SESSION 3: FITNESS GENETICS AND GENETICS OF CHRONIC DISEASES

Dr. Rahul Kushwah

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AnantLife

REVIEW FROM LECTURE 2

- Nutritional Genetics
- Folate and MTHFR
- Iron overload
- Genome, Gene, Allele
- Vitamin A deficiency diet planning
- Choline and PEMT
- Gluten intolerance
- Mechanism of gluten intolerance
- **Lactose intolerance**
- **Caffeine Metabolism**
- **Fat tasting predisposition**
- **Fats and diet planning**

SESSIONS 1 - 8

Session	Topic	Evaluations
1	INTRODUCTION TO MOLECULAR GENETICS, MOLECULAR BIOLOGY AND HUMAN GENETICS	Discussion – Participation
2	NUTRITIONAL AND DIETARY GENETICS: HOW DO OUR GENES REGULATE OUR NUTRITION AND NUTRITIONAL HEALTH?	Discussion - Participation
3.	FITNESS GENETICS AND GENETICS OF CHRONIC DISEASES: HOW DO OUR GENES REGULATE OUR RESPONSE TO EXERCISE AND HOW DO GENES REGULATE THE RISK OF CHRONIC METABOLIC DISORDERS?	Discussion - Participation
4.	DETOXIFICATION GENETICS: HOW DO OUR GENES REGULATE DETOXIFICATION WHICH INDIRECTLY IMPACTS OVERALL HEALTH AND DISEASE RISK?	Discussion - Participation
5.	NEUROGENETICS: HOW DO OUR GENES REGULATE THE SYNTHESIS AND BREAKDOWN OF NEUROTRANSMITTERS AND ITS IMPACT ON OUR HEALTH ?	Take home exam on sections 1-5, due during session 6
6.	GENETICS OF ENDOCANNABINOID PATHWAYS: HOW DO OUR GENES REGULATE THE RESPONSE TO CANNABIS?	Discussion - Participation
7.	SKIN GENETICS: HOW DO OUR GENES REGULATE OUR SKIN HEALTH ?	Take home assignment – due during session 8
8.	DISCUSSION AND PRACTICAL APPLICATIONS OF GENETIC TESTS DISCUSSED IN SESSIONS 2-7	Discussion - Participation

SESSION OBJECTIVES:

- How does genetics impact fitness and performance ?
- How does genetics impact response to different exercise regimens ?
- How does genetics impact the risk of developing diabetes and dyslipidemia?

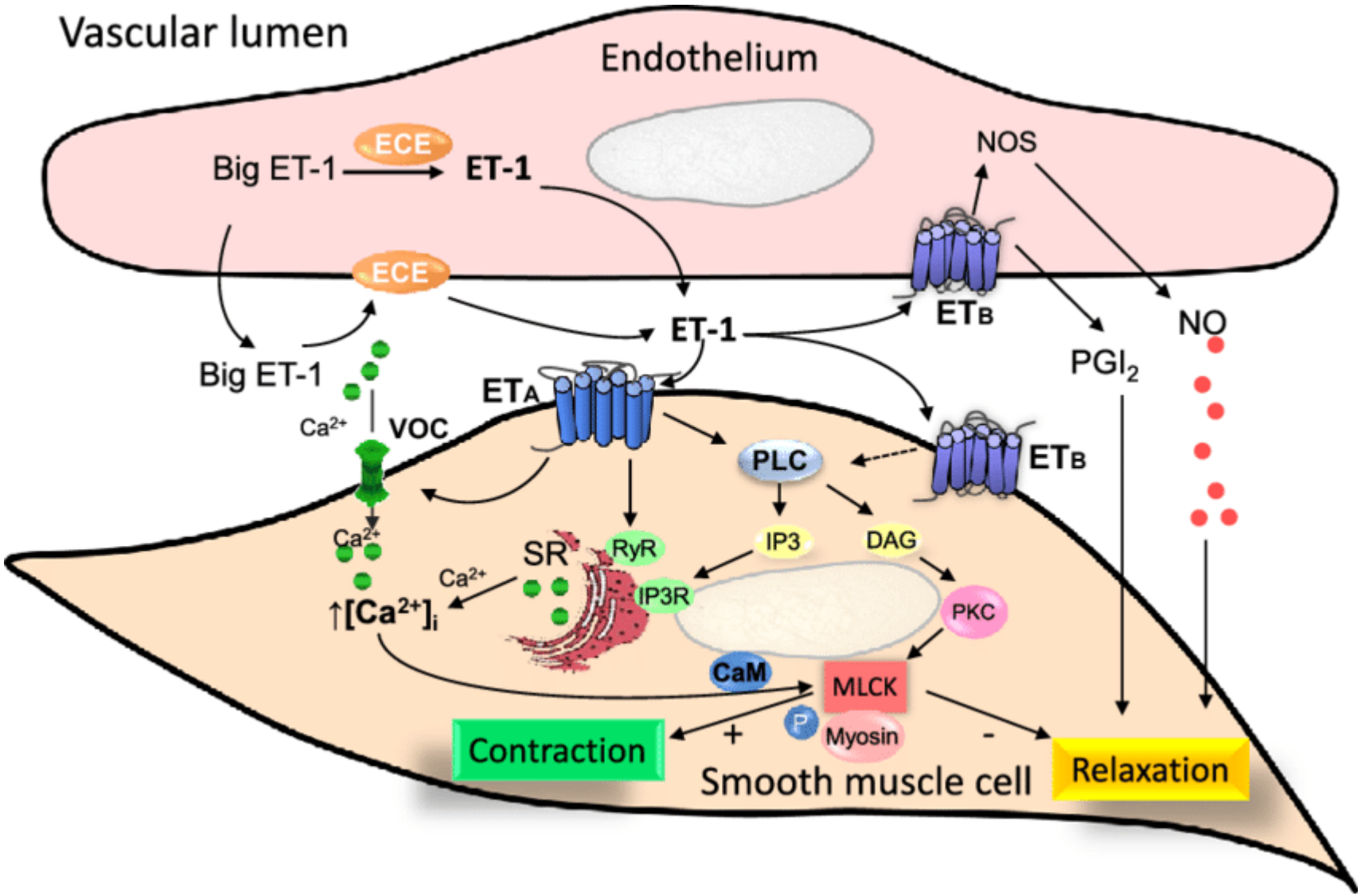
FITNESS GENETICS

- Genetics and hypertension – sedentary lifestyle
- Genetics and soft tissue injury
- Genetics and impact on endurance/aerobic exercise
- Genetics and ability to perform in endurance activities
- Genetics and pain tolerance
- Genetics and muscle biology

EDN1 – FITNESS AND HYPERTENSION

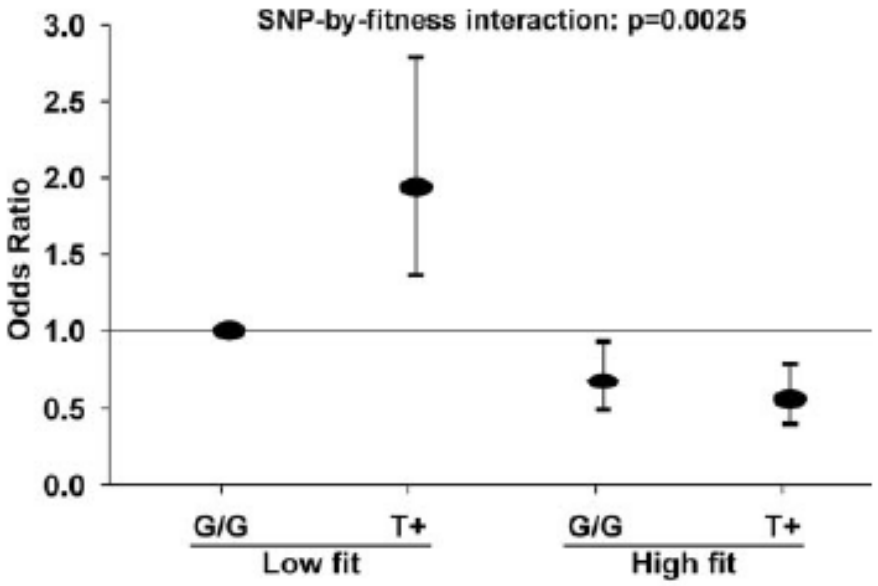
- Hypertension has been observed in individuals with low cardiovascular activity
- Genetics is a strong determinant of hypertension
- Genetics can substantially increase the risk of hypertension in absence of cardiovascular fitness – EDN1
- Endothelin 1 (ET-1), also known as preproendothelin-1 (PPET1), is a potent vasoconstrictor that in humans is encoded by the EDN1 gene and produced by vascular endothelial cells.
- Mutations in EDN-1 associated with hypertension in low cardio setting

EDN1 – FITNESS AND HYPERTENSION



EDN1 – FITNESS AND HYPERTENSION

- T allele is associated with increased risk of hypertension in individuals with low fitness levels
- Expression of the genotype effect is modulated by physical activity or cardiorespiratory fitness level
- T allele was associated with blunted systolic blood pressure and pulse pressure responses to a 20-week endurance training program



EDN1 – FITNESS AND HYPERTENSION

- Exercise regimen that showed an effect
- During the first 2 weeks, the subjects trained at an HR corresponding with 55% of the baseline maximal oxygen consumption for 30 minutes per session.
- Duration and intensity of the training sessions were gradually increased to 50 minutes and the HR associated with 75% of the baseline maximal oxygen consumption, respectively, which were then sustained for the last 6 weeks.
- Training frequency was 3 times per week, and all of the training was performed on cycle ergometers.

- What does this mean?

STRENGTH TRAINING FOR WEIGHTLOSS

Strength training promotes muscle gain with increases calorie burn and promotes weightloss

BUT

IT DOES NOT WORK FOR EVERYONE. WHY??

