

What is the Role of Genetics in Obesity

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Genetics and Genomics

Wilhelm Johannsen coined the term “gene” in 1909

Thomas Morgan publishes “The Mechanism of Mendelian Heredity” in 1915 explaining that genes exist on chromosomes and are the basic units of Inheritance

Hans Winkler proposes in 1920 the term “genome” to describe all the genes of an organism

James Watson, Francis Crick and Rosalind Franklin discover the double helix structure of DNA in 1953

Marshall Nirenberg deciphers the genetic code in 1966

Genentech produces first drug in 1978 made through recombinant DNA technology: Insulin

Genetics and Genomics

DNA fingerprinting for forensics and paternity testing developed in 1984

First DNA microarray and scanner introduced in 1989

Human genome is sequenced and the final version published in 2003

- ~6,000,000,000 bases

- ~20,000 genes

- ~99% of the genome is the same for all humans

Goal: Genome-wide database to determine patterns of common human sequence variations

Aim: What variations are the disease-causing genes?

The Good Old Days

The old central dogma of biology was that the flow of genetic information was from DNA to RNA to protein

Today, that is basically true.... But its about as simplified as explaining all of pulmonology by saying air goes in and out and blood goes round and round

We now know that a single gene can account for many gene products depending on the environment where gene expression occurs

Examples of Mendelian Diseases (Single Gene)

Autosomal Dominant

Familial hypercholesterolemia	1/500
Polycystic kidney disease	1/1,250
Hereditary spherocytosis	1/5,000
Marfan's syndrome	1/4,000
Huntington's disease	1/15,000

Autosomal Recessive

Sickle cell anemia	1/625 (African Amer)
Cystic fibrosis	1/2,000
Tay-Sachs disease	1/3,000
Phenylketonuria	1/12,000
Mucopolysaccharidoses	1/25,000
Glycogen storage disease	1/50,000
Galactosemia	1/57,000

X-linked

Duchenne muscular dystrophy	1/7,000
Hemophilia	1/10,000

Examples of Complex Diseases

Asthma

Autoimmune diseases

Cancers

Diabetes

Heart disease

Hypertension

Inflammatory bowel disease

Mental retardation

Mood disorders

Obesity

Refractory error

Infertility

Genetics and Genomics

“Mendelian disorders” are the easiest to analyze and are best understood because they are due to ~1 gene

However most diseases are complex meaning that many genes only contribute to the risk of the disease

This has led to the concept of “susceptibility alleles” where the inheritance of a genetic variant does not guarantee that the disease will occur

“Common disease, common variant hypothesis”

The genetic influence on complex diseases are due to common variants present in more than 5% of the population. Variants can be thought of as “risk factors” for disease

Gene Expression

There are genes inside of genes

The same gene can encode multiple proteins

Active genes occur on both DNA strands

Proteins regulate gene expression

RNA regulates gene expression

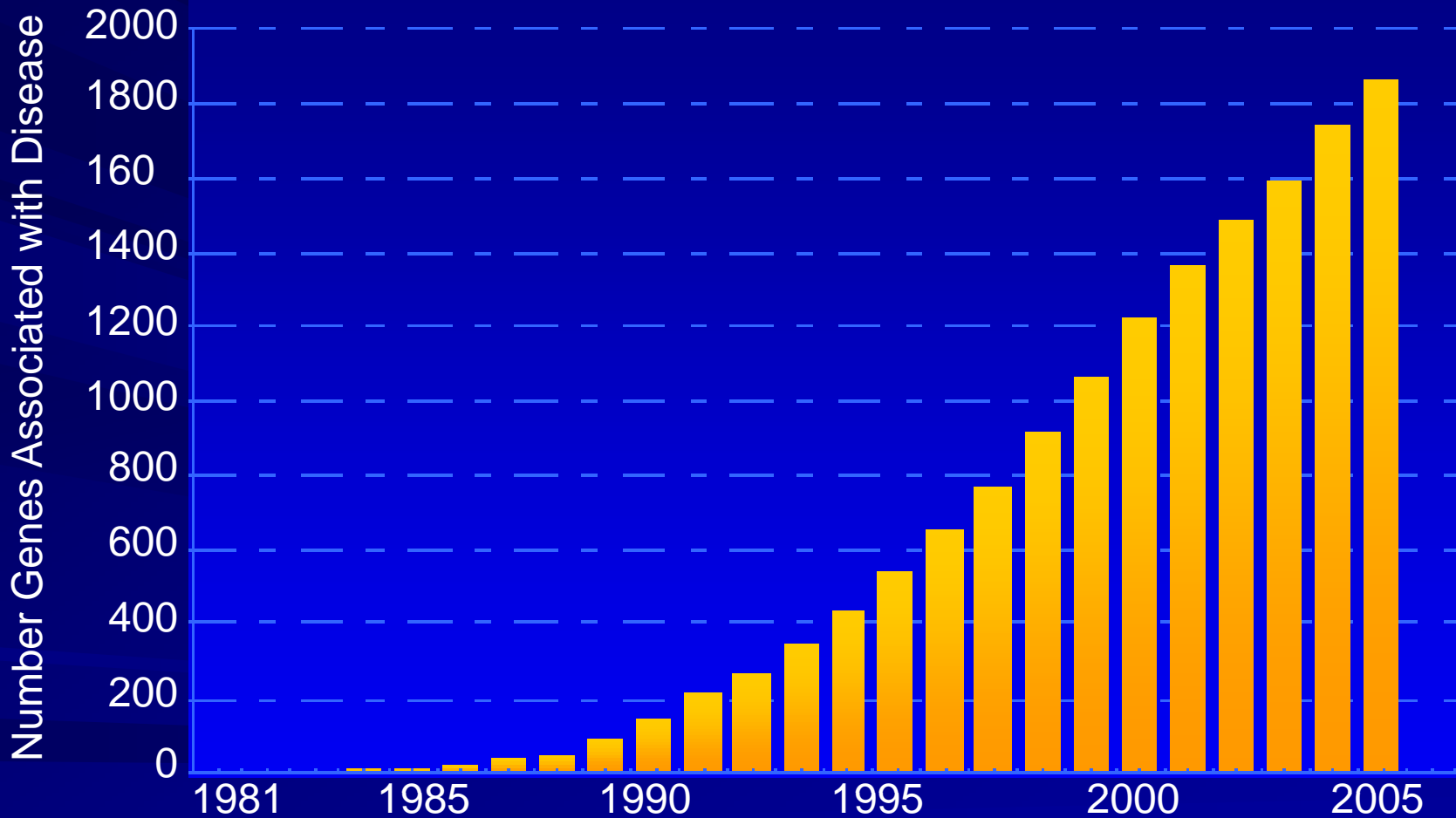
RNA processing yields multiple RNAs

Small RNA and siRNA regulate mRNAs

Posttranslational modification of proteins yields diverse products

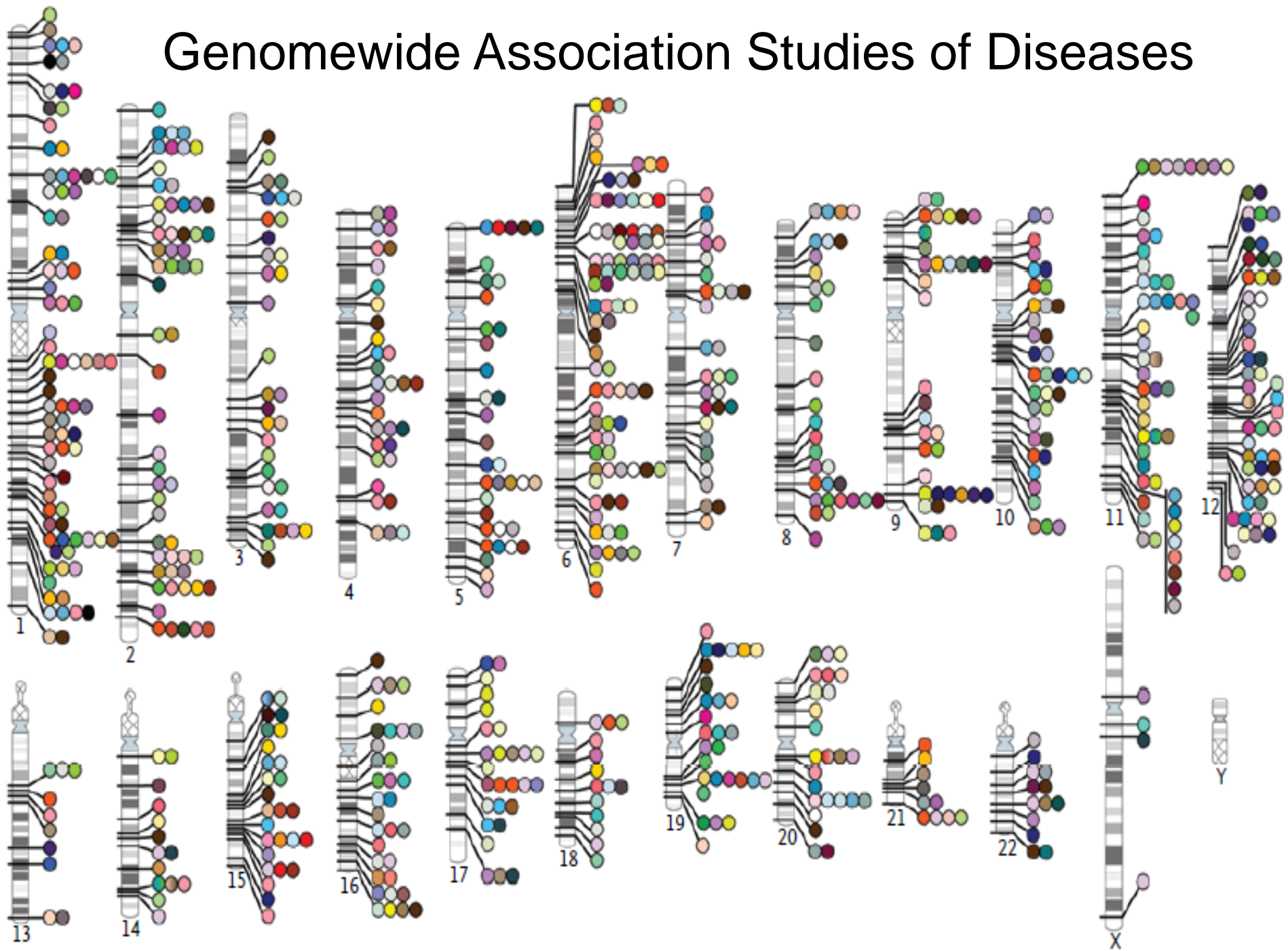
Changing the rate of protein synthesis from the ribosome yields proteins with the same amino acid sequence but different 3-D structure and function!

Cumulative Pace of Disease Gene Discovery 1981-2005



Source: Online Mendelian Inheritance in Man

Genomewide Association Studies of Diseases



Key for Genomewide Association Studies of Diseases

Acute lymphoblastic leukemia	Cleft lip/palate	Homocysteine levels	Osteoporosis	Serum metabolites
Adhesion molecules	Cognitive function	Idiopathic pulmonary fibrosis	Otosclerosis	Skin pigmentation
Adiponectin levels	Conduct disorder	IgE levels	Other metabolic traits	Smoking behavior
Age-related macular degeneration	Colorectal cancer	Inflammatory bowel disease	Ovarian cancer	Speech perception
AIDS progression	Corneal thickness	Intracranial aneurysm	Pancreatic cancer	Sphingolipid levels
Alcohol dependence	Coronary disease	Iris color	Pain	Statin-induced myopathy
Alzheimer disease	Creutzfeldt-Jakob disease	Iron status markers	Paget's disease	Stroke
Amyotrophic lateral sclerosis	Crohn's disease	Ischemic stroke	Panic disorder	Systemic lupus erythematosus
Angiotensin-converting enzyme activity	Cutaneous nevi	Juvenile idiopathic arthritis	Parkinson's disease	Systemic sclerosis
Ankylosing spondylitis	Dermatitis	Kidney stones	Periodontitis	Telomere length
Arterial stiffness	Drug-induced liver injury	LDL cholesterol	Peripheral arterial disease	Thyroid cancer
Asthma	Eosinophil count	Leprosy	Phosphatidylcholine levels	Tooth development
Atherosclerosis in HIV	Eosinophilic esophagitis	Leptin receptor levels	Phytosterol levels	Total cholesterol
Atrial fibrillation	Erythrocyte parameters	Liver enzymes	Platelet count	Triglycerides
Attention deficit hyperactivity disorder	Esophageal cancer	LP (a) levels	Primary biliary cirrhosis	Type 1 diabetes
Autism	Essential tremor	LpPLA(2) activity and mass	PR interval	Ulcerative colitis
Basal cell cancer	Exfoliation glaucoma	Lung cancer	Prostate cancer	Urate
Bipolar disorder	Eye color traits	Major mood disorders	Protein levels	Varicose thromboembolism
Biliary atresia	F cell distribution	Malaria	Psoriasis	Vertical cup-disk ratio
Bilirubin	Fibrinogen levels	Male pattern baldness	Pulmonary funct. COPD	Vitamin B12 levels
Birth weight	Folate pathway vitamins	Matrix metalloproteinase levels	QRS interval	Vitamin D insufficiency
Bladder cancer	Freckles and burning	MCP-1	QT interval	Vitiligo
Blind or brown hair	Gallstones	Melanoma	Quantitative traits	Warfarin dose
Blood pressure	Glioma	Menarche & menopause	Recombination rate	Weight
Blue or green eyes	Glycemic traits	Multiple sclerosis	Red vs non-red hair	White cell count
BMI, waist circumference	Hair color	Myeloproliferative neoplasms	Renal function	YKL-40 levels
Bone density	Hair morphology	Narcolepsy	Response to antidepressants	
Breast cancer	HDL cholesterol	Nasopharyngeal cancer	Response to antipsychotic therapy	
C-reactive protein	Heart failure	Neuroblastoma	Response to hepatitis C treat	
Cardiac structure/function	Heart rate	Nicotine dependence	Response to statin therapy	
Carnitine levels	Height	Obesity	Restless legs syndrome	
Carotenoid/tocopherol levels	Hemostasis parameters	Open angle glaucoma	Rheumatoid arthritis	
Celiac disease	Hepatitis	Open personality	Schizophrenia	
Chronic lymphocytic leukemia	Hirschsprung's disease	Optic disc parameters		
	HIV-1 control	Osteoarthritis		

Genomics Weekly Update

Google “genomics and disease prevention”

Select www.cdc.gov/genomics/

Pharmacogenomics
Birth defects
Blood Disorders
Cancer
Diabetes
Cardiovascular disease
Environment & Occupational Health
Ethical Legal and Social Issues
Mental health
Genetic Testing
Infectious Disease
Neurologic conditions
Newborn screening
Aging
Autoimmune disease
Chronic disease

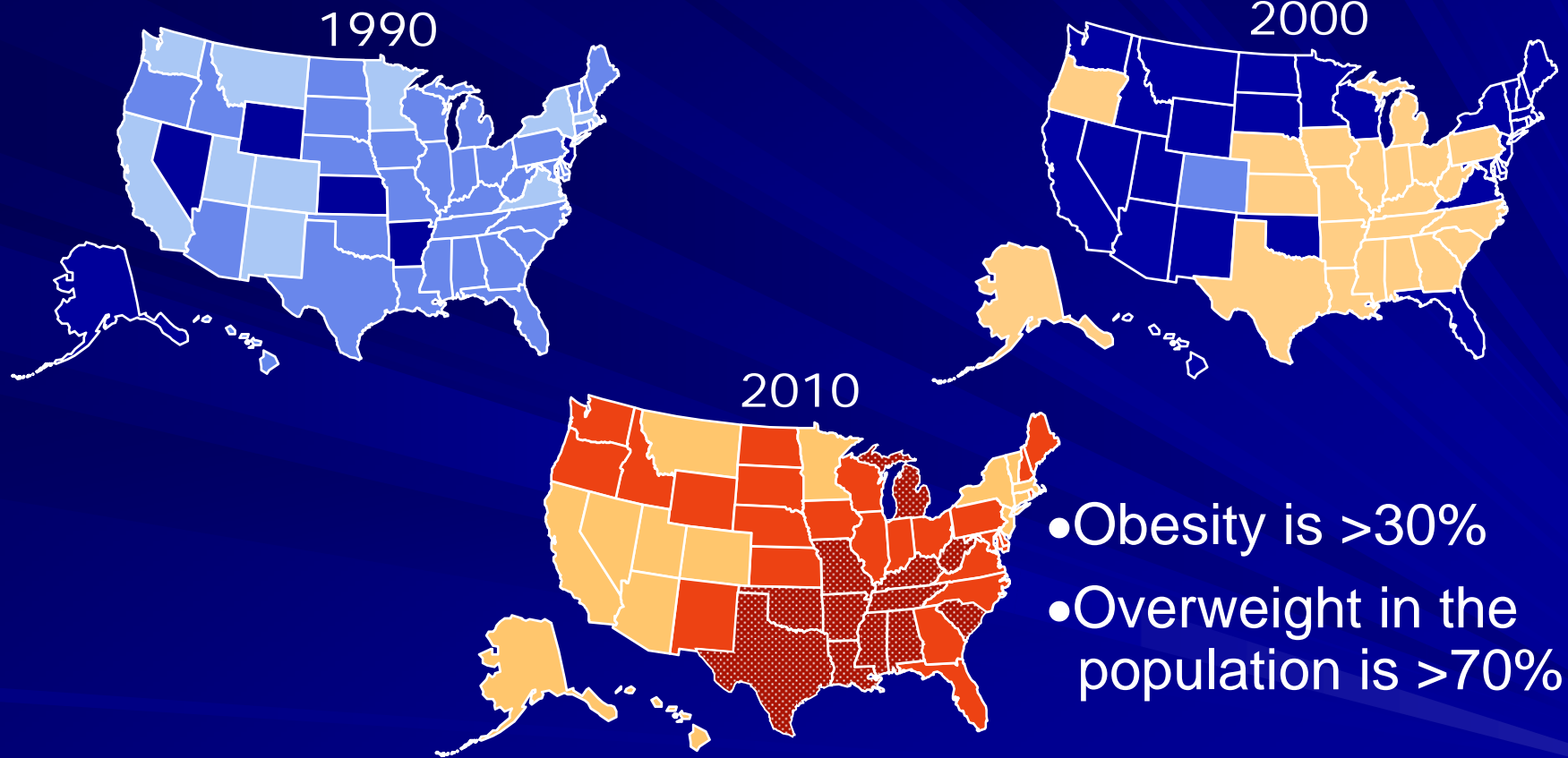
Is Obesity Genetic?



Environment?
Genes?



Obesity Trends (BMI ≥ 30), U.S. Adults BRFSS, 1990, 2000, 2010



The Rate of Increase in Obesity

Genetics does not change at a rate to explain the rapid increase in overweight and obesity. Therefore environment must play a major role

The question becomes to what extent does genetics “set the stage” for overweight and obesity to be expressed?

Data from the Pima Indian population illustrates the magnitude of the role played by environment

Environmental Influences

Same People, Same Genes, Different Address

	USA Pima	Mexico Pima
BMI ¹	33.4	25
Urban Diet ²	50% Fat Calories	
Native Diet ²	15% Fat Calories	

¹Ravussin E et al. Diabetes Care 1994;17(9):1067-1074

²Pratley RE. Proc Nutr Soc 1998;57:175-81

Finding Obesity Genes

Clearly environment influences obesity, but remember the question is how does genetics predispose an individual to become overweight or obese

If we look at families, there appears to be a strong history of obesity; perhaps 40 to >70% concordance

Hypothesis: Obesity is genetic

Question: “True-True cause and effect?”
versus

“True-True but unrelated?”

Example: People who develop cancer wear shoes therefore, shoes cause cancer

Obesity Genes: Many or Few?

D2S1788	2q22.3	66 White families (349 subjects)	3.08
D2S347	2q14.3	1,249 White European-origin sibling pairs	4.44
D2S347	2q14.3	53 Caucasian families (758 subjects)	3.42
	2q37	451 Caucasian families (4,247 subjects)	3.34
D3S1764	3q22.3	1,055 pairs (White, Black, Mexican American, and Asian)	3.45 (Black)
D3S2427	3q26.33	507 Caucasian families (2,209 subjects)	3.3
D3S2427	3q26.33	128 African-American families (545 subjects)	4.3
D3S2427	3q26.33	1,055 pairs (White, Black, Mexican American)	3.4
D3S3676	3q26.33	128 African-American families (545 subjects)	4.3
D4S1627	4p13	37 Utah families (994 subjects)	3.4
D4S3350	4p15.1	37 Utah families (994 subjects)	9.2
D4S2632	4p15.1	37 Utah families (994 subjects)	6.1
D6S403	6q23.3	27 Mexican-American families (261 subjects)	4.2
D6S1003	6q24.1	27 Mexican-American families (261 subjects)	4.2
D7S817	7p14.3	182 African families (789 subjects)	3.83
D7S1804	7q32.3	401 American families (3,027 subjects)	4.9
D8S1121	8p11.23	10 Mexican-American families (470 subjects)	3.2
D10S212	10q26.3	18 Dutch families (198 subjects)	3.3
Chromosome 10 region	10q26.3	279 White families (1,848 non-Hispanic subjects)	3.2
D11S2000	11q22.3	182 African families (789 subjects)	3.35
D11S912	11q24.3	264 Pima Indian and American families (1,766 pairs)	3.6
D12S1052	12q21.1	66 White families (349 subjects)	3.41
D12S1064	12q21.33	66 White families (349 subjects)	3.41
D12S2070	12q24.21	260 European-American families (1,297 subjects)	3.57
	12q24	933 Australian families (2,053 subjects)	3.02
D13S257	13q14.2	401 American families (3,027 subjects)	3.2
D13S175	13q12.11	580 Finnish families	3.3
D13S221	13q12.13	580 Finnish families	3.3
D13S1483	13q13.2	1,124 American families (3,383 subjects)	3.2
D19S571	19q	109 French Caucasian families (447 subjects)	3.8
D20S149	20q13.31-qter	92 American families (513 subjects, 423 pairs)	3.2
D20S476	20q13	92 American families (513 subjects, 423 pairs)	3.06
D20S438	20q12	103 Utah families (1,711 subjects)	3.5
D20S107	20q12	92 American families (513 subjects, 423 pairs)	3.2
D20S211	20q13.2	92 American families (513 subjects, 423 pairs)	3.2

DRD4	Dopamine receptor D4
GHRH	Ghrelin precursor
GPR24	G protein-coupled receptor 24
HTR1B	5-hydroxytryptamine receptor 1B
HTR2A	5-hydroxytryptamine receptor 2A
HTR2C	5-hydroxytryptamine receptor 2C
IDE	Insulin-degrading enzyme
MC3R	Melanocortin 3 receptor
MC4R	Melanocortin 4 receptor
MC5R	Melanocortin 5 receptor
NPR3	Natriuretic peptide receptor C
NPY	Neuropeptide Y
NPY2R	Neuropeptide Y receptor Y2
NR3C1	Glucocorticoid receptor
POMC	Proopiomelanocortin
PYY	Peptide YY
TH	Tyrosine hydroxylase
UBL5	Ubiquitin-like 5
Y2R	Neuropeptide Y receptor Y2
Adipogenesis	
ACDC	Adiponectin
ADPN	Adiponitrin
AFM1	Adipose most abundant gene transcript 1
APOA1	Apolipoprotein A1
APOA2	Apolipoprotein A2
APOA4	Apolipoprotein A4
APOB	Apolipoprotein B
APOD	Apolipoprotein D
APOE	Apolipoprotein E
CBFA2T1	Core-binding factor, runt domain, α subunit 2
FOXC2	Forkhead box C2
GMB3	Guanine nucleotide binding protein, β polypeptide 3
INSIG2	Insulin-induced gene 2
LDLR	Low-density lipoprotein receptor
LIPC	Lipase, hepatic
LIPE	Lipase, hormone sensitive
LMNA	Lamin A/C
LPL	Lipoprotein lipase
MACS2	SAH \uparrow family member, acyl-coenzyme A synthetase for fatty acids
PLN	Perilipin
PON1	Paraoxonase 1
PPARA	Peroxisome proliferative activated receptor, α
PPARD	Peroxisome proliferator-activated receptor, δ
PPARG	Peroxisome proliferator-activated receptor, γ
SAH	SA hypertension-associated homolog
SCARB1	Scavenger receptor class B, member 1
SORBS1	Sorbin and SH3 \uparrow domain containing 1
SREBF1	Sterol regulatory element binding transcription factor 1
Energy metabolism and thermogenesis	
ACPF	Acid phosphatase 1
ADA	Adenosine deaminase
ADRA2B	Adrenergic, α 2B-, receptor
ADRB2	Adrenergic, β 2-, receptor
ADRB3	Adrenergic, β 3-, receptor
ATP1A2	ATPase, \uparrow Na $^+$ /K $^+$ transporting, α 2 (+) polypeptide
CALP10	Calpain 10
ENPP1	Ectonucleotide pyrophosphatase/phosphodiesterase 1

HSPA1B	Heat shock 70,000 protein 1B
PPARGC1A	Peroxisome proliferator-activated receptor, γ , coactivator 1 α
PTPN1	Protein tyrosine phosphatase, nonreceptor type 1
TUB	Tubby, mouse, homolog of
UCP1	Uncoupling protein 1
UCP2	Uncoupling protein 2
UCP3	Uncoupling protein 3
Leptin-insulin signaling pathway	
ABCC8	ATP \uparrow binding cassette, subfamily C, member 8
BTC	Beta2-tikulin
GCGR	Glucagon receptor
IDE	Insulin-degrading enzyme
IGF2	Insulin-like growth factor 2
INS	Insulin
IRS1	Insulin receptor substrate 1
IRS2	Insulin receptor substrate 2
LEP	Leptin
LEPR	Leptin receptor
PTPRF	Protein tyrosine phosphatase, receptor type F
RETN	Resistin
TBC1D1	TBC1 domain family, member 1
TCF1	Transcription factor 1, hepatic; LFB1, hepatic nuclear factor (HNF1), albumin proximal factor
Inflammatory cytokines	
IL6	Interleukin 6
IL6R	Interleukin 6 receptor
IL10	Interleukin 10
LTA	Lymphotoxin alpha (TNF) superfamily, member 1
SERPINE1	Snake proteinase inhibitor, clade E, member 1
TNF	Tumor necrosis factor
Hormone signaling pathway	
AR	Androgen receptor
CCKAR	Cholecystokinin A receptor
CRHR1	Corticotropin-releasing hormone receptor 1
CYP11B2	Cytochrome P450, family 11, subfamily B, polypeptide 2
CYP19A1	Cytochrome P450, family 19, subfamily A, polypeptide 1
ESR1	Estrogen receptor 1
ESR2	Estrogen receptor 2
GHRHR	Growth hormone releasing hormone receptor
MAOA	Monoamine oxidase A
MAOB	Monoamine oxidase B
MED12	Mediator of RNA polymerase II transcription, subunit 12
NR0B2	Nuclear receptor subfamily 0, group B, member 2
NCOA3	Nuclear receptor coactivator 3
PGR	Progesterone receptor
SGK	Serum/glucocorticoid-regulated kinase
SLC6A3	Solute carrier family 6, member 3
SLC6A14	Solute carrier family 6, member 14
VDR	Vitamin D receptor
Renin-angiotensin pathway	
ACE	Angiotensin I converting enzyme
AGT	Angiotensinogen
HSD11B1	Hydroxysteroid (11-beta) dehydrogenase 1

* Please refer to Rankinen et al. (52) for a more comprehensive summary.

So, Where Do We Start Looking for Obesity Genes?

“Candidate gene studies”

Genes for which there is evidence of regulation of energy balance in animal studies are tested for an association with obesity in the human population

“Genome-wide linkage studies”

Related individuals are tested for the presence or absence of a chromosomal region to determine if that region segregates with obesity

“Genome-wide association studies”

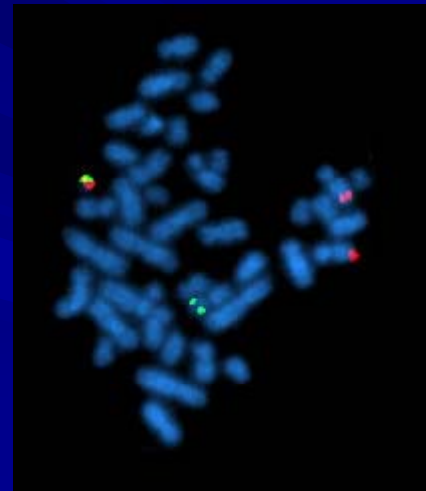
No prior assumptions about relatedness. The whole genome is analyzed to find associations with disease

Finding Genes: Genetic Mapping

Cytogenic maps (banding Patterns) are the lowest resolution



Acute myelogenous leukemia



Bcr/abl rearrangement (FISH)

How Do We Find Genetic Variants or “Susceptibility Genes” for Disease?

Genetic maps are constructed using various “marker” techniques and then trying to arrange everything in the correct order

- Linkage analysis

- RFLPs

- VNTRs

- Microsatellite polymorphisms

- SNPs

Finding Susceptibility Genes

Where to begin?

How about Linkage Analysis

1. Genes for a trait or disease are on chromosomes
2. If two genes are on the same chromosome, they should be inherited together (linked) unless cross-over occurs during meiosis
3. The farther apart 2 genes are from each other, the greater the chance that the genes will become separated: Partial linkage or no linkage. The closer the genes the less likely they will separate
4. Linkage maps for the markers of traits or diseases tell us where the markers are in relation to each other on the chromosome...(but we still don't know exactly where or what the gene is)

Genetic Mapping

How can we think about genes and maps?

Linkage

Think of the genome map as being like a map of the USA showing only the interstate highways
(Bet you can find Texas, but you can't get to Hico)



Genetic maps give an estimate of the distance between places but no details.

Likewise, genetic maps guide us to where a gene might be

How Do We Find Disease Susceptibility Genes?

Other ways to do genetic mapping

Restriction fragment length polymorphisms (RFLPs)

There are bacterial enzymes that break DNA whenever a certain nucleotide sequence is present. (In our road analogy, the enzyme chops the road every time a double line starts or a turn lane occurs, etc.)

If the same RFLP occurs only in people with a certain trait or disease, then that RFLP is a marker for that trait or disease....(but now we don't know where we are unless the RFLPs can be arranged in the right order and we still don't know exactly where or what the gene is)

How Do We Find Disease Susceptibility Genes?

These strategies are similar to that for RFLPs

VNTRs: Variable Number Tandem Repeats are polymorphisms in non-coding regions of DNA. For each VNTR, it is the number of times a sequence is repeated

Microsatellite polymorphisms are repetitions of a very small number of base pairs. The number of repeats varies between different people

Genomewide Association Studies for Assessment of Risk of Disease

A single nucleotide polymorphism (SNP) say “snip”
Is a point mutation of 1 nucleotide substitution in DNA

They almost always occurs in non-coding region

They are scattered through out the genome

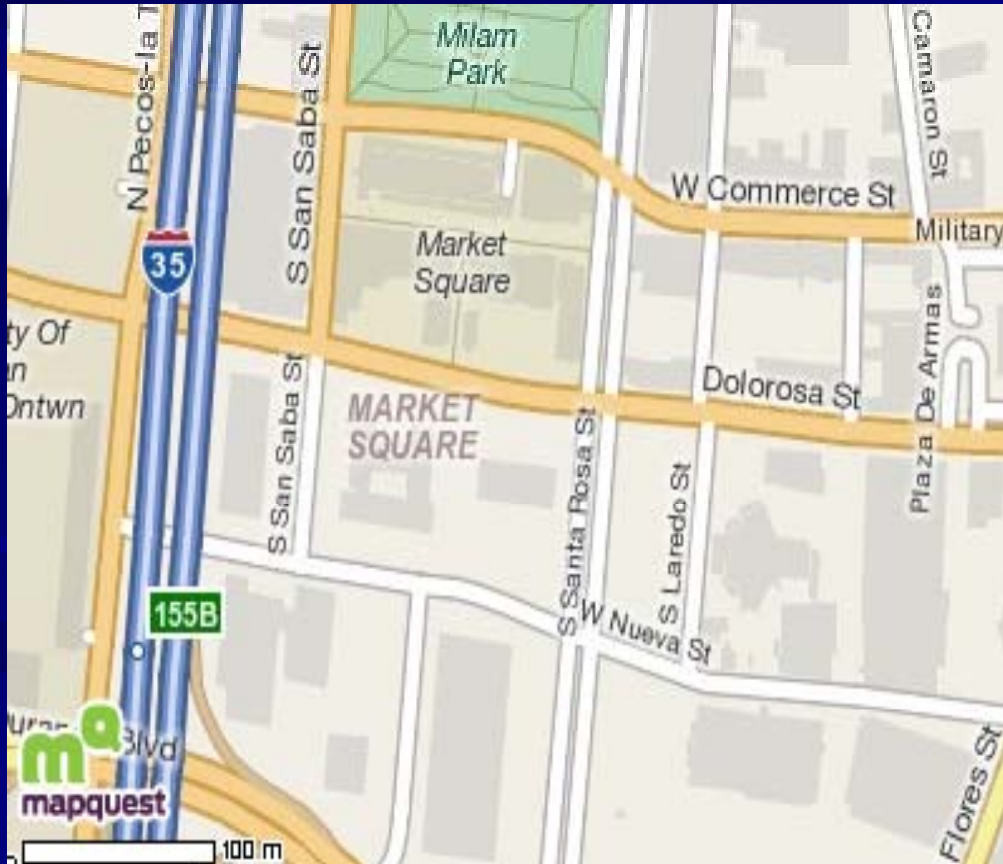
They do not cause disease, just associated with it

SNPs are very common in human DNA: The 0.8% of the genome or 2,400,000 bases that vary in each person or 10,000,000 bases in the whole population

Hypothesis: By studying sequences of DNA that contain SNPs associated with a disease trait, relevant genes associated with a disease may be found

Genetic Mapping

These RFLP, VNTR, SNP maps, like street maps, are more detailed and get us closer to a gene's location...



Close, but no cigar
We still don't know:
which house?
who is in the house?
which room?
what were they doing?
What are they doing?

Candidate Gene Studies

Strong associations between obesity and

MC4R (melanocortin 4 receptor)

PCSK1 (prohormone convertase)

BDNF (brain-derived neurotrophic factor)

ADRB3 (beta-adrenergic receptor 3)

Candidate Gene Studies

MC4R (melanocortin 4 receptor)

Expressed in the CNS and plays a key role regulating food intake and energy homeostasis

A rare mutation in MC4R rendering it nonfunctional causes monogenetic severe early-onset obesity

However, the common variants of MC4R (V103I and 1251L), which map as MC4R have no significant association with obesity traits

Frequency of 103I allele is 3% in the population

Frequency of 1251L is 2% in the population and is protective against obesity if 251L allele is present

Candidate Gene Studies

PCSK1 (prohormone convertase)

This enzyme converts prohormones to hormones involved with energy metabolism

Rare mutations resulting in PCSK1 enzyme deficiency result in extreme childhood obesity

As a candidate gene, 9 variants of PCSK1 were found in obese persons. 2 were consistently associated with adult obesity (N221D and Q665E-S690T)

Frequency of the alleles was ~4-7%

Each allele increased the risk of obesity only 1.3x

Candidate Gene Studies

BDNF (brain-derived neurotrophic factor)

In animals, BDNF has been studied for its effects on the stress response, survival, eating habits, body weight and hyperactivity

Mutations in BDNF cause hyperphagia and obesity

Variants of BDNF (Val66Met → met66met) show a lower BMI of ~ -0.75) suggesting that the presence of Val66-Met increases the risk of obesity

Candidate Gene Studies

ADRB3 (beta-adrenergic receptor 3)

This gene was one of the first to be implicated with obesity. ADRB3 is involved with regulation of lipolysis and thermogenesis

Recent analysis of a large population (>27,000) found no association between obesity and ADRB3 variants

The story continues, but the bottom line is that of the 127 candidate genes reported on the Human Obesity Gene Map, only 5 variants of 4 candidate genes are strongly associated with obesity.

Further, strongly association \neq strong effect on obesity

Genome-Wide Linkage Studies

The analysis is based on about 600 polymorphic markers across the genome. The resolution is poor because the markers are separated by about 10-cM

If an association is found, then genotyping is needed to narrow down where the gene might be

253 loci have been implicated in obesity based on this mapping

Of the 253 loci, only 15 have been replicated in additional analyses

The strategy does not appear to be effective

Genome-Wide Association Studies for Assessment of Risk of Disease

Theory:

“Discovery 1”

Analyze people with and without a disease and see if those with the disease have a common SNP

If yes, then that SNP is associated with a gene involved with the disease

“Replication”

Repeat the analysis if another SNP can be found

“Replication 2”

Continue, if possible to narrow down where the gene might be

Genome-Wide Association Studies

An association between a SNP and a disease exists if the *p-value* of the overall association is “ $<5 \times 10^{-8}$ ”

Briefly, this *p-value* means that the odds that a SNP is associated with the disease is ~95%

Again, note that a strong or weak association has nothing to do with whether that genetic segment has a strong or weak effect on the disease. It simply means that the genetic segment is usually associated with the disease

Large Scale Genome-Wide Association Studies

FTO Gene

FTO (fat mass and obesity associated gene) was the first incontrovertible obesity gene reported in 2007

Replication of the data (~39,000 people) validated FTO as an obesity susceptibility locus and a 3rd study reached the same conclusion

FTO maps 188 kb downstream from MC4R
(remember the melanocortin 4 receptor?)

FTO codes for alpha-ketoglutarate-dependent dioxygenase
It is up-regulated in the hypothalamus during starvation and increases food intake

History: FTO was originally identified as a gene for type 2 diabetes. After adjusting for BMI, zero association was found for T2D

Large Scale Genome-Wide Association Studies

Genomic Investigation of Anthropometric Traits (GIANT)
International consortium combining genomic data from the USA and Europe to achieve large enough sample sizes to power detailed genetic analyses

Of 10 loci thought to be associated with obesity, only 2 proved to be incontrovertible (FTO and MC4R variant)

Subsequent analysis of ~ 60,000 people revealed 8 solid obesity loci

Large Scale Genome-Wide Association Studies

FTO	(fat mass & obesity associated protein)
SH2B1	(SH2B adaptor protein)
MTCH2	(mitochondrial carrier homologue 2)
NPC1	(Neimann-Pick disease, type 1)
<i>near</i> MAF	(musculoaponeurotic fibrosarcoma oncogene)
<i>near</i> PTER	(phosphotriesterase related gene)
<i>near</i> MC4R	(melanocortin receptor 4)
<i>near</i> NEGR1	(neuronal growth factor)
<i>near</i> TMEM18	(transmembrane protein 18)
<i>near</i> KCTD15	(K ⁺ channel tetramerization domain)
<i>near</i> GNPDA2	(glucosamine-6-Phos deaminase 2)
4 loci between	
SEC16B & DGKD	(SEC16B homologue & diacylglycerol kinase)
BCDIN3D & FAIM2	(Brain-derived neurotrophic factor & Fas apoptotic inhibitory molecule 2)

Genome-Wide Association Analyses for Obesity

The high-density multistage genome-wide association analyses have thus discovered 15 loci consistently associated with obesity

The approximate location of each loci is known

Note, however, that the exact identity of the obesity susceptibility variants at each loci remains unknown!

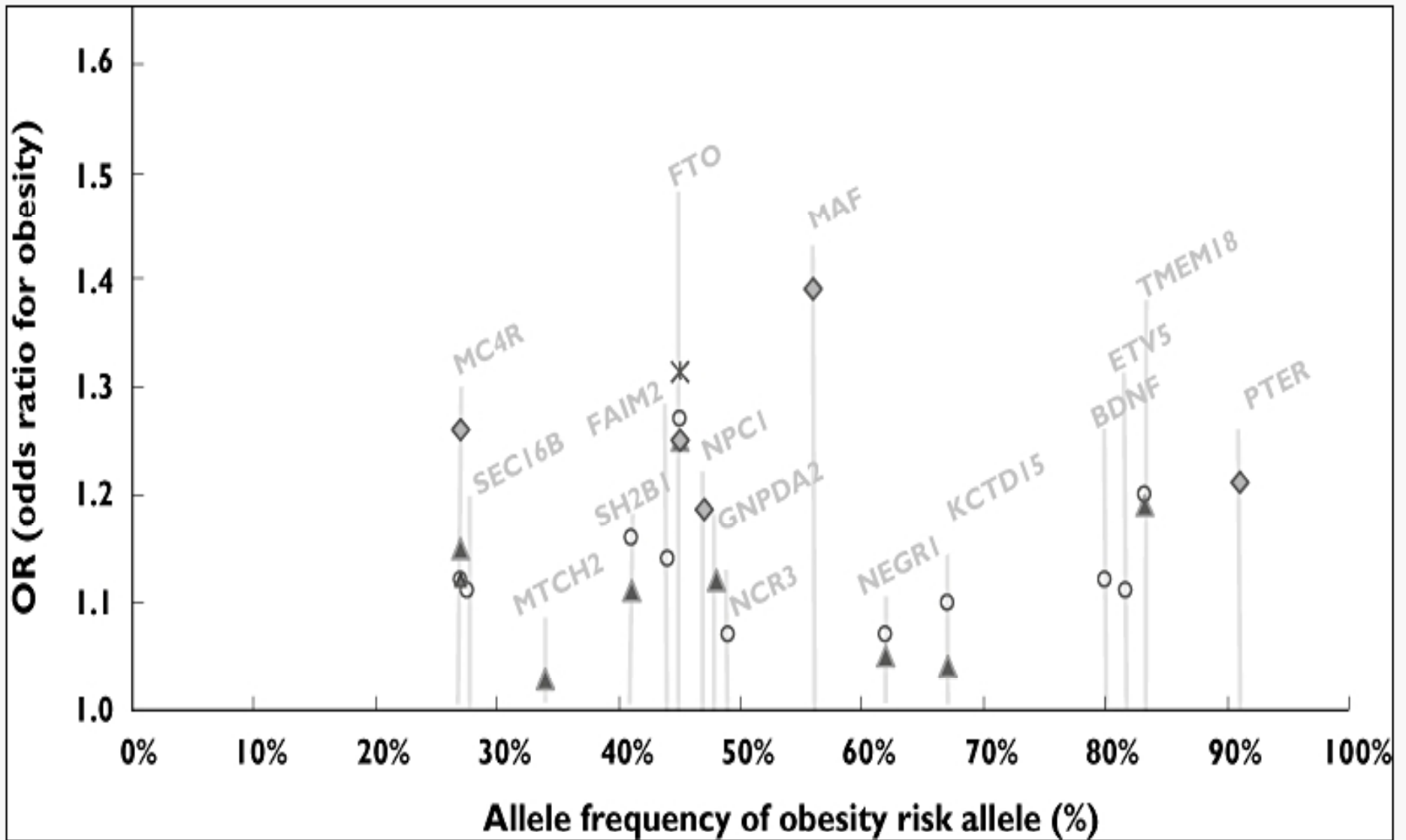
Do the susceptibility loci explain why obesity occurs?

Each loci contributes to obesity (effects are additive)

Each loci contributes about 0.85 to 2.1 Kg weight

OR

The odds ratio for obesity increases about 1.25 for each loci present



Frayling et al 2007, Loos et al (2008), Willer et al (2009), Thorleifsson (2009), Meyer (2009)

Genome-Wide Association Analyses for Obesity

The effects of the obesity susceptibility loci are additive but this does not explain obesity

How many people carry the obesity loci and which obesity loci?

What is the effect of these loci in a population?

EPIC-Norfolk cohort study

20,000 people were genotyped

The average weight of people with 13 obesity susceptibility loci (2% of the population) was only about 4 Kg more than those with ≤ 3 obesity loci

OR

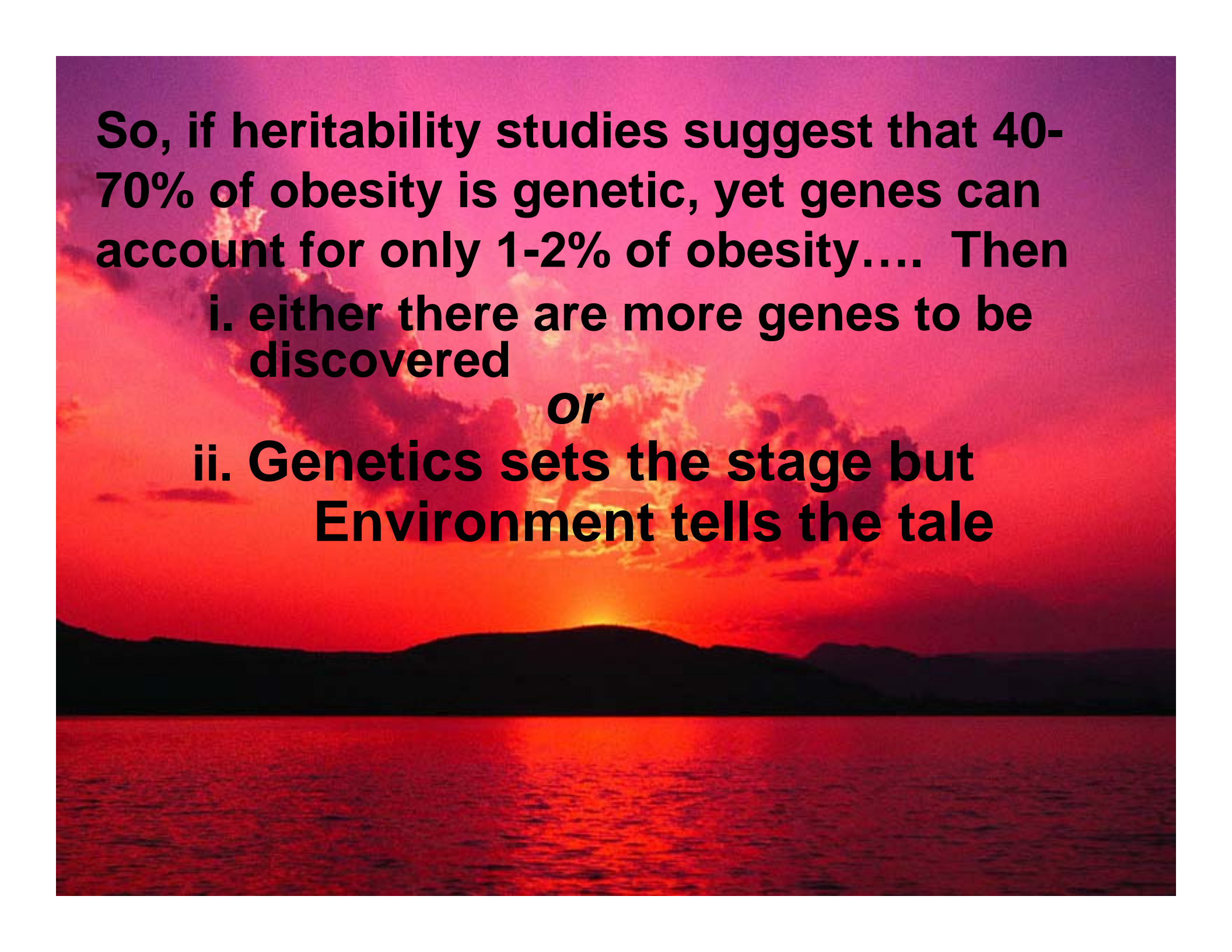
The obesity loci explained only ~1% of the variance in BMI of the Norfolk population

Genes and Lifestyle

Another approach to asking about the effect of obesity susceptibility genes on the problem of obesity is to study the effect of those genes in people with different life styles

Recent work demonstrates that the effect of FTO differs depending on energy expenditure

Specifically, the effect of FTO on BMI is greater in those who are sedentary and its effects are minimal in those people who are active



So, if heritability studies suggest that 40-70% of obesity is genetic, yet genes can account for only 1-2% of obesity.... Then

i. either there are more genes to be discovered

or

**ii. Genetics sets the stage but
Environment tells the tale**

Reference materials