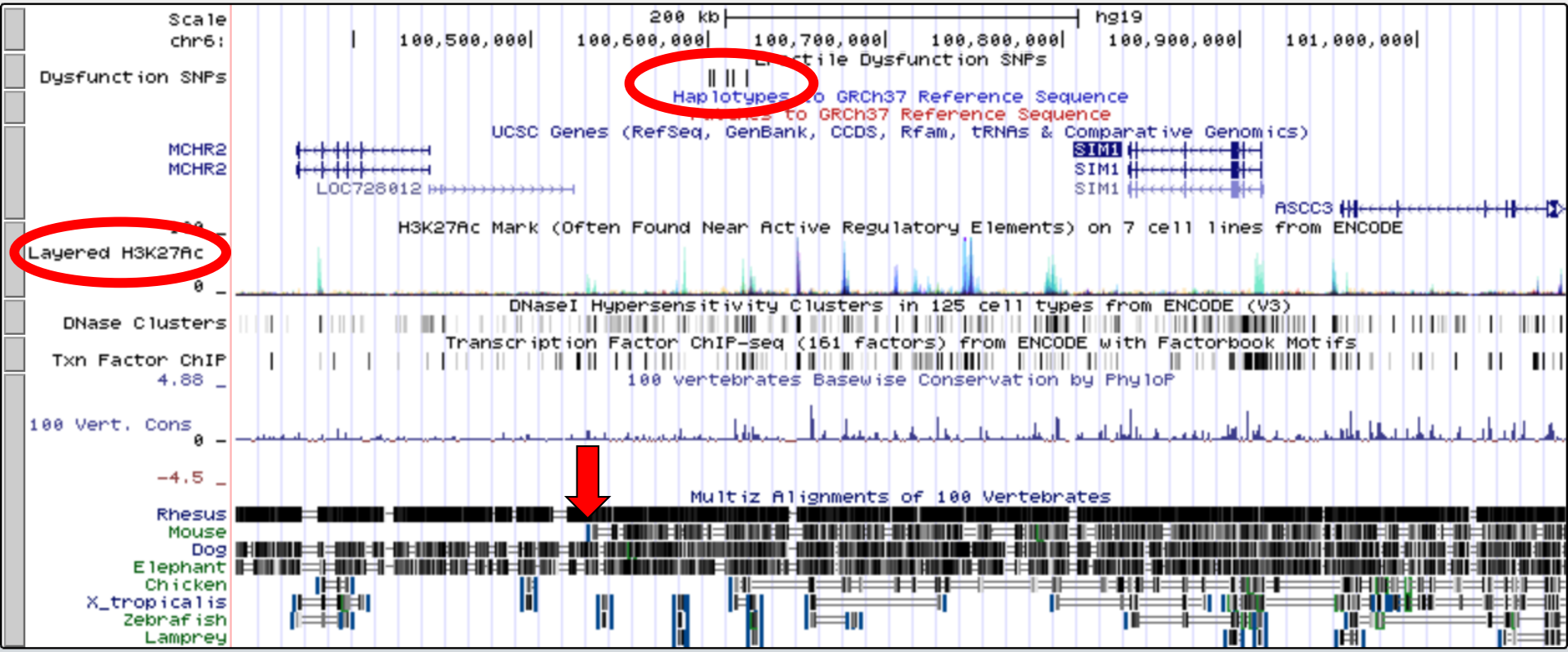
ENCODE Enhancer Markers





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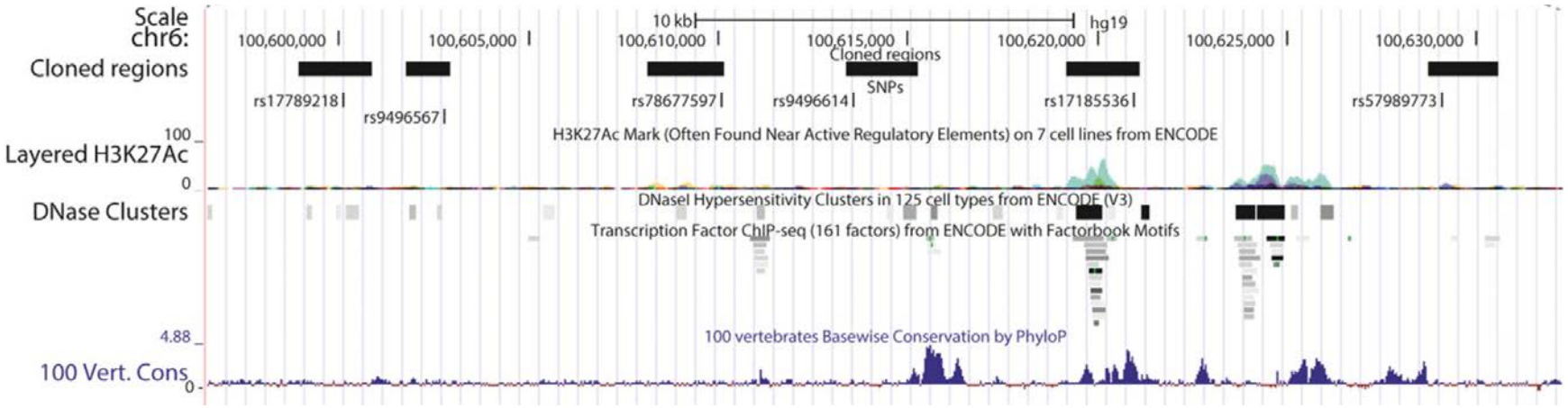
Are Erectile Dysfunction Credible Set SNPs in Enhancers?



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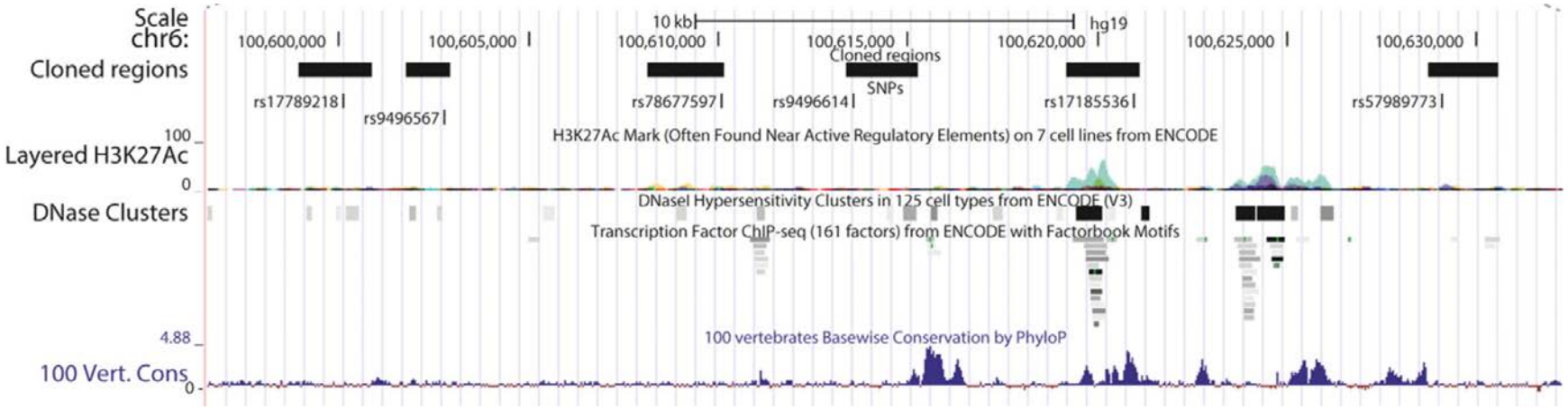
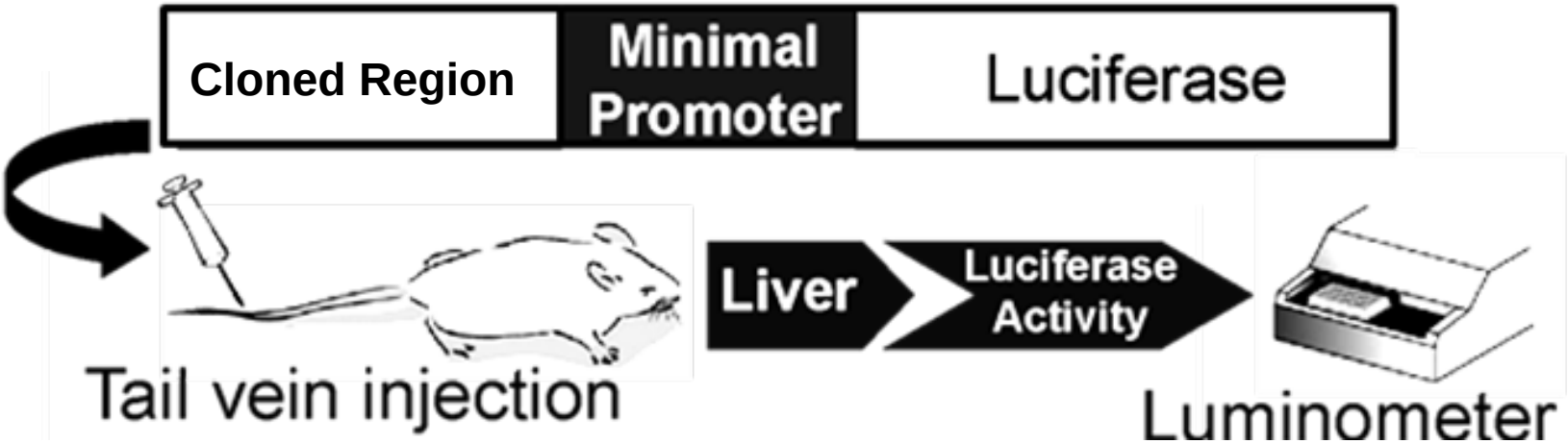
Luciferase Assays to look for Differential Enhancer Activity





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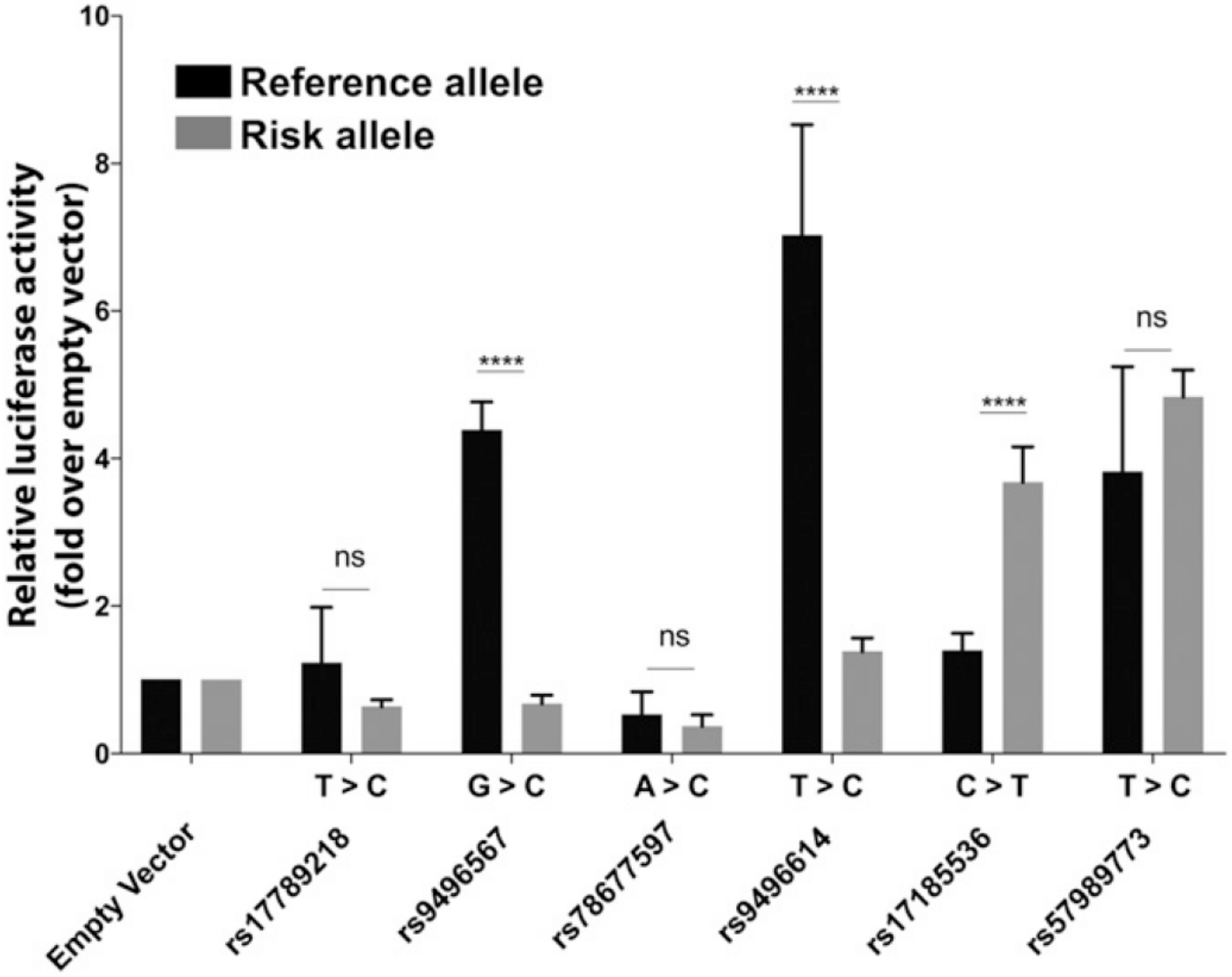
3 ED Risk SNPs Show Differential Enhancer Activity



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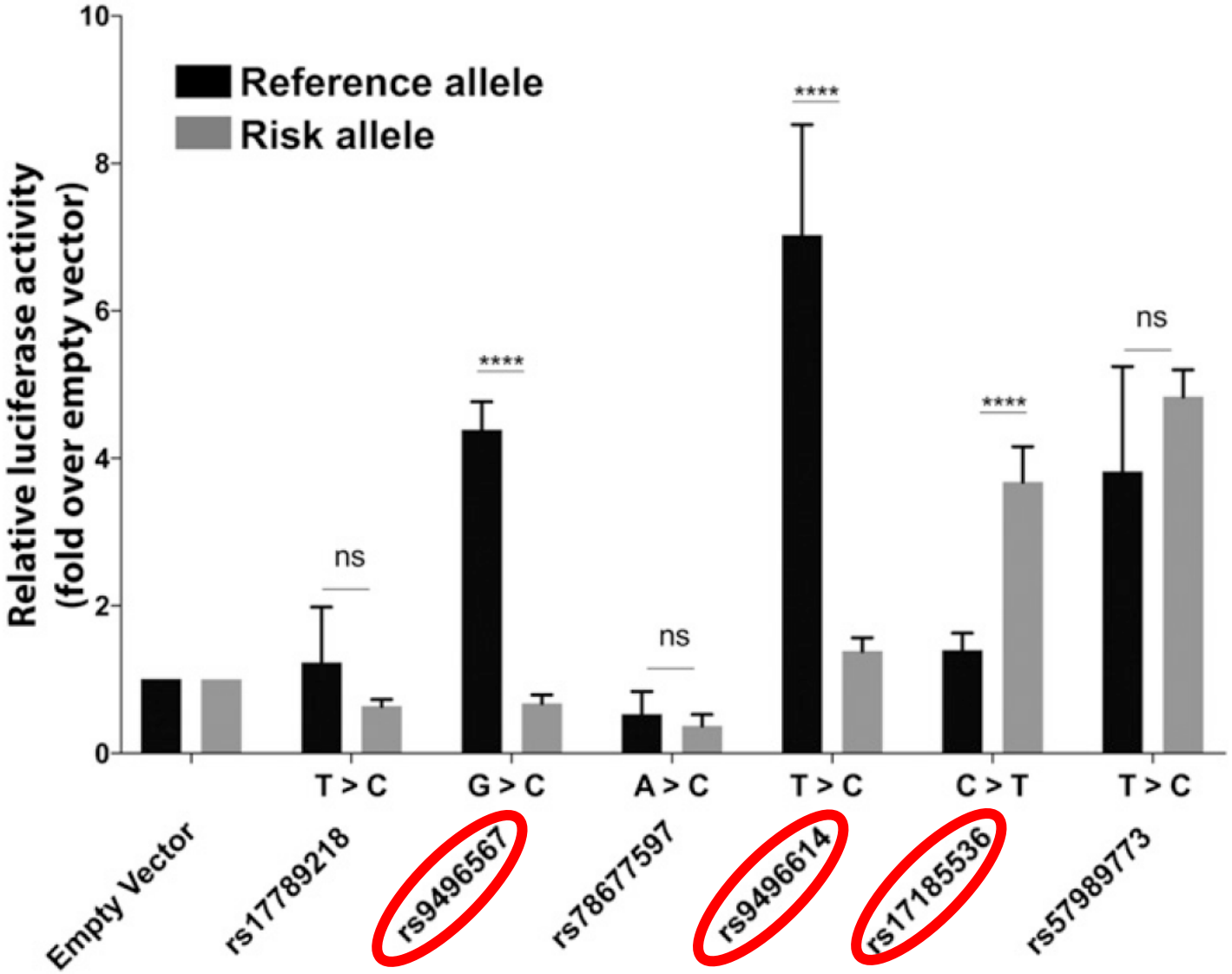

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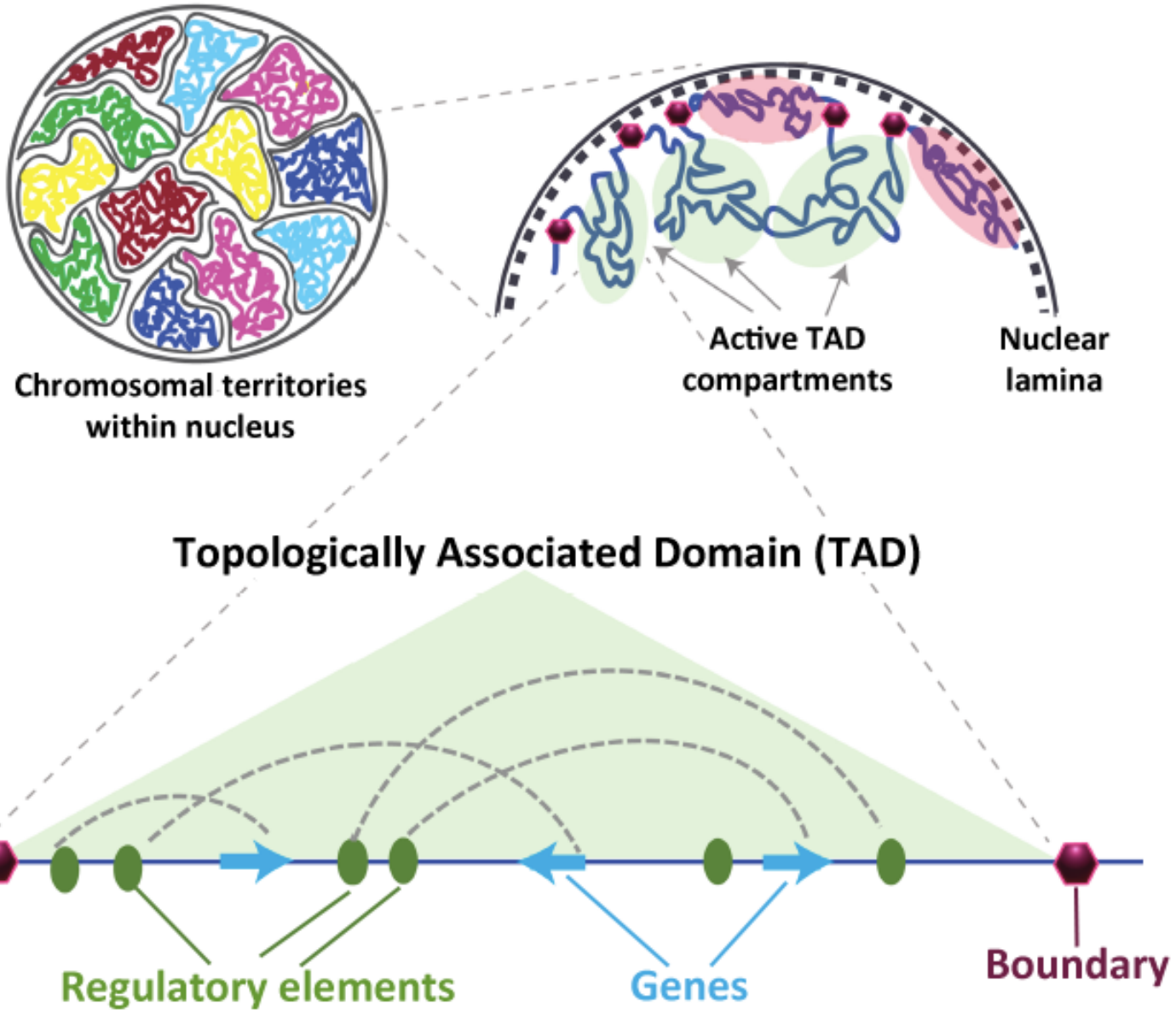
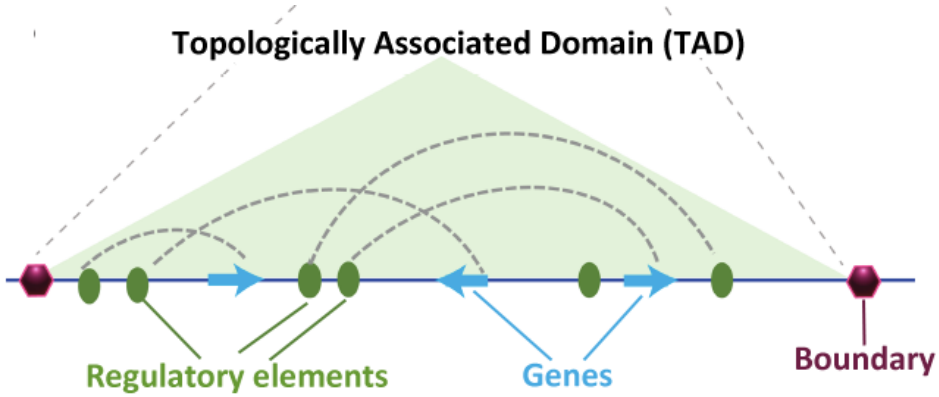
Can We Link the Putative Enhancers to a Specific Gene?

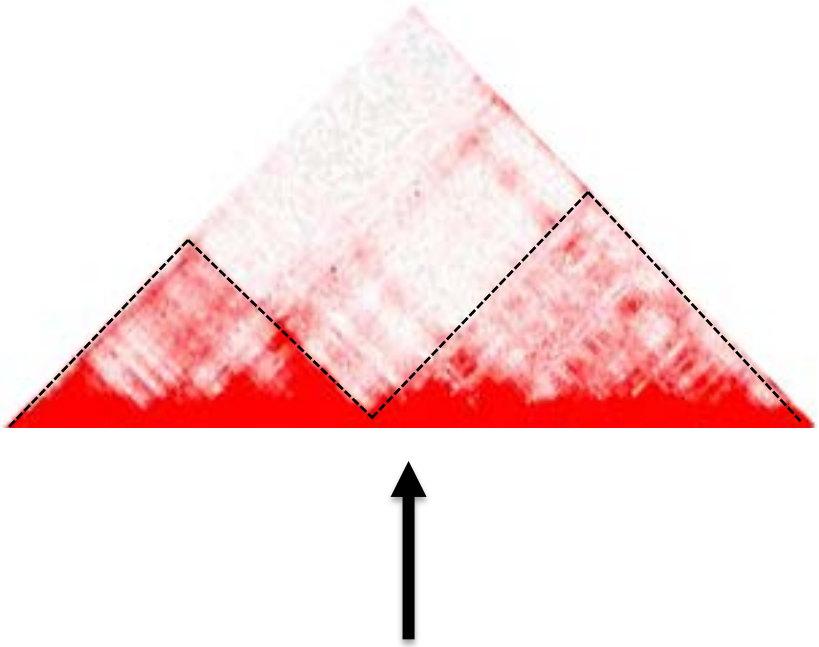
Chromosomes are Organized into Topologically Associating Domains (TADs)



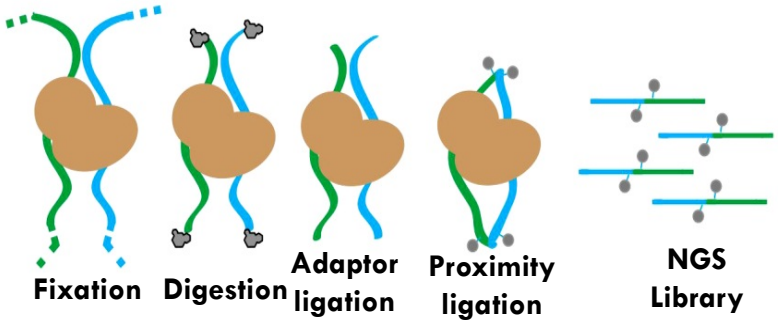
Matharu and Ahituv
PLoS Genetics 2015

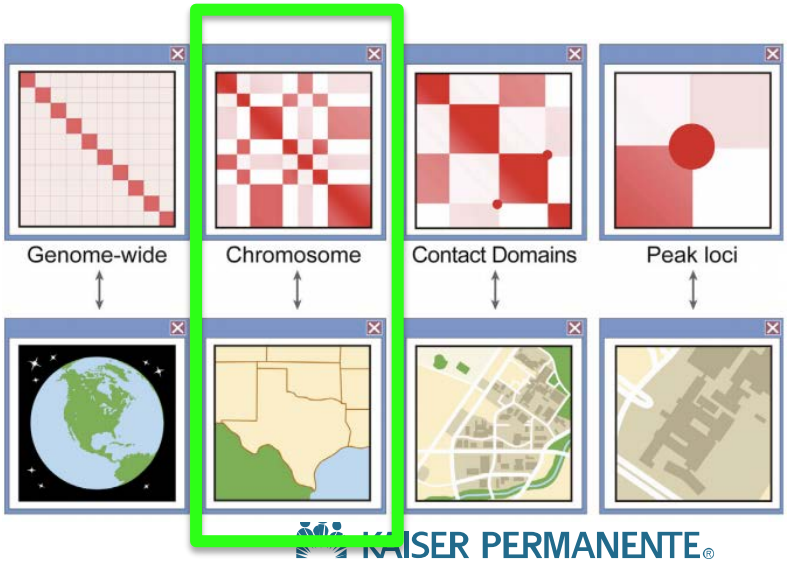
Hi-C contact map





Chromatin conformation capture (Hi-C)





Ramani *et al*. Nature Protocols 2016

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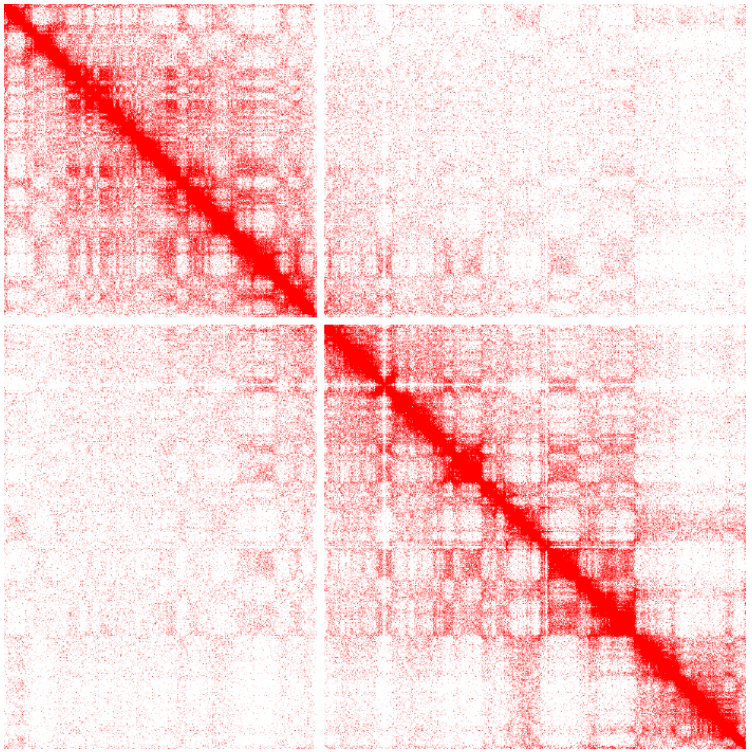
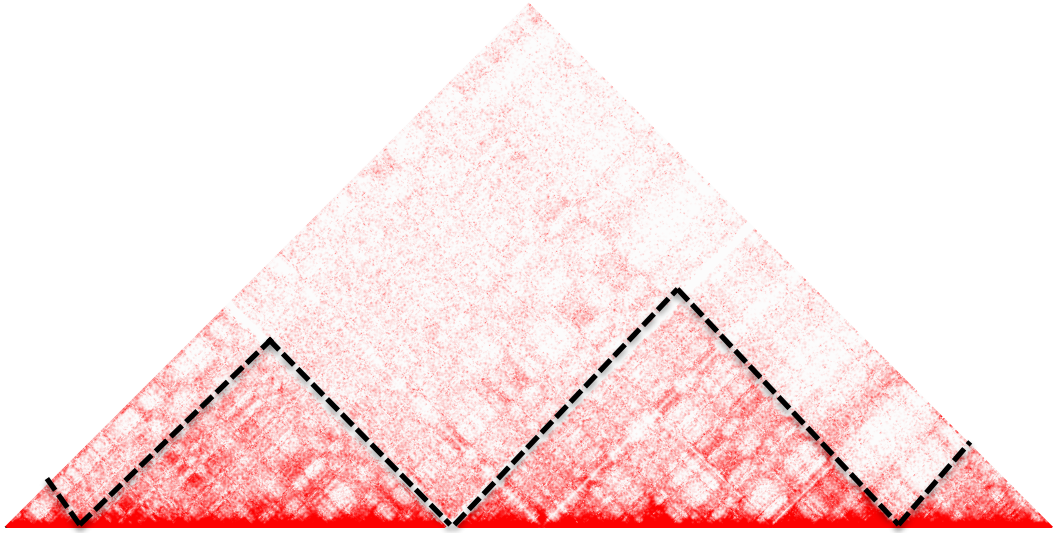
Chromosome Conformation Capture Example



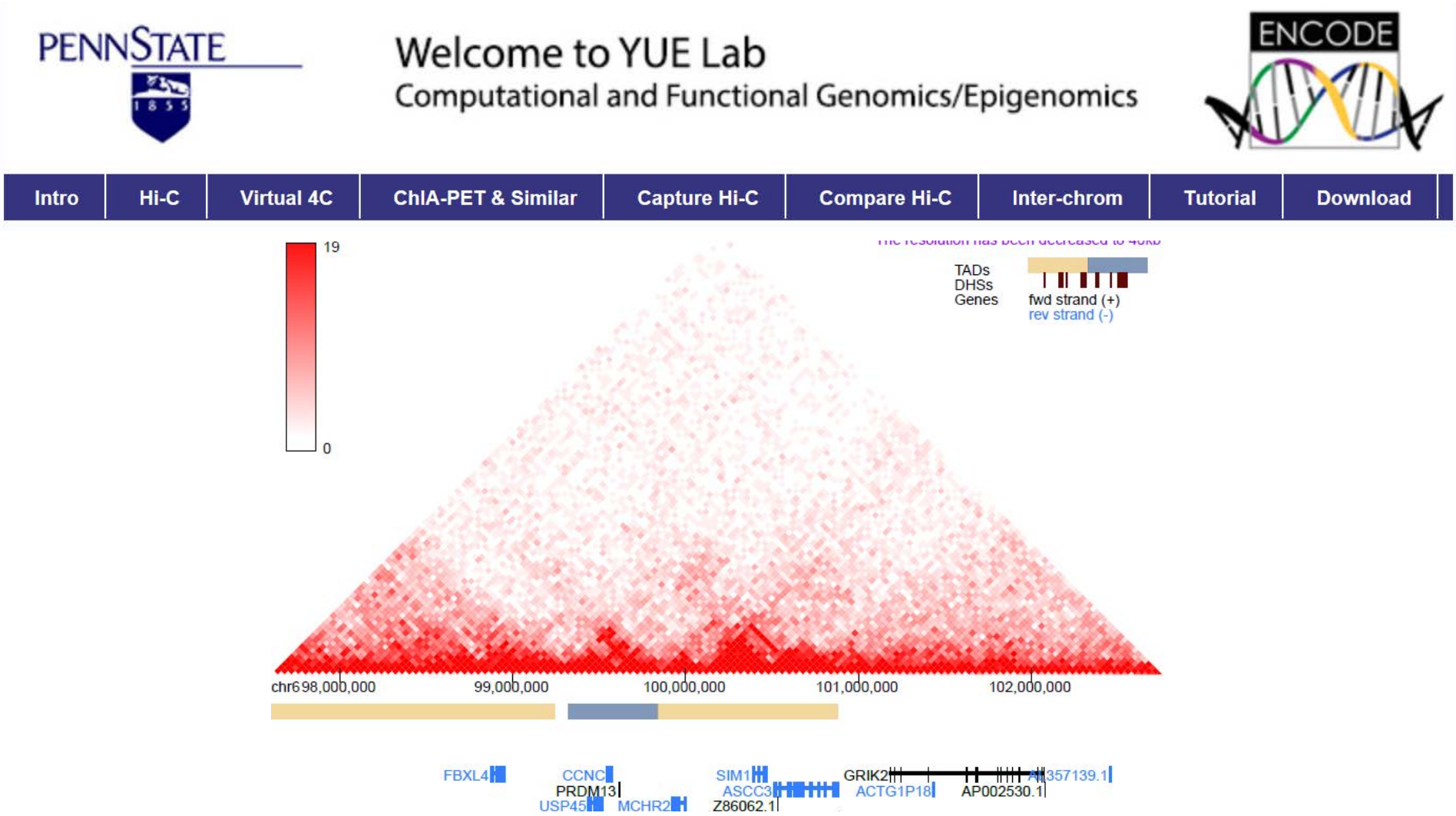
Modified from Lazar *et al*. Genome Research 2018

Chromosome Conformation Capture Example



Modified from Lazar *et al*. Genome Research 2018

TADs in the Region of Erectile Dysfunction Risk Locus



http://promoter.bx.psu.edu/hi-c/

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TADs in the Region of Erectile Dysfunction Risk Locus

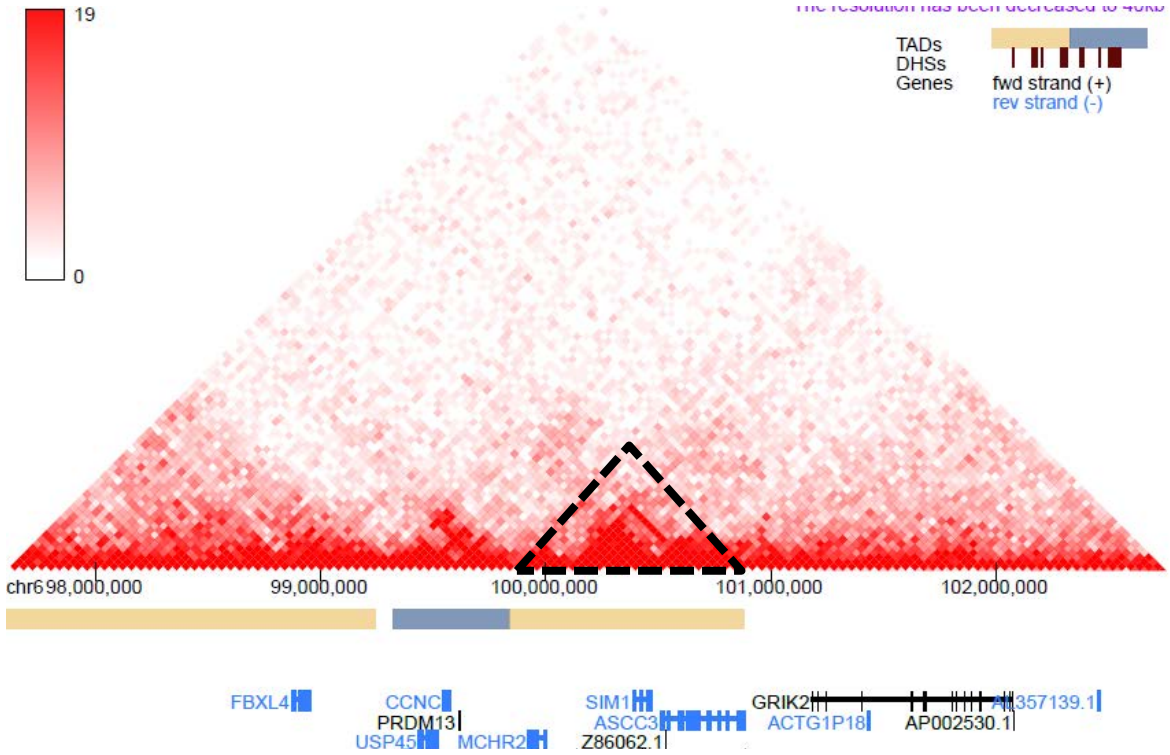
PENNSTATE

Welcome to YUE Lab

Computational and Functional Genomics/Epigenomics

ENCODE

Intro | Hi-C | Virtual 4C | ChIA-PET & Similar | Capture Hi-C | Compare Hi-C | Inter-chrom | Tutorial | Download



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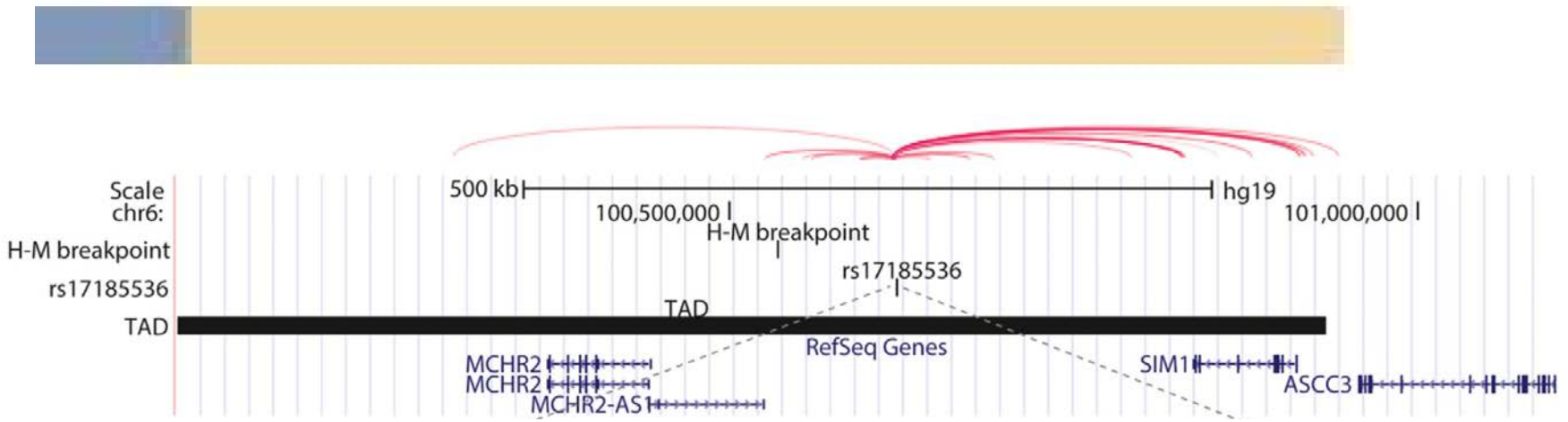
rs17185536 Interacts with the *SIM1* Promoter



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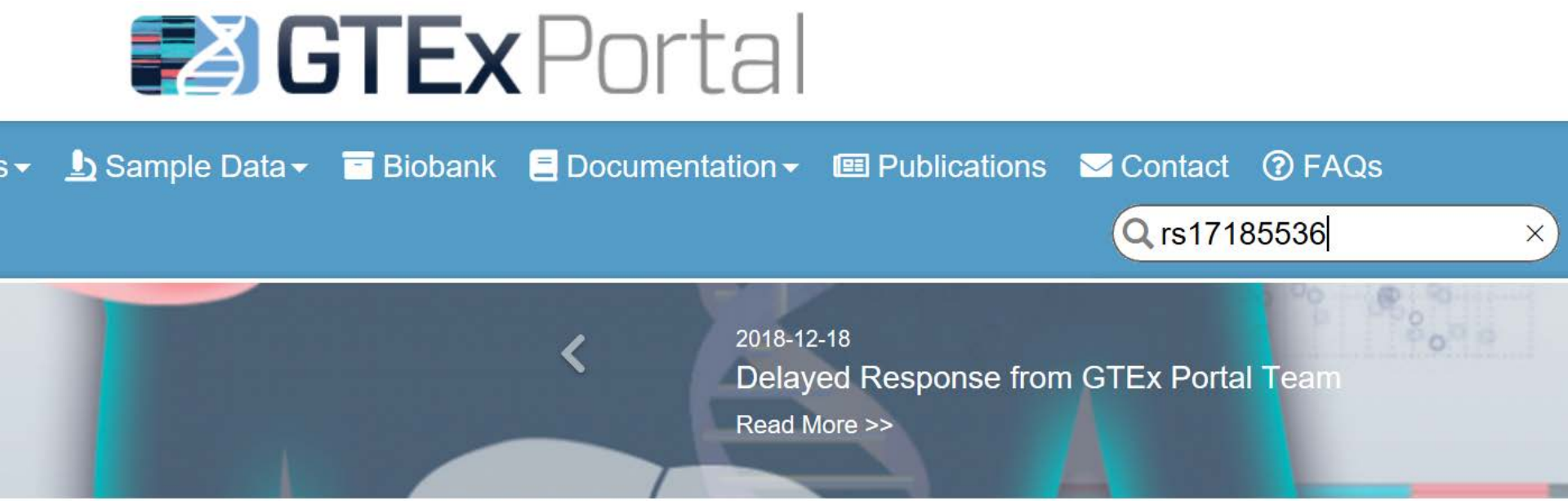
Do Credible Set SNPs Affect *SIM1* Gene Expression?



https://www.gtexportal.org/home

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The Associated SNPs are not in GTEx

No significant eQTLs were found for SNP 6_100620931_C_T_b37 in tissue All eQTL Tissues

https://www.gtexportal.org/home

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SIM1 is Part of the Leptin-Melanocortin Pathway

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Melanocortin Agonists Stimulate Sexual Function

Table 2. SEXUAL EXCITEMENT INDUCED IN MALE RABBITS BY ACTH AND MSH PEPTIDES

Peptide dose injected into the lateral ventricle of each animal		No. of animals treated	No. of animals displaying sexual excitement*
$\beta^{(1-24)}$ ACTH	10·0 μg	17	17
	5·0 μg	6	6
	2·5 μg	2	2
	1·5 μg	2	1
	1·0 μg	7	2
DW–75	10·0 μg	11	11
	5·0 μg	2	2
	2·5 μg	2	2
	1·5 μg	2	2
	1·0 μg	4	4
σ-MSH	5·0 μg	3	3

* Three or more penile erections in 3 h.

Reference 15: Bertolini *et al*. Nature 1969

Melanocortin Agonists Stimulate Sexual Function

TABLE 1. Behavioral responses of ovariectomized, estrogen-primed rats receiving various hormone and control treatments

Treatment	No. tests	% animals showing lordosis	% tests with lordosis	Latency to lordosis on last test (hr)	% animals with heat lasting more than 10 hr
1.0 mg protesterone	21	100	76.2	4.5	57.1
0.1 mg ACTH preparation	21	85.7	71.4	4.4	57.1
10 IU chorionic gonadotropin	18	0	0	—	—
12 μg EB	9	0	0	—	—
0.2 ml ethyl oleate	18	0	0.	—	—

Reference 16: Feder and Ruf. Endocrinology 1969

Melanocortin Agonists Stimulate Sexual Function

TABLE II. ***Real-time RigiScan activity after Melanotan II and placebo (mean values)***

RigiScan Parameter	Melanotan II*	Placebo	*P* Value
Events (n)	2.66	0.7	0.0010
Total erectile duration (min)	97.5	25.3	0.0180
Tip rigidity 80%–100% (min)	45.3	1.9	0.0470
Tip rigidity 60%–79% (min)	10.1	1.1	0.0140
Average tip rigidity (%)	46.8	6.5	0.0001
Erectile latency (min)	97.8	NA	—
Tip rigidity activity units	58.6	4.54	0.0210
Tip tumescence activity units	29.1	6.0	0.0100

Reference 17: Wessells *et al*. Urology 2000

Melanocortin Agonists Stimulate Sexual Function

TABLE III. ***Effect of Melanotan II on sexual desire***

Sexual Desire*	Melanotan (n = 19)	Placebo (n = 21)
Very low or none at all	6	17
Low	3	3
Moderate	5	1
High	5	0
Very high	0	0

Reference 17: Wessells *et al*. Urology 2000

Melanocortin Agonists Stimulate Sexual Function

TABLE IV. ***Clinically important side effects of Melanotan II and placebo***

Side Effect	Melanotan II (n = 19)	Placebo (n = 21)
Nausea*		
None	11	19
Mild	3	2
Moderate	1†	0
Severe	4‡	0
Stretch/yawn§		
None	11	21
Mild	3	0
Moderate	2	0
Severe	3	0

Reference 17: Wessells *et al*. Urology 2000

Cells Expressing *SIM1* and *MC4R* May be Important

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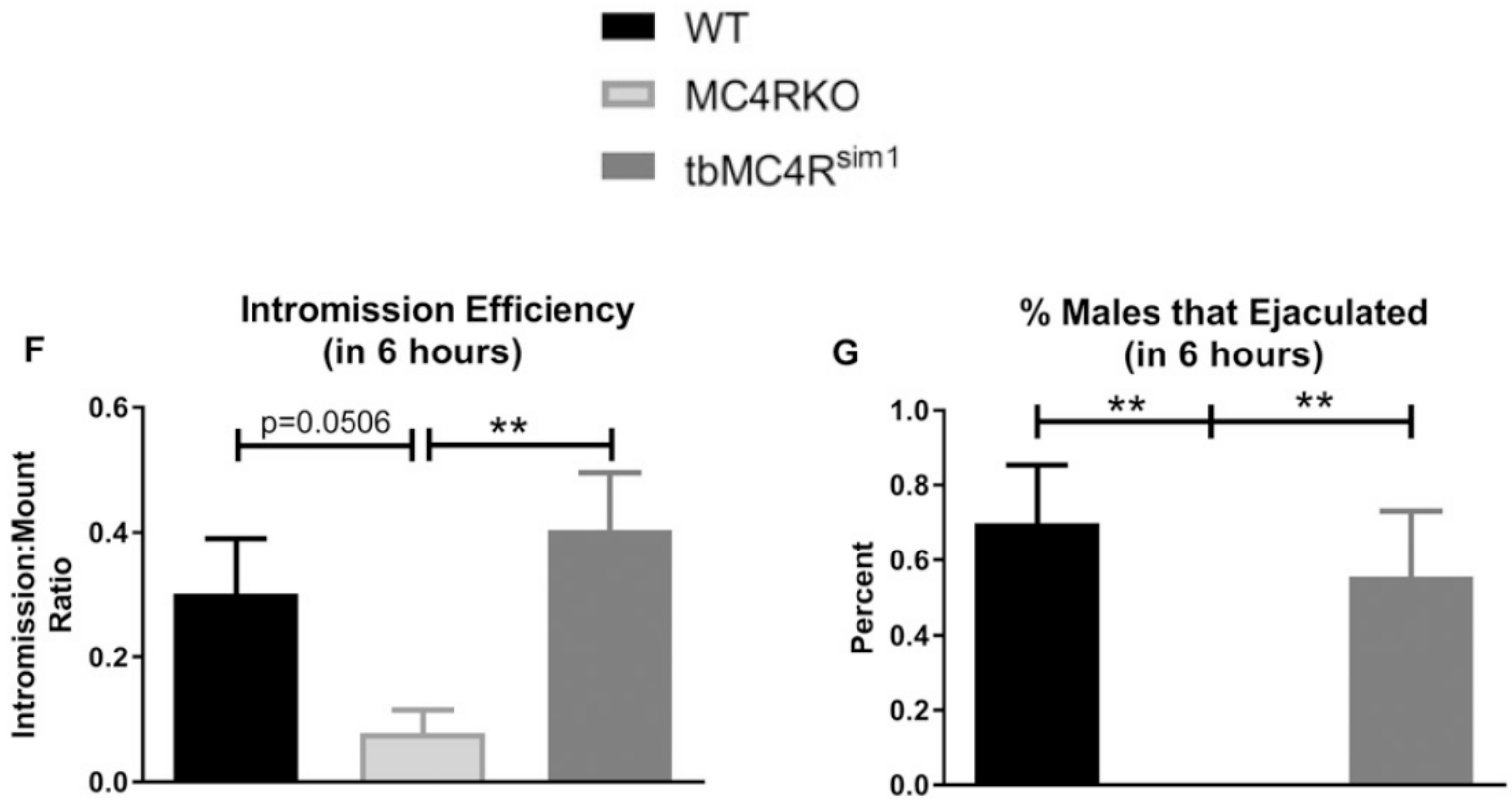
Expression of *MC4R* on *SIM1*$^{+}$ Cells Restores Sexual Function



Reference 19: Semple and Hill. Endocrinology 2018

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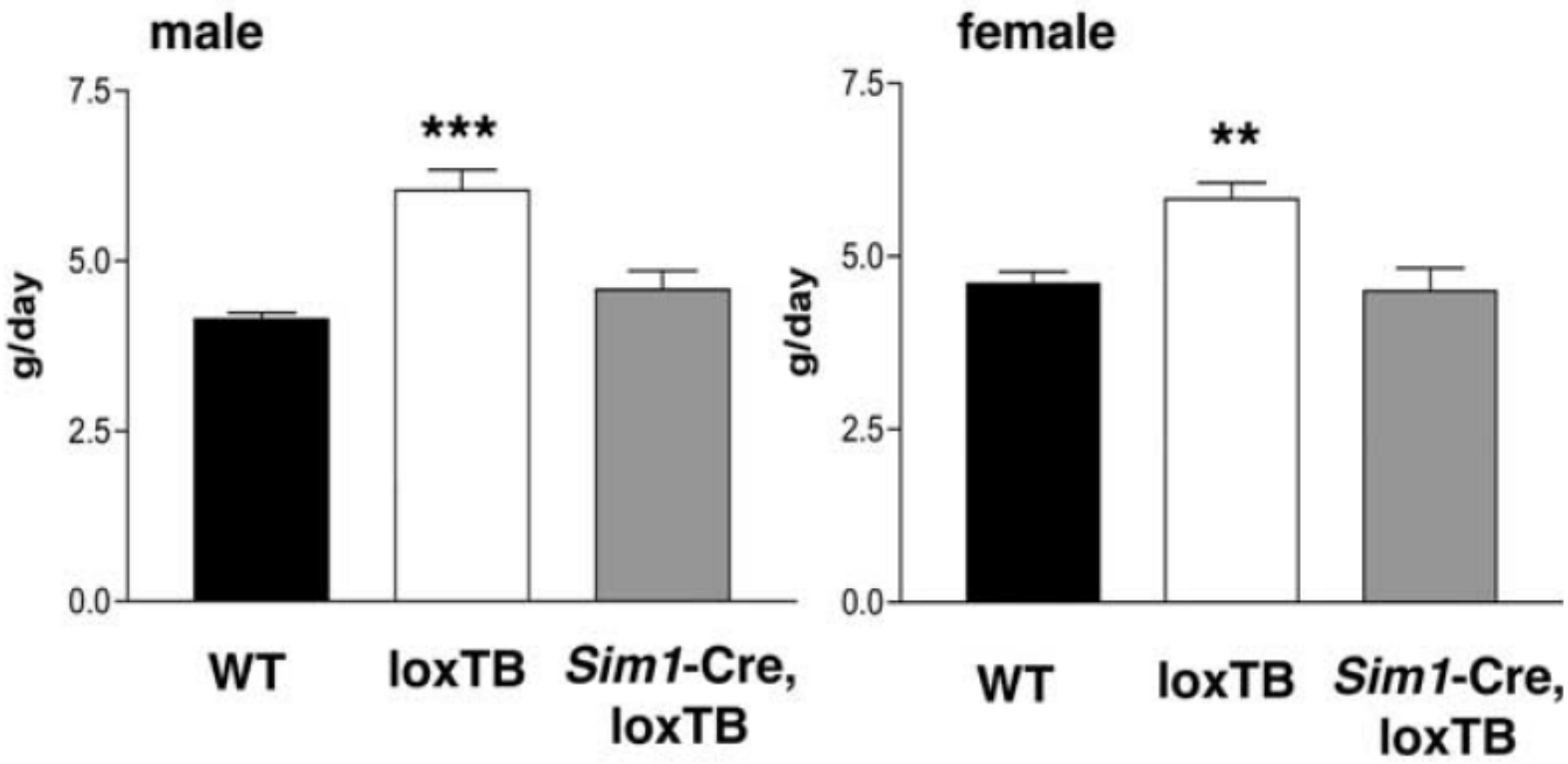
Expression of *MC4R* on *SIM1*$^{+}$ Cells Reduces Food Intake



Balthasar *et al*. Cell 2005

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SIM1 and *MC4R* Knockouts Cause Obesity in Humans

Table 1. Summary of Genes and Rare Coding Variants That Are Unique to the Obese or Lean Population

Gene Group and Gene	OMIM	Mouse Knockouts	Mouse Transgenics	Human Mutations	Associations	Obese[a]		Lean[a]	
						NS	S	NS	S
Monogenic obesity:									
BRS3	300107	Obese[9]	None	None	None	1	0	3	0
CARTPT	602606	Obese[10]	None	Obese[11]	Yes[12–14]	1	1	0	1
FABP4	600434	Obese[15]	None	None	Yes[16]	1	0	2	0
HTR2C	312861	Obese[17]	None	None	Yes[18,19]	1	0	0	0
IL6	147620	Obese[20]	None	None	Yes[21–27]	0	1	0	0
LEP	164160	Obese[28]	Lean[29]	Obese[30]	Yes[31–38]	0	3	0	1
MC3R	155540	Obese[39]	None	Obese[40]	Yes[41,42]	2	0	1	1
MC4R	155541	Obese[43]	None	Obese[44]	Yes[45–49]	8	1	2	1
NHLH2	162361	Obese[50]	None	None	None	2	0	1	1
NMU	605103	Obese[51]	None	None	None	1	0	1	0
NPB	607996	Obese[52]	None	None	None	1	0	2	0
NPBWR1	600730	Obese[53]	None	None	None	3	0	1	0
NPY1R	162641	Obese[54]	None	None	None	1	1	2	1
NPY2R	162642	Obese[55]	None	None	Yes[56–58]	2	3	2	0
NPY5R	602001	Obese[59]	None	None	Yes[60]	1	1	1	0
NR0B2	604630	No apparent phenotype[61]	None	Obese[62,63]	Yes[63–65]	3	0	2	0
PNPLA2	609059	Obese[66]	None	None	None	3	1	2	2
POMC	176830	Obese[67]	None	Obese[68]	Yes[69–77]	2	3	1	3
PYY	600781	Obese[78]	None	Obese[79]	Yes[56–58,80]	2	0	1	0
SIM1	603128	Obese[81]	Lean[82]	Obese[83,84]	None	6	2	0	2
UCP3	602044	No apparent phenotype[85]	Lean[86]	Obese[87]	Yes[88–99]	5	1	2	3
Total						46	18	26	16

Reference 20: Ahituv *et al*. American Journal of Human Genetics 2005

Is the Association of *SIM1* and ED Driven by Obesity?

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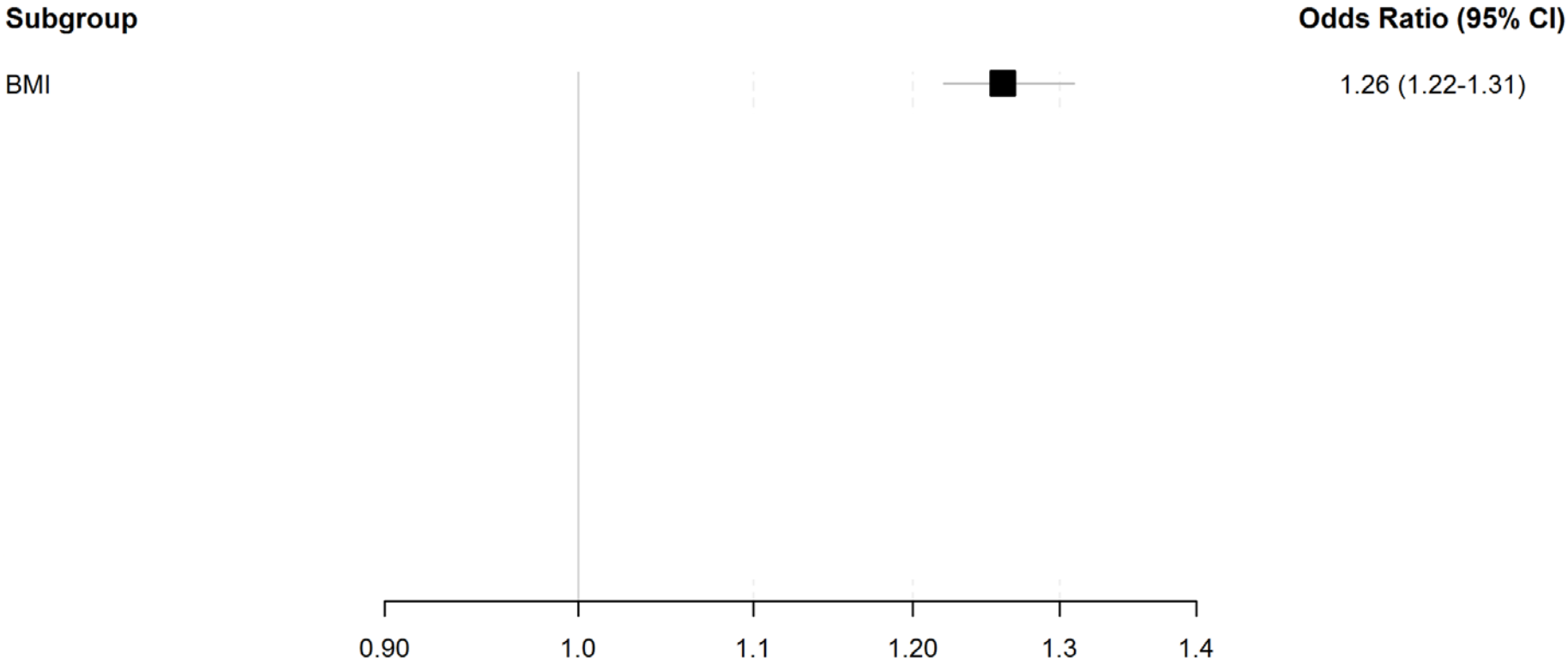
ED Association is not Driven by Body Mass Index (BMI)



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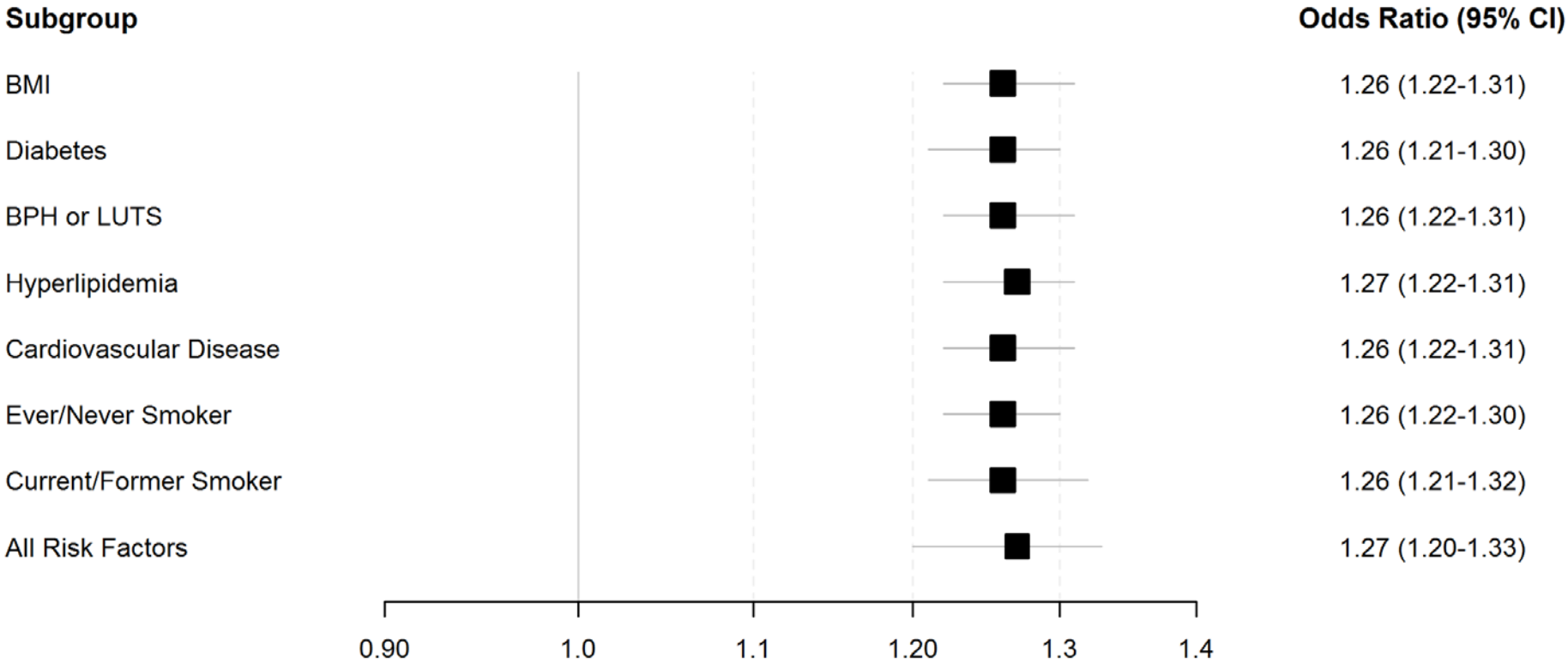
ED Association is not Driven by Body Mass Index (BMI)



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Conclusions

We hypothesize that the *SIM1* enhancer harboring rs17185536 or the other erectile dysfunction-associated alleles that show differential enhancer activity are active in neurons that control erectile function but not in those controlling feeding and body weight homeostasis.

Based on both human and animal studies of the effects of melanocortin agonists on sexual function in females, it is possible that our erectile dysfunction risk locus may also affect female sexual function, including sexual desire and sexual arousal (23, 24).

Our functional analyses, along with previous studies in the literature, point toward a previously unknown mechanism underlying erectile dysfunction, which opens the possibility of developing drug therapies with a more specific target. Those treatments may have the potential to improve sexual function in both men and women.

A Previous Melanocortin-based Treatment for ED

Discovery that a melanocortin regulates sexual functions in male and female humans

Mac E. Hadley *

Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2

α-Melanotropin (α-MSH)

Ac-Ser-Tyr-Ser-Nle-Glu-His-DPhe-Arg-Trp-Gly-Lys-Pro-Val-NH_2

Melanotan I (MTI)

Ac-Nle-c[Asp,His,DPhe,Arg,Trp,Lys]-NH_2

Melanotan II (MTII)

Hadley. Endocrinology 2005

A Serendipitous Side Effect

One mistake in my deliberations was made, however. MTI had previously been administered at a dose as high as 10 mg without physiological consequences (other than tanning). I forgot, however, that MTII was only about half the molecular weight of MTI (Fig. 1). Therefore, when I took an equivalent (10 mg) dose of MTII, I inadvertently received about twice the number of molecules of the peptide. Unlike MTI, however, MTII caused a rather immediate, unexpected response: nausea and, to my great surprise, an erection (no figure provided). While I lay in bed with an emesis pan close by, I had an unrelenting erection (about 8 h duration) which could not be subdued even with a cold pack. When my wife came upon the scene, she proclaimed that I "must be crazy." In response, I raised my arm feebly into the air and answered, "I think we may become rich."

Hadley. Endocrinology 2005

The Hadleys

Mac Hadley

Gertrude Hadley

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