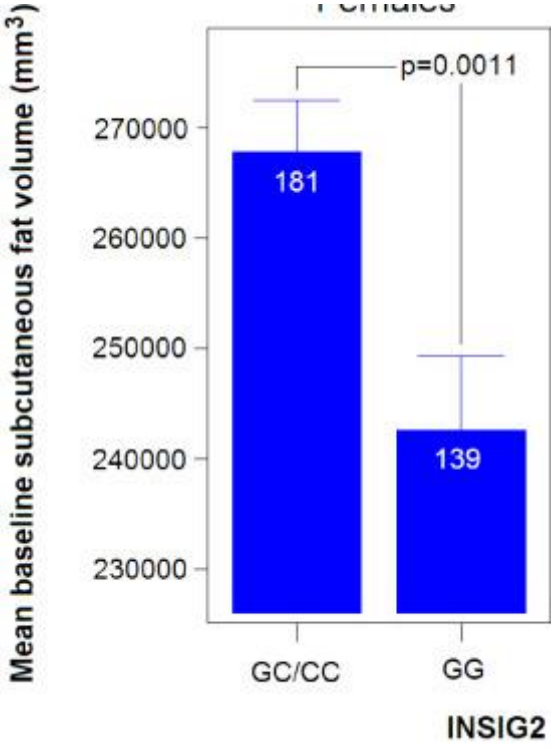
INSIG2 – A gene that plays a role in weightloss and obesity. Loss of INSIG2 function promotes cholesterol buildup and fat gain.

Found in ER, regulated by insulin.

Regulates adipogenesis

STRENGTH TRAINING FOR WEIGHTLOSS

Impaired INSIG2 activity correlates with fat gain



Individuals with C allele of INSIG2 gain subcutaneous fat with strength training

WHAT DOES THIS MEAN?

If you have the C allele of INSIG2, strength training will lead to fat gain and will not assist with weightloss

IF CARRYING VARIANT…

- Endurance focussed workout
- 70% Cardio Exercises – Elliptical, Running, Cycling, Jogging, Swimming
- 30% Strength exercises
- Strength training – focus on lower weights and increased number of reps to build endurance

IMPACT OF ENDURANCE AEROBIC TRAINING

- Endurance training – cardio
- Improved cardiovascular function
- Weightloss and calorie burn
- Reduced risk of diabetes and metabolic disorders
- Although everyone benefits from endurance training, a segment of population is likely to benefit even strongly with endurance training

Adaptations to Aerobic Training: Cardiorespiratory Endurance

- Cardiorespiratory endurance
  - Ability to sustain prolonged, dynamic exercise
  - Improvements achieved through multisystem adaptations (cardiovascular, respiratory, muscle, metabolic)
- Endurance training
  - ↑ Maximal endurance capacity = ↑ VO_{2max}
  - ↑ Submaximal endurance capacity
    - Lower HR at same submaximal exercise intensity
    - More related to competitive endurance performance

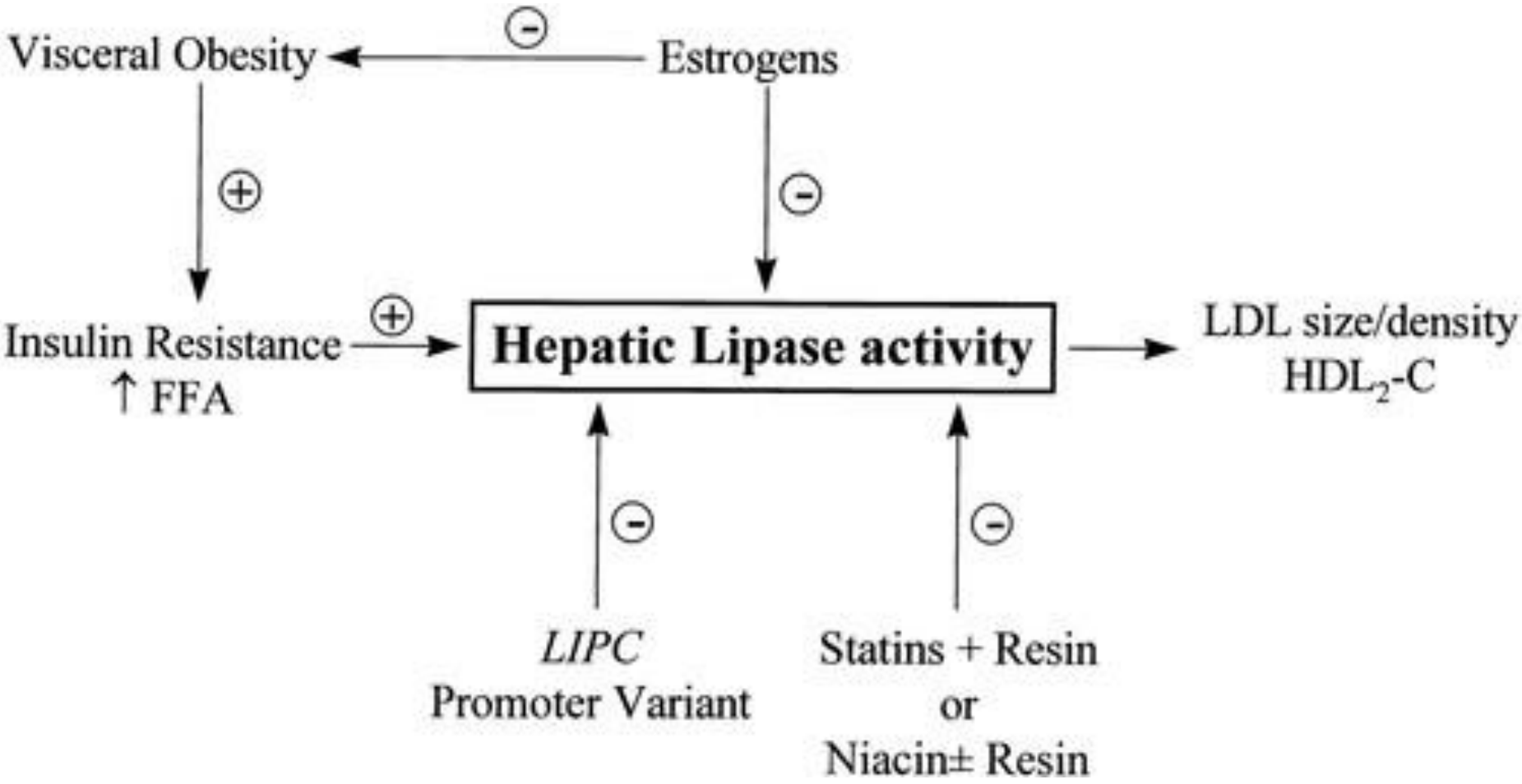
Adaptations to Aerobic Training: Major Cardiovascular Changes

- Heart size – heart adapts to increased blood volume
- Stroke volume – blood pumped by LV in one contraction
- Heart rate
- Cardiac output
- Blood flow
- Blood pressure
- Blood volume
- Cholesterol – HDL increase and LDL decrease - Genetics

LIPC AND FITNESS

- Hepatic lipase is a key rate-limiting enzyme in lipid and lipoprotein metabolism that is modified by exercise
- Hepatic lipase catalyzes the hydrolysis of triacylglycerols and phospholipids of lipoprotein particles - LDLs
- Overall, hepatic lipase activity decreases with exercise; however, there is heterogeneity in this response, with some subjects showing no significant changes in hepatic lipase activity with exercise (underlying genetics)
- Hepatic lipase activity is increased by androgens and decreased by estrogens, which may account for higher concentrations of HDL2 in women.

LIPC AND FITNESS



LIPC AND FITNESS

	Baseline Values				Response to Exercise Training			
		LIPC genotype				*LIPC* genotype		
Characteristic	Overall* ($n = 76$)	CC ($n = 51$)	CT ($n = 25$)	*P*	Overall* ($n = 76$)	CC ($n = 51$)	CT ($n = 25$)	*P*
VLDL-TG, mg/dl	112 ± 7	115 ± 8	105 ± 12		−14 ± 6%*	−22 ± 6%§	7 ± 12%	0.05
Large VLDL, nmol/l	5 ± 0.6	6 ± 0.7	5 ± 0.9		−30 ± 13%†	−40 ± 12%‡	−3 ± 33%	
Med. VLDL, nmol/l	32 ± 2.0	32 ± 2.3	32 ± 3.8		−19 ± 6%‡	−29 ± 7%§	8 ± 10%	0.01
Small VLDL, nmol/l	44 ± 2.1	41 ± 2.5	48 ± 3.6		5 ± 5%	4 ± 5%	7 ± 11%	
Total VLDL, nmol/l	79 ± 3	78 ± 3	80 ± 6		−3 ± 4%	−9 ± 4%*	10 ± 8%	0.03
VLDL size, nm	51 ± 1.3	53 ± 1.7	48 ± 1.5	(0.09)	−5 ± 1.8%†	−6 ± 2.2%†	−1 ± 3.0%	

- LIPC -514C>T
- C allele carriers preferentially respond to vigorous training by reductions in LDL levels

LIPC AND FITNESS

- LIPC-480 TT genotype (variant found in protein region) predicted an increase in CHD (Coronary Heart Disease) for subjects who participated in normal levels of physical activity, but this increase was not found for subjects with the high-risk genotype who took part in vigorous physical activity.

- Activities considered strenuous—those that caused fatigue, increased heart rate, or sweating for 20 minutes three times a week

- Mutations carrier have reduced coronary flow reserve (increase in exercise induced blood flow to coronary arteries) and exercise may increase it decreasing tri-glyceride-rich remnant lipoproteins that alter endothelial function

LPL AND FITNESS

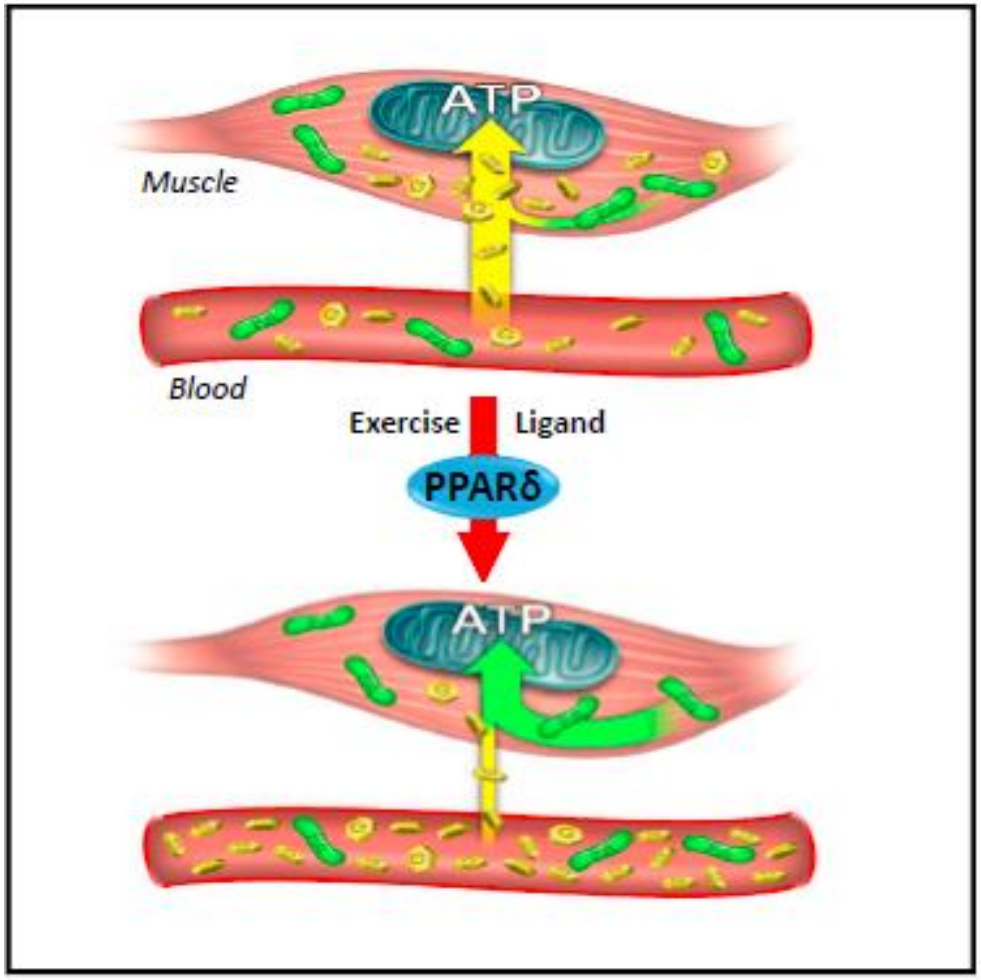
- It is a water-soluble lipase enzyme that hydrolyzes triglycerides in lipoproteins, such as those found in chylomicrons and very low-density lipoproteins (VLDL), into two free fatty acids and one monoacylglycerol molecule (breaks down LDL)
- Mutations that cause familial lipoprotein lipase deficiency reduce or eliminate lipoprotein lipase activity, which prevents the enzyme from effectively breaking down triglycerides in the bloodstream. As a result, triglycerides attached to lipoproteins accumulate in the blood and tissues, leading to inflammation of the pancreas (pancreatitis), enlarged liver and spleen (hepatosplenomegaly), fatty deposits in the skin (eruptive xanthomas), and the other signs and symptoms of familial lipoprotein lipase deficiency.
- Mutations in LPL also affect response to exercise

LPL AND FITNESS

- LPL gain of mutation – CC allele associated with increased LPL activity - LPL-S447X
- Mutation associated with increased transcription of LPL, which decreases susceptibility to translation inhibition -> more LPL activity
- Mutation associated with greater response to endurance activities

	Noncarriers of the X447	Carriers of the X447	P
ΔBMI, kg/m^2	0.016 ± 0.056 (205)	−0.33 ± 0.12 (44)	0.01
ΔFat mass, kg	−0.47 ± 0.12 (197)	−1.2 ± 0.3 (40)	0.01
ΔFat-free mass, kg	0.41 ± 0.08 (197)	0.45 ± 0.18 (40)	0.84
Δ%Body fat	−0.65 ± 0.13 (197)	−1.4 ± 0.3 (40)	0.03

PPARD AND FITNESS

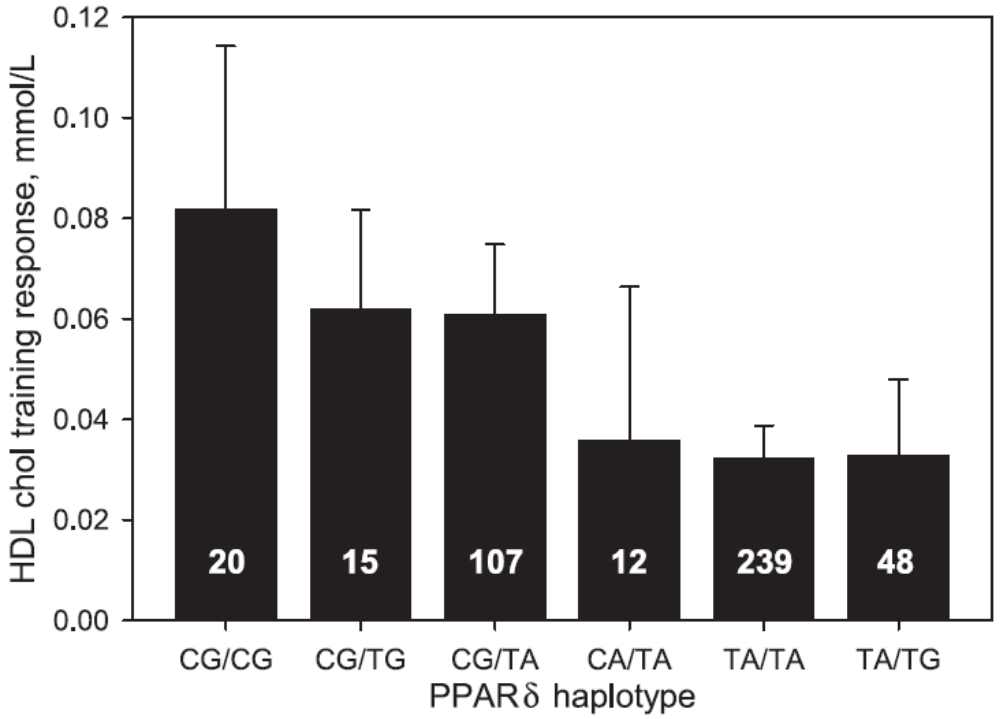


This gene encodes a member of the peroxisome proliferator-activated receptor (PPAR) family. The encoded protein is thought to function as an integrator of transcriptional repression and nuclear receptor signaling.

- Exhaustion of systemic glucose limits endurance exercise
- PPARδ regulates substrate utilization without mitochondrial biogenesis
- PPARδ represses glycolytic genes in muscle to slow glucose consumption
- Glucose sparing by PPARδ dramatically extends running time

PPARD AND FITNESS

- C variant associated with endurance
- C variant – associated with significantly greater increase in HDL with endurance exercises, corresponding to improvement in cardiovascular health

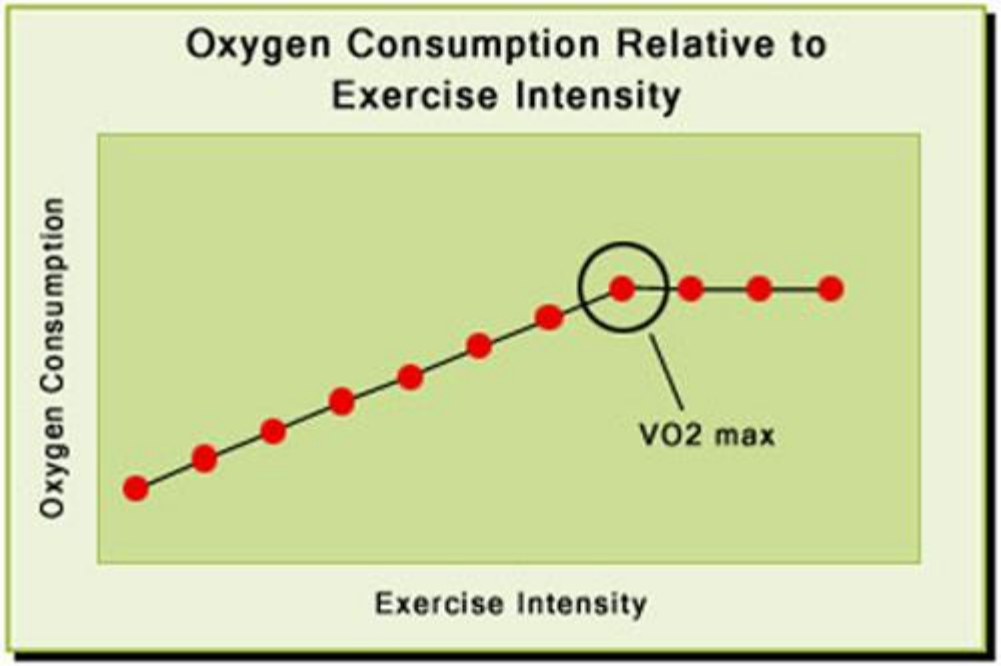


IF CARRYING VARIANT…

- Endurance exercises will expedite weightloss, improve overall cardiovascular fitness
- Walking briskly.
- Running / jogging.
- Dancing.
- Swimming.
- Biking.
- Climbing stairs at work.
- Playing sports such as tennis, basketball, soccer or racquetball.
- High Intensity Interval Training

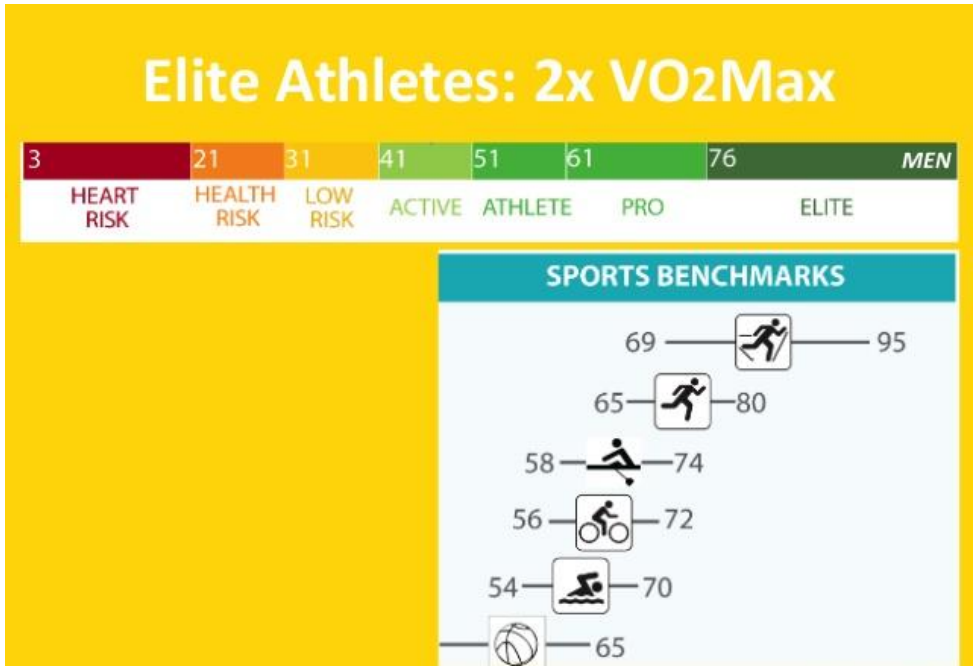
ENDURANCE TRAINING POTENTIAL

- VO2 max, also known as maximal oxygen uptake, is the measurement of the maximum amount of oxygen a person can utilize during intense exercise. It is a common measurement used to establish the aerobic endurance of an athlete prior to or during the course of training



ENDURANCE TRAINING POTENTIAL

- Increased VO2 max -> increased athletic potential
- Dependent on genetic factors



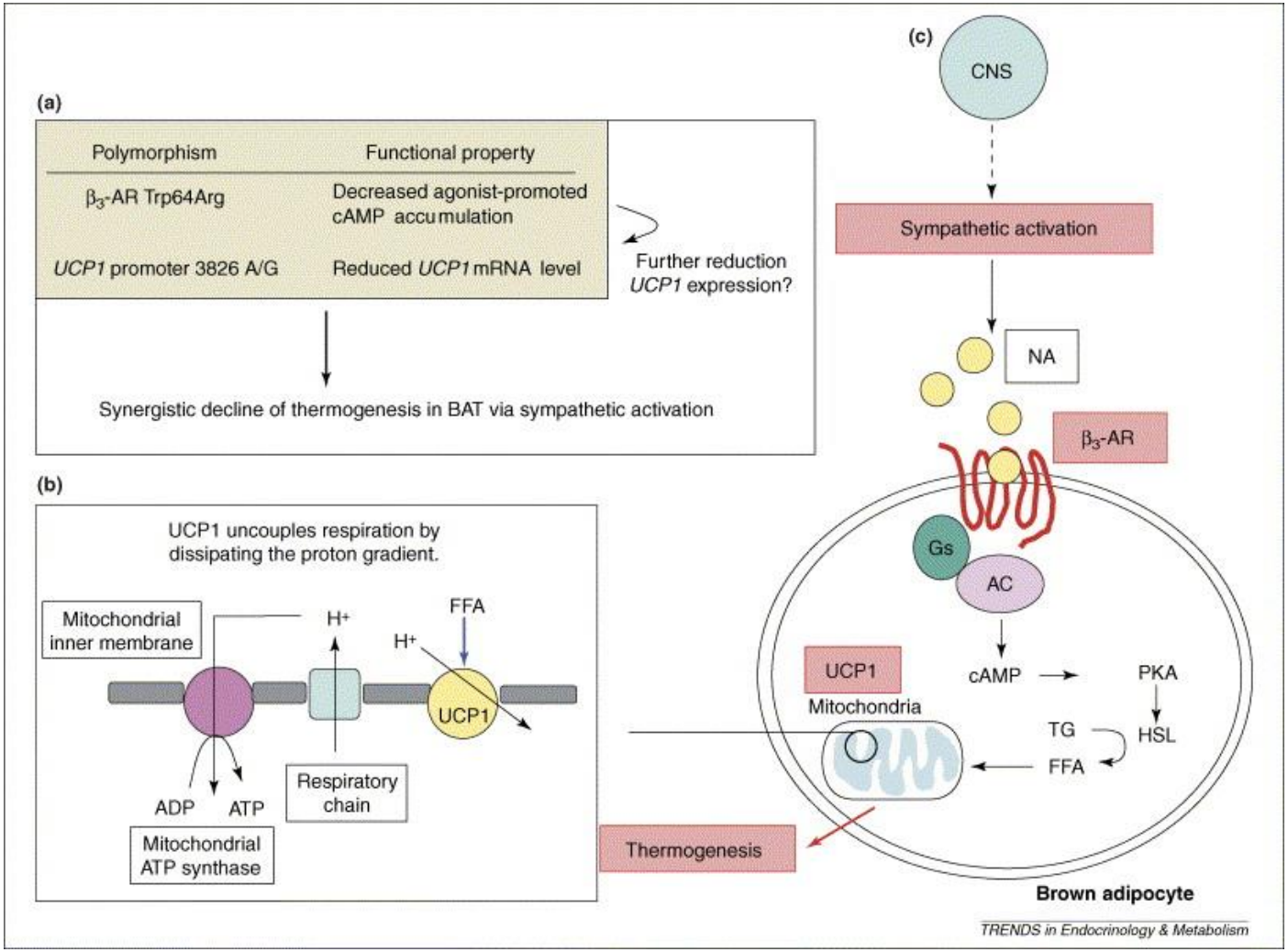
ADRB3 ENDURANCE TRAINING

- Encodes for beta-adrenergic 3 receptor
- Functions in lipolysis and thermogenesis in skeletal muscle

- C allele associates with elite endurance performance (p=0.0008)

- study: elite Spanish athletes for endurance or strength sports
- TT genotype: no association in endurance or strength vs controls
- TC genotype: association in endurance vs controls but not strength vs controls
- CC genotype: very rare; association in strength vs controls

ADRB3 AND ENDURANCE



- Same variant associated with cardiovascular issues and obesity
- The mechanism of how it contributes to athletic performance not completely understood
- Thermogenesis regulation?

OXIDATIVE STRESS AND EXERCISE

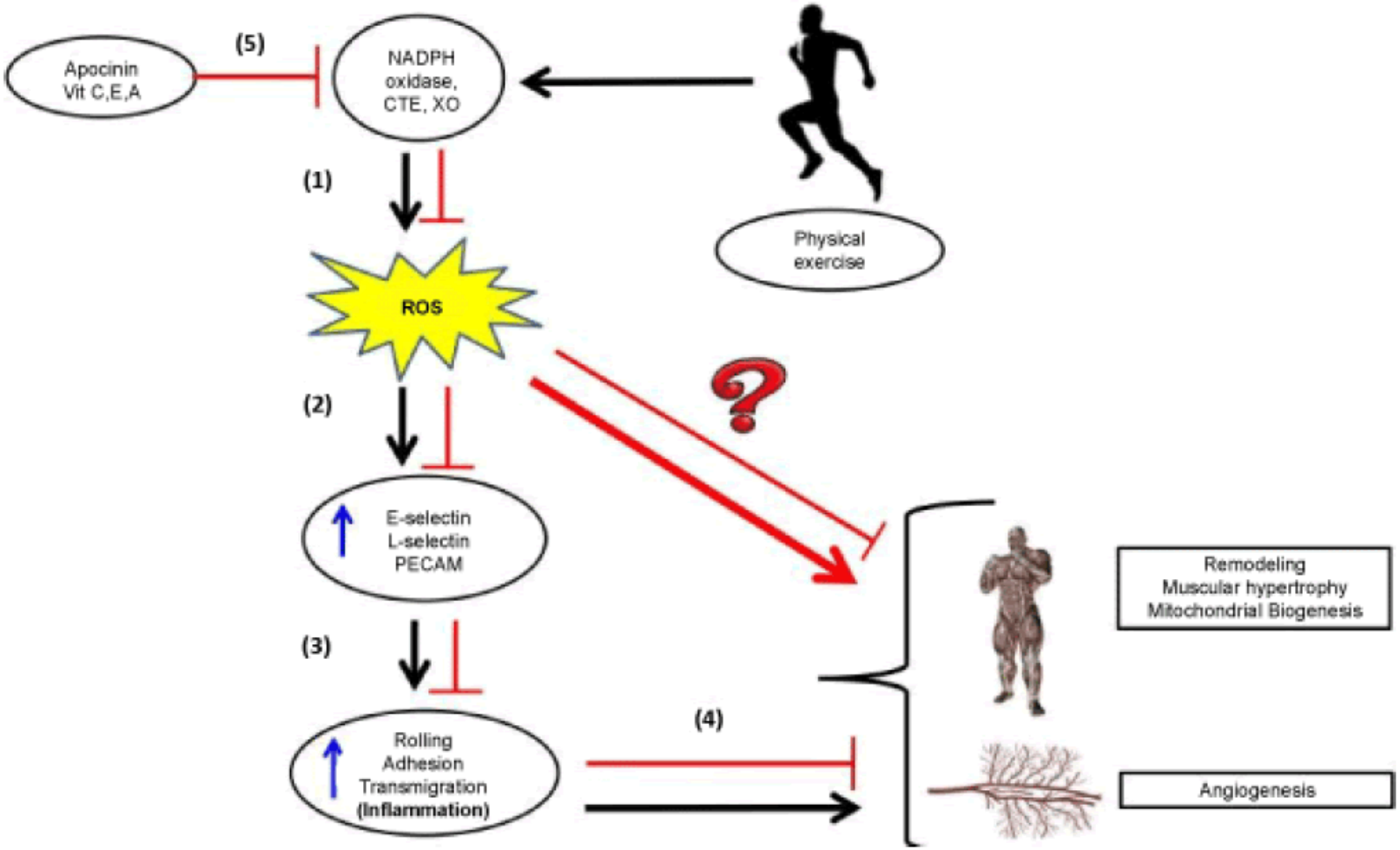
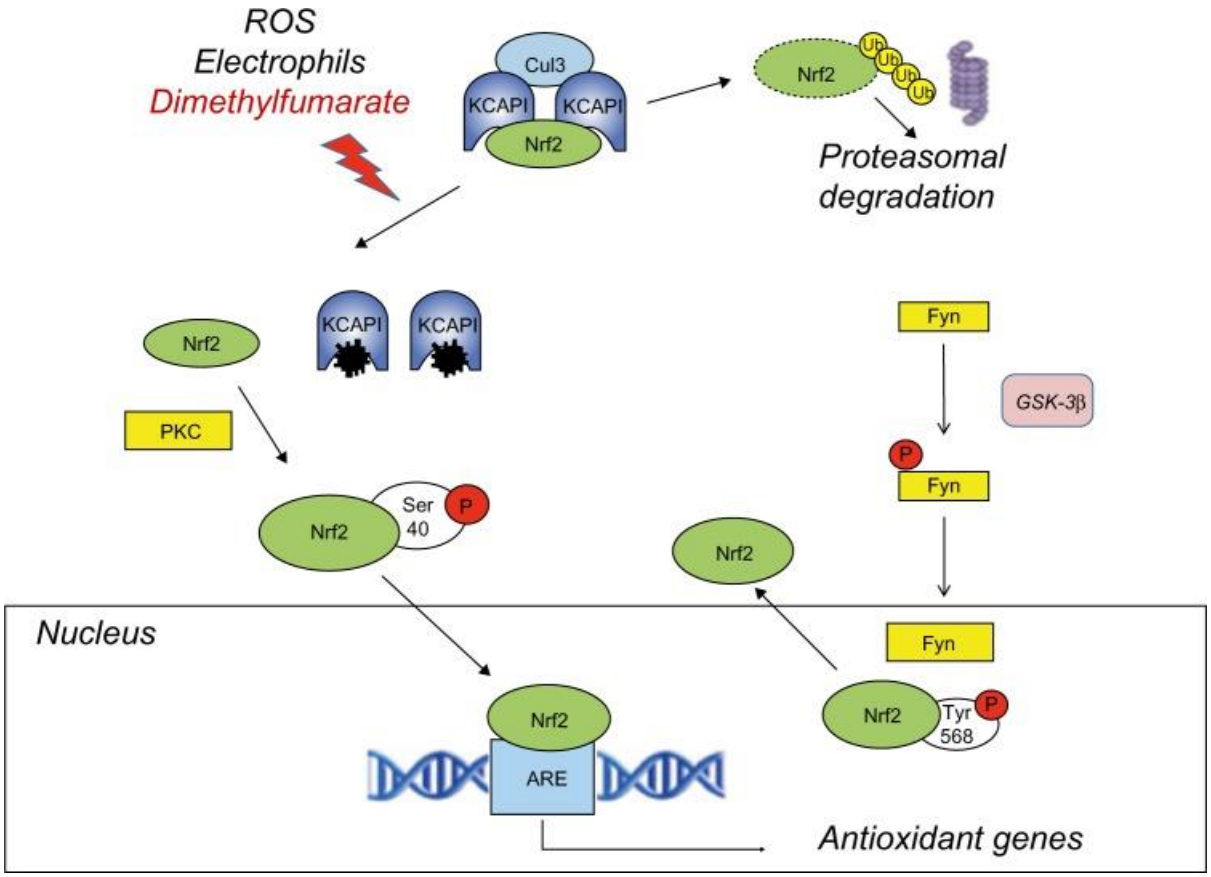


Figure 1: Interaction between exercise, oxidative stress and skeletal muscle adaptive response.

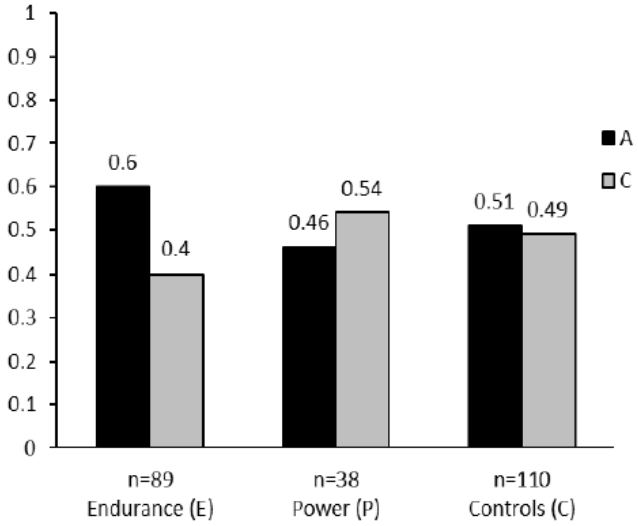
NRF2 ENDURANCE TRAINING

- Nrf2 is a basic leucine zipper (bZIP) protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation.
- Several drugs that stimulate the NFE2L2 pathway are being studied for treatment of diseases that are caused by oxidative stress.



NRF2 ENDURANCE

- NRF2 – A variant preferentially associated with endurance athletes
- Runners, cyclists and rowers
- Reduced muscle damage
- Increased VO2 max



Endurance vs. Power: χ^2=3.72, *P*=0.054

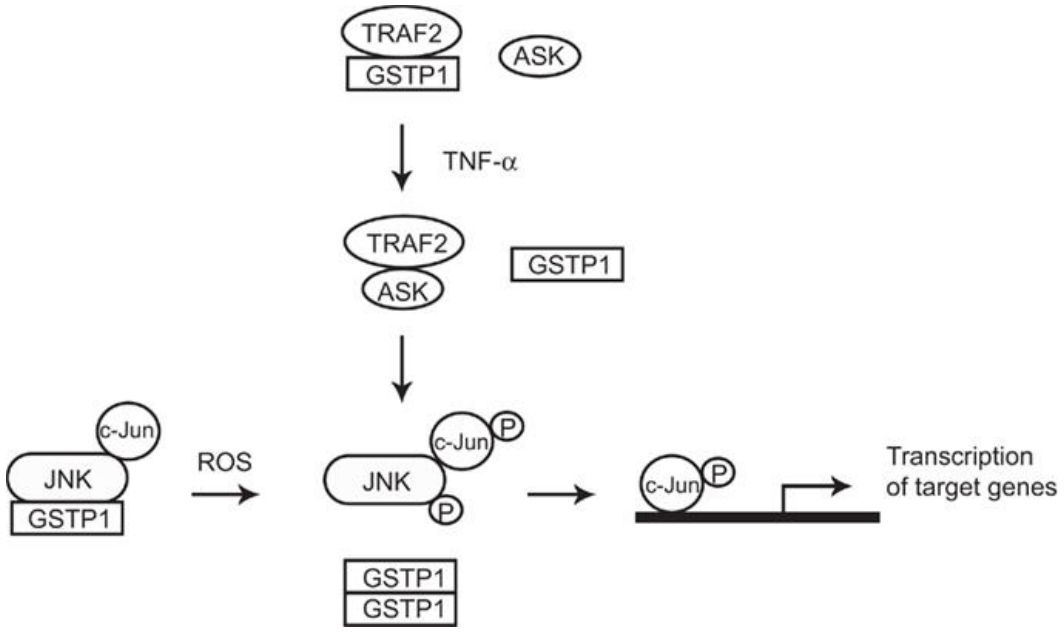
Endurance vs. Controls: χ^2=3.001, *P*=0.08

Power vs. Controls: χ^2=0.36, *P*=0.5

	Athlete groups	n	AA	AC	CC
rs12594956					
NRF-2 A/C	Endurance (E)	89	43 (48)	21 (24)	25 (28)
	Power (P)	38	5 (13)	25 (66)	8 (21)
	Controls (C)	110	23 (21)	66 (60)	21 (19)

GSTP1 ENDURANCE TRAINING

- GSTP1 encodes for glutathione S-transferase P1
- Glutathione S-transferases (GSTs) are a family of phase II enzymes which play crucial roles in cellular protection against oxidative stress by exhibiting detoxification and reactive oxygen species (ROS) scavenging activities
- Modulates signal transduction



GSTP1 ENDURANCE

- GG allele associated with increased VO2 max in response to endurance exercises

	Pre-test		Post-test		Time (training) effect	Interaction time*genotype effect		
	AA	GG + AG	AA	GG + AG	Alpha level	Alpha level	η^2	Observedpower
Body mass (kg)	60.6 ± 6.2	60.6 ± 7.4	59.8 ± 6.1	60.4 ± 7.5	p = 0.007	p = 0.075	0.05	0.43
Fat-free mass (kg)	45.4 ± 2.5	45.4 ± 2.8	45.3 ± 2.5	45.9 ± 2.7	p = 0.162	p = 0.042	0.07	0.53
BMI	21.8 ± 2.1	21.7 ± 3.0	21.5 ± 2.0	21.7 ± 3.0	p = 0.013	p = 0.162	0.03	0.29
VO_{2max}(ml·min^{-1})	1977 ± 247	2086 ± 256	2027 ± 293	2271 ± 323	p < 0.001	p = 0.029	0.06	0.60
VO_{2max}(ml·kg-1·min^{-1})	32.7 ± 3.6	34.7 ± 4.3	34.1 ± 5	38.2 ± 5.2	p < 0.001	p = 0.026	0.06	0.61
VE_{max}(l·min^{-1})	76.9 ± 14.6	76.5 ± 16.7	77.1 ± 15.6	86.5 ± 12	p = 0.005	p = 0.007	0.10	0.79
VO_2/AT (ml·kg-1·min^{-1})	25.2 ± 3.3	26.9 ± 3.8	26.4 ± 3.9	27.8 ± 3.5	p = 0.053	p = 0.819	<0.001	0.06
HR_{max}(beats·min^{-1})	189.9 ± 8	188.2 ± 7.9	188.4 ± 8.1	189.9 ± 7.2	p = 0.940	p = 0.026	0.08	0.61

Note: BMI – body mass index; VO_{2max} – maximum oxygen uptake; V_{Emax} – maximum minute ventilation; HR_{max} – maximum heart rate; VO_2/AT (m
– percentage of VO_{2max} at anaerobic threshold, η^2 = effect size

GSTP1 ENDURANCE

- First, the A to G substitution at position 313 has been shown to be functional, and results in a miscoded GSTP1 protein.
- The Val105 variant (G allele) with lower enzymatic activity represents impaired GSTP1 functions in catalytic reactions to remove excessive ROS, which may be beneficial for exercise.
- Second, aerobic exercise-induced reactive oxygen radicals are recognized as an important regulator of the adaptations in skeletal muscles in response to aerobic exercise by triggering or affecting many cell signalling pathways
- Muscle adaptation in presence of lower GSTP1 activity

NFIA-AS2 AND ENDURANCE

- NFIA-AS2 encodes for NFIA antisense RNA -2
- NFIA-AS2 is involved in the regulation of expression of the nuclear factor IA (NFIA) gene or erythroid/myeloid-specific RNAs.
- NFIA, as a transcription factor, induces erythropoiesis, whereas its silencing drives granulopoiesis.
- NFIA-AS2 is a silencer of NFIA

NFIA-AS2 AND ENDURANCE

- G allele was associated with activation of erythropoiesis (high level of haemoglobin), high number of reticulocytes and erythrocytes)
- A allele was associated with activated granulopoiesis (high number of neutrophils and greater leucocyte/erythrocyte ratio)
- NFIA-AS2 G allele was associated with increased VO2 max levels by 24.6-48.85 increase in VO2 max levels, and was presented in almost 96% of the elite endurance athletes
- G allele – reduced repression of NFIA – promoting erythropoiesis

IF SOMEONE HAS INCREASED POTENTIAL….

- Increased predisposition to a greater VO2 max
- Increased performance ability in aerobic/endurance activities
- Fitness program geared towards sustaining VO2 max
- High Intensity Interval training

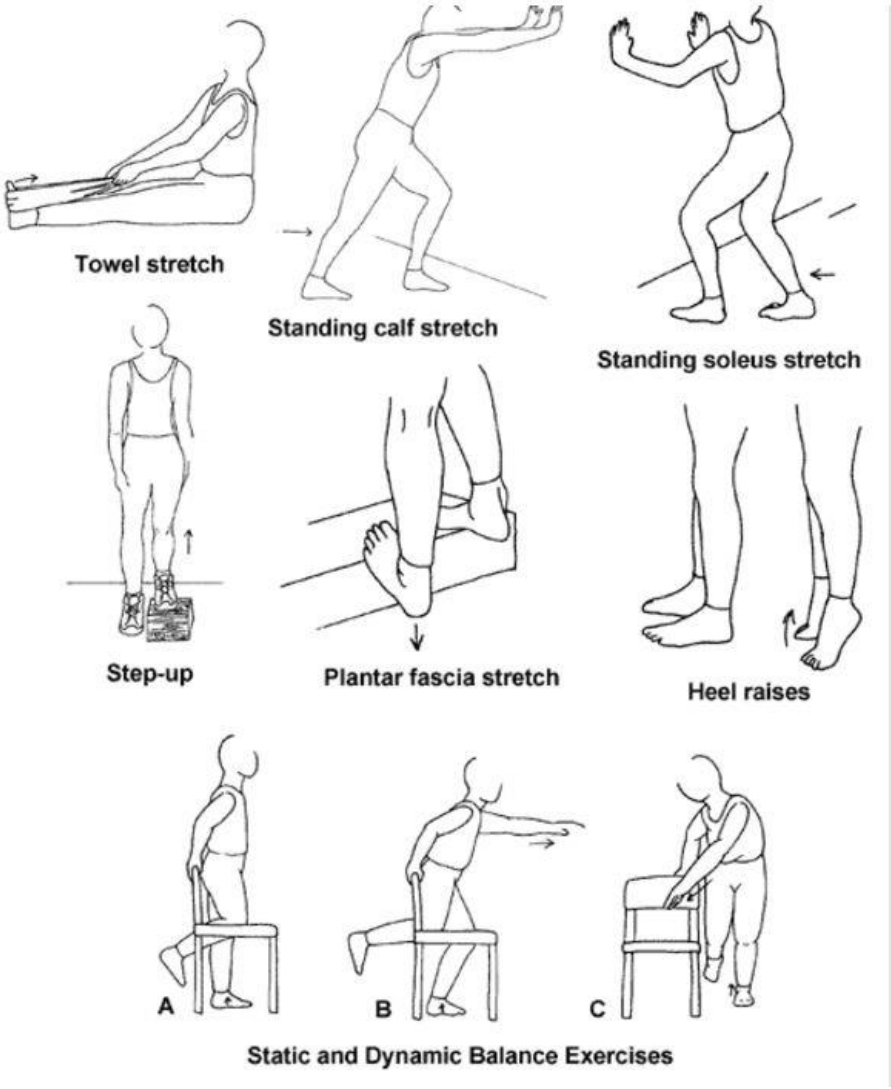
COL5A1 AND INJURY

- The COL5A1 gene provides instructions for making a component of type V collagen. Collagens are a family of proteins that strengthen and support many tissues in the body, including skin, ligaments, bones, tendons, and muscles.
- A component of type V collagen called the pro-α1(V) chain is produced from the COL5A1 gene. Collagens begin as rope-like procollagen molecules that are each made up of three chains. Two combinations of chains can produce type V collagen: three pro-α1(V) chains or two pro-α1(V) chains and one pro-α2(V) chain (which is produced from the COL5A2 gene).
- Mutations associated with:
  - Carpal Tunnel Syndrome
  - Ehlers – Danlos syndrome – stretchy skinning, scarring, hypermobility, abnormal collagen and tissue weakening
  - Keratoconus – gradual thinning of the cornea

COL5A1 TT GENOTYPE

- COL5A1 TT Variant associated with increased risk of soft musculoskeletal injuries
- Variant likely impacts the structural integrity of COL5A1 which impacts Collagen V
- Tennis Elbow
- ACL injury (ACL stabilized knee joint)
- Achilles Tendon Pathology

WHAT TO DO IF AT RISK?



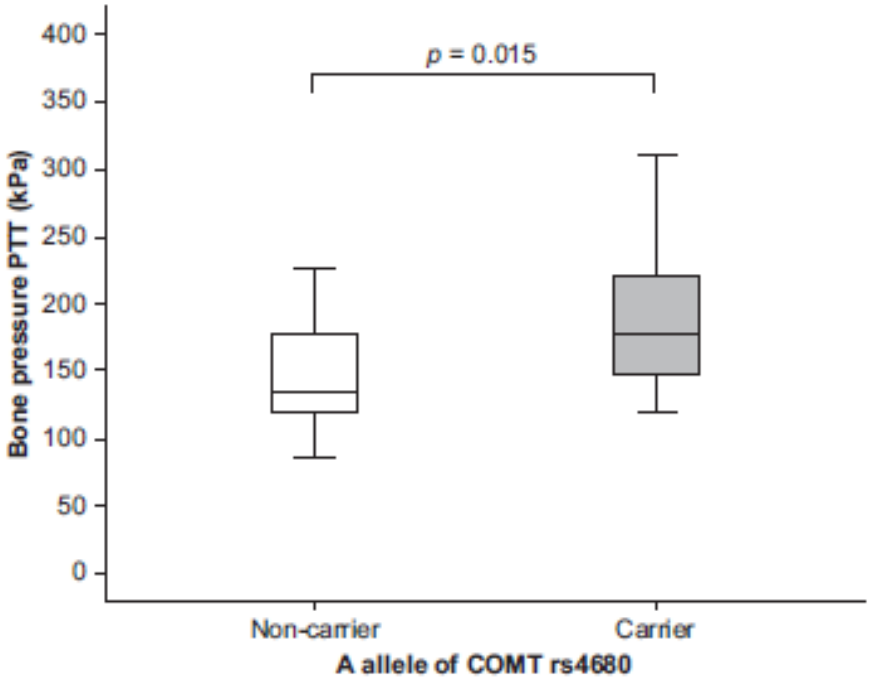
COMT AND PAIN TOLERANCE

- Catechol-O-methyltransferase (COMT) is an enzyme that inactivates biologically-active catechols, including the important neurotransmitters dopamine, noradrenaline and adrenaline.
- These neurotransmitters are involved in numerous physiological processes, including modulation of pain.
- Genetic variation in the COMT gene has been implicated in variable response to various experimental painful stimuli, variable susceptibility to develop common pain conditions, as well as the variable need for opioids in the treatment of cancer pain.

COMT AND PAIN TOLERANCE

- Dopamine is often known as the brain's "pleasure chemical", because of its role in transmitting signals related to pleasurable experiences.
- When the dopamine system is highly active, the brain reduces its production of other chemicals: the endogenous opioids, or so-called enkephalins – suppress pain.
- Highly active COMT – faster dopamine breakdown– increased enkephalins production – better pain tolerance
- Reduced COMT – poor dopamine breakdown – less enkephalins production – poor pain tolerance

COMT AND PAIN TOLERANCE



- A allele carriers – reported higher bone pressure ie less pain tolerance
- T allele - Met, lower COMT enzymatic activity, therefore higher dopamine levels; lower pain threshold.
- G allele- Val, higher COMT enzymatic activity, therefore lower dopamine levels; higher enkephalins, higher pain threshold

GENETICS AND MUSCLE BIOLOGY

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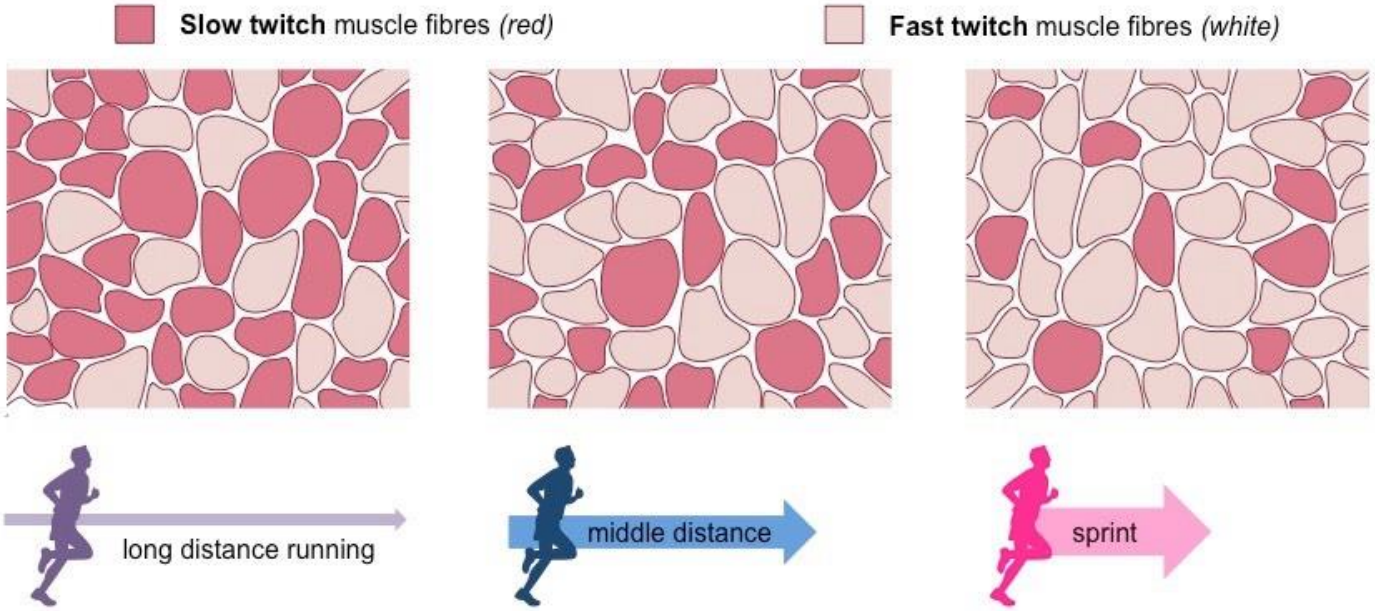
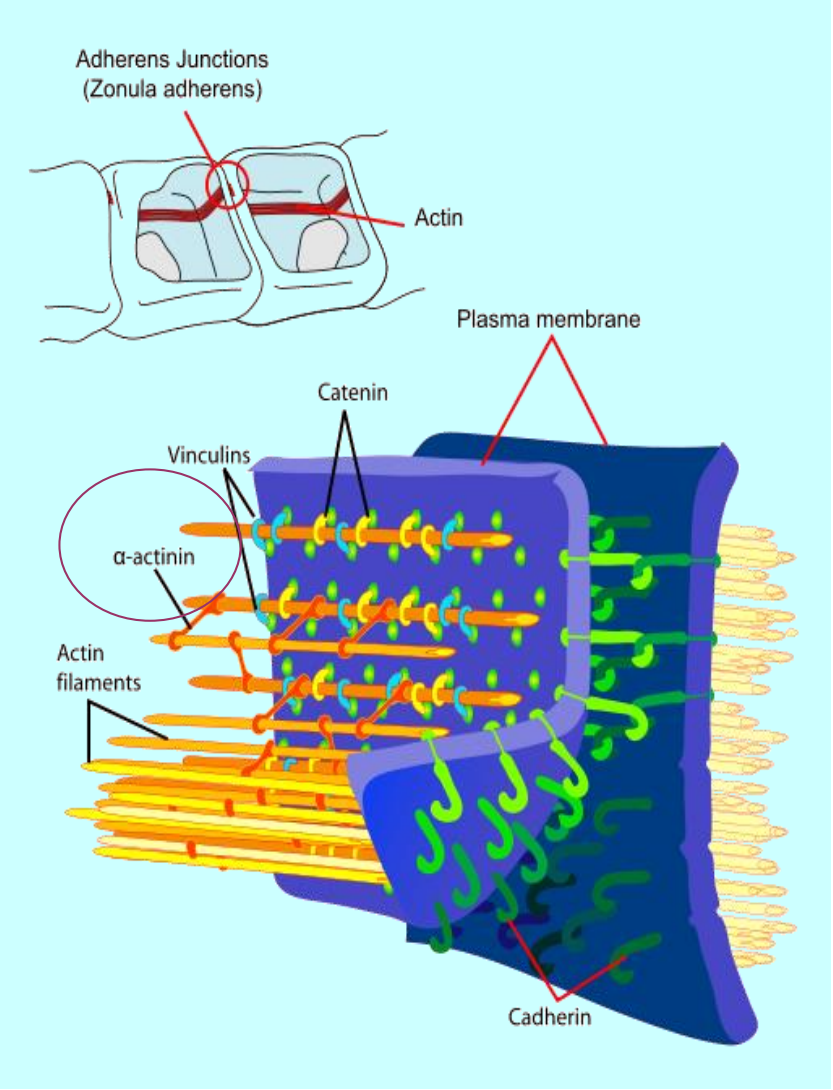
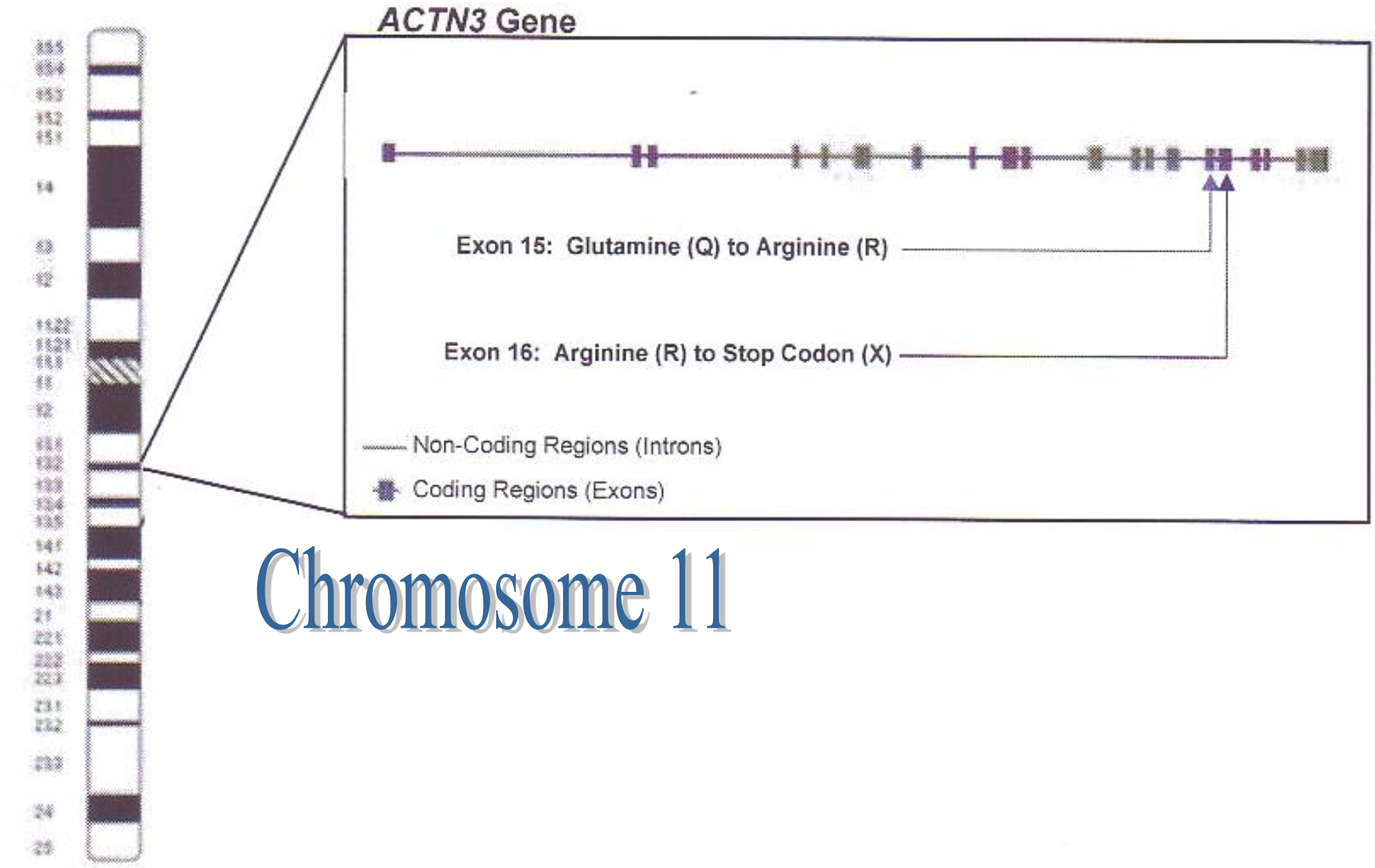


MUSCLE FIBERS FACE OFF	
SLOW TWITCH	**FAST TWITCH**
Efficient in using oxygen	Do not burn oxygen to create energy
Delayed muscle firing	Fast to fire; best for explosive body movements
Do **not** fatigue easily	Tire out quickly
Best suited for: endurance sports, including cycling, marathon running and long-distance triathlons!	**Best suited for:** short bursts of activity, including sprinting races, pole vaulting and cross fit-style events

ACTN3 Gene and Actinin

- ACTN Gene
  encode forming of actin binding proteins = Actinins
- Actinins
  stabilize Actin filaments = stronger contractions
- Two main types of
  ACTN gene: ACTN2 and ACTN3
  Actinins: type 2 and 3
- ACTN2 is expressed in
  all muscle fibers
- ACTN3 is only in
  fast twitch fibers.





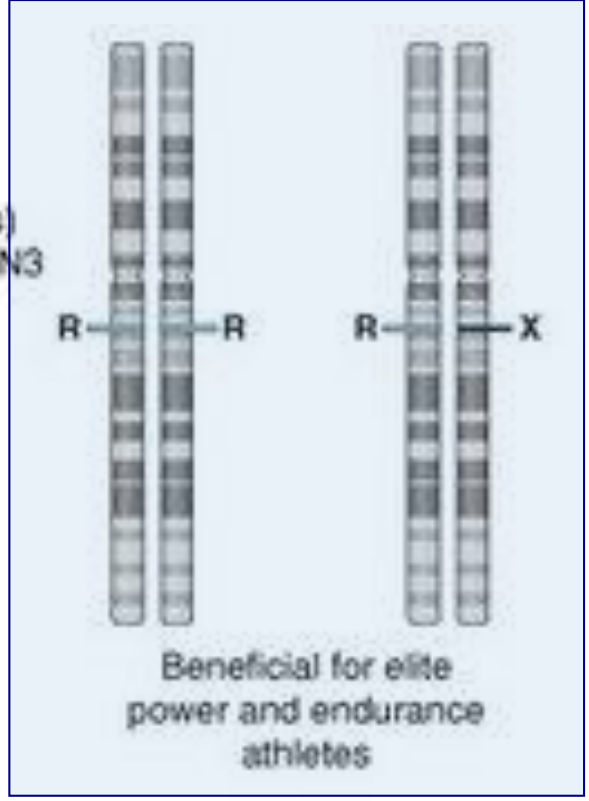
Chromosome 11

Chromosome 11

Research suggests that elite athletes who rely on the power of fast-twitch fibers in their muscles, like sprinters, share a common genotype. These fibers contain a protein produced by the R allele (version) of the ACTN3 gene.

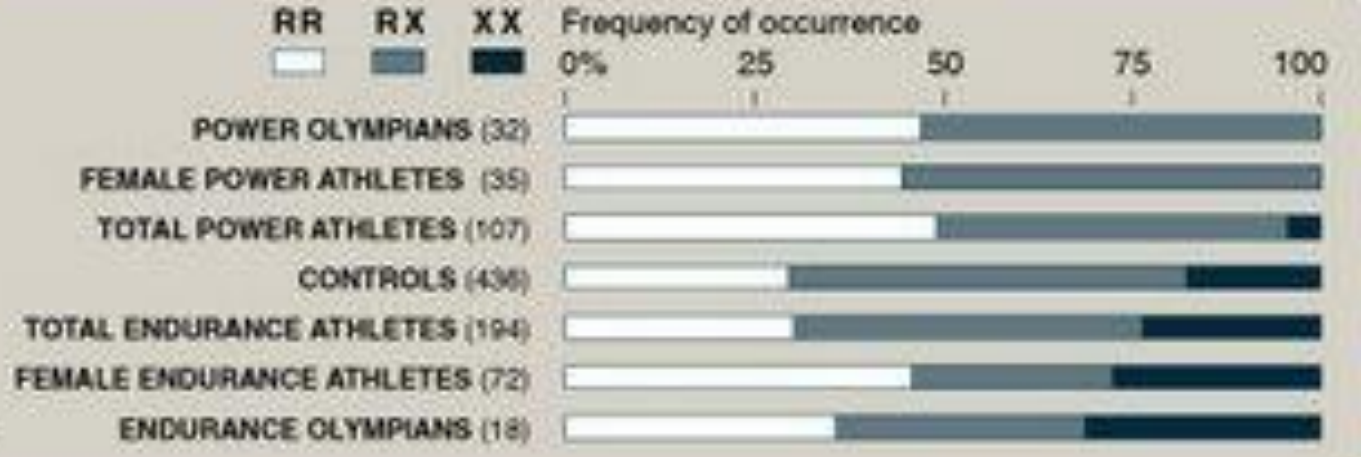
ACTN3

Possible variations (genotypes) of the ACTN3 gene.



Genotype frequency among elite power/sprint athletes and elite endurance athletes.

Confidence intervals are 95%.



Sources: Stephen M. Roth, Ph.D., University of Maryland; American Journal of Human Genetics

ACE GENE AND MUSCLE BIOLOGY

- The ACE gene provides instructions for making a protein called angiotensin-converting enzyme, which converts a hormone called angiotensin I to another form called angiotensin II.
- Angiotensin regulates function/biology of skeletal muscles
- 2 variants – I and D
- DD – associated with increased fast twitch fibers and highest levels of the enzyme ie gain of function

EXERCISE GENETICS

- Develop fitness plan / strategy to maximize benefit
- Develop fitness plan to maximize potential
- Dietary plan in accordance with dietary genetics
- Weightloss planning using dietary and fitness genetics

Genetics of Metabolic Diseases

- Genetics of diabetes
- Genetics behind cholesterol levels, cardiovascular health

DIABETES AND GENETICS

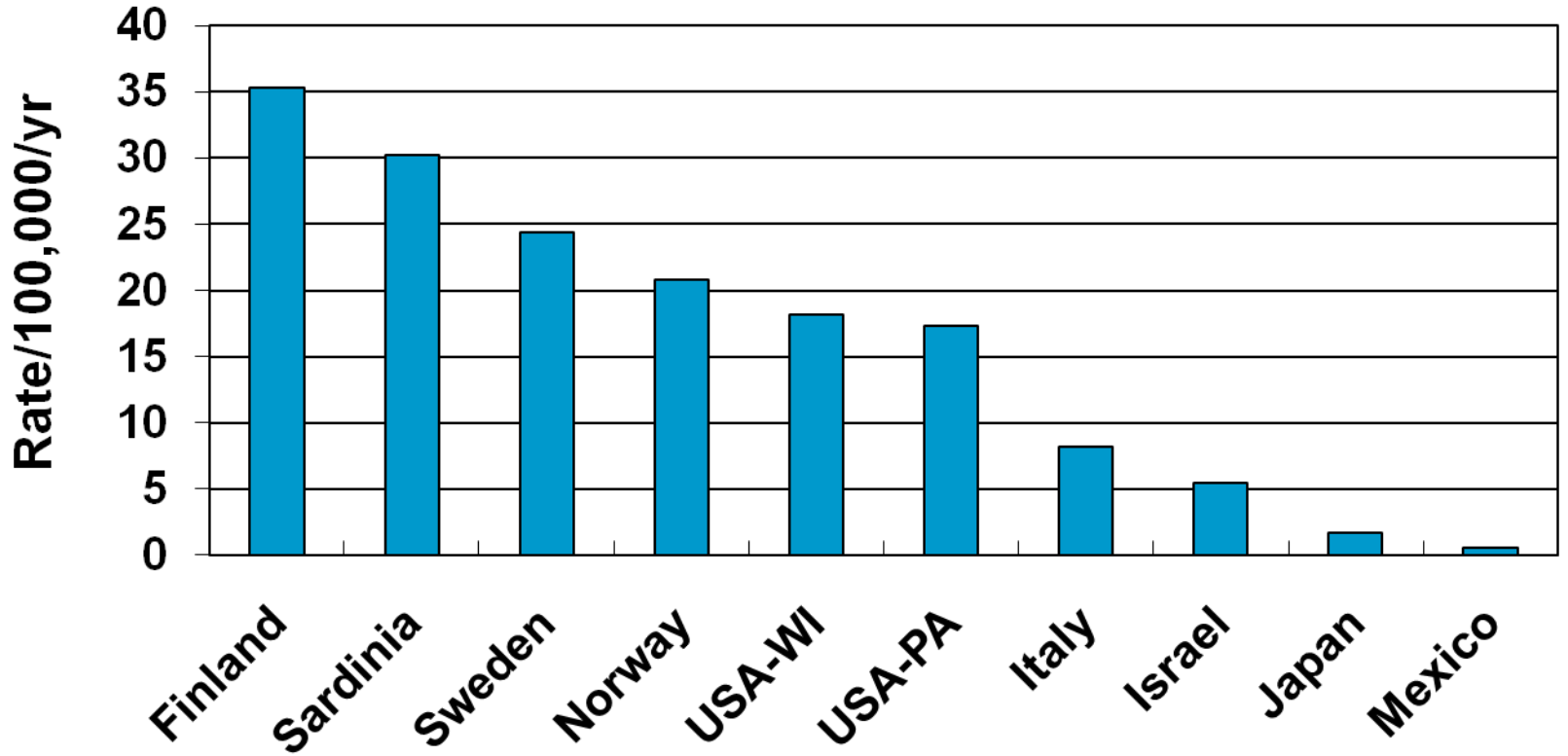
Type 1 Diabetes

- Caused by the destruction of the pancreatic beta cells
  - Insulin is no longer produced
  - Leads to hyperglycemia, ketoacidosis (very high ketone levels) and potentially death if not treated with insulin
  - 25 – 30 million people worldwide
  - Also called juvenile onset diabetes, insulin dependent diabetes
  - Type 1 A – immunogenic, Type 2A – secondary complication to other disease eg CF / toxins
- Treatment goals for T1D
  - Maintaining near normal levels of blood glucose
  - Avoidance of long-term complications

Type 1 Diabetes

- 2nd most common chronic childhood disease
- Peak age at onset is around puberty
  - But T1D can occur at any age
- Incidence is increasing worldwide by ~3% per year
  - Related to increase in T2D?

T1D Incidence Worldwide



Importance of Environmental Risk Factors in T1D

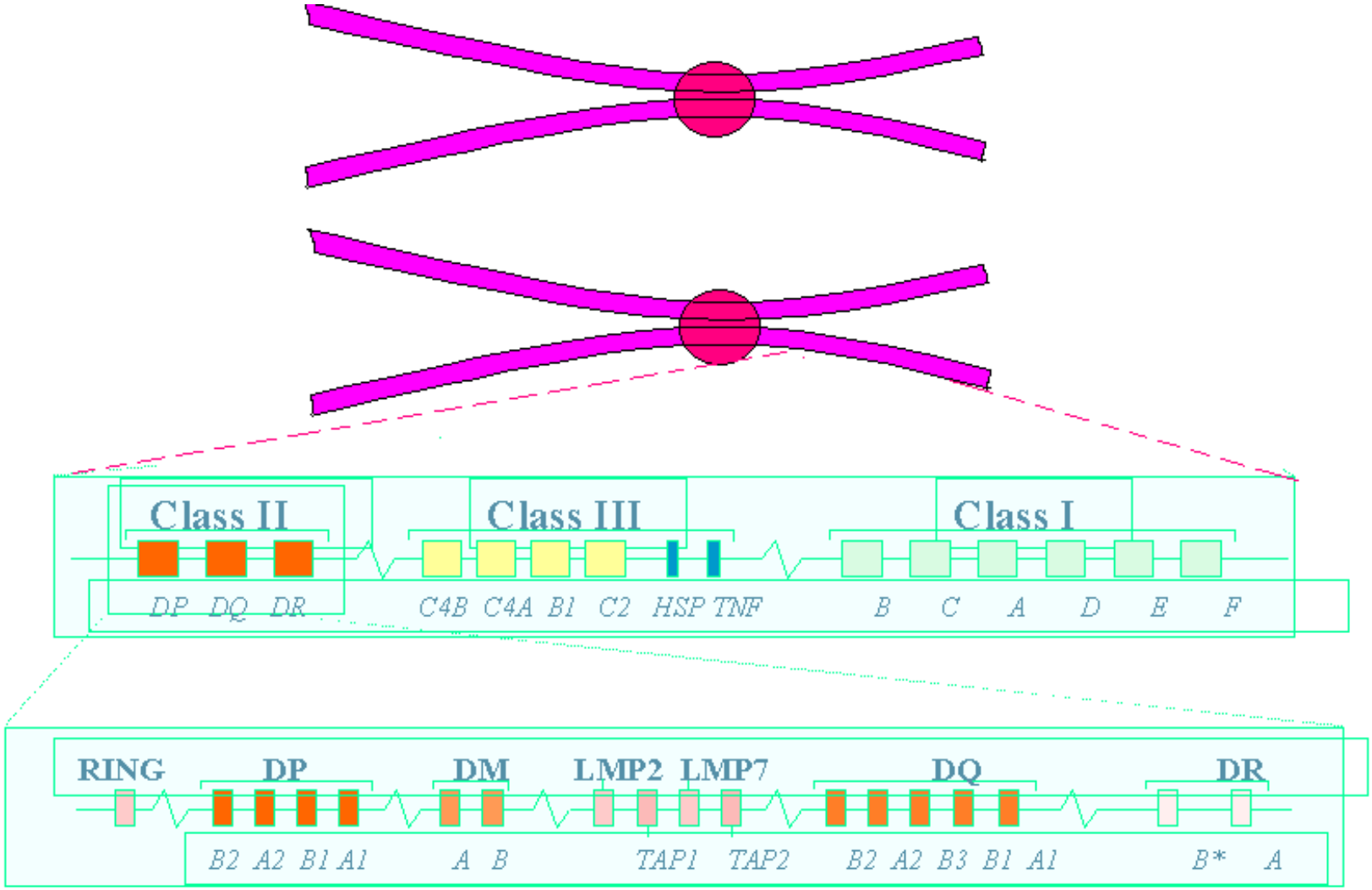
- Seasonality at diagnosis – mainly winter such as flu
- Migrants assume risk of host country – epigenetics and environment (particularly in children)
- Risk factors from case-control studies
  - Infant/childhood diet – breast milk protective, cow milk is not
  - Viruses – exposures as early as in utero - enteroviruses
  - Hormones – peak onset at puberty
  - Stress
  - Improved hygiene – hygiene hypothesis
  - Vitamin D

Importance of Genetic Risk Factors in T1D

- Concordance in identical twins greater in MZ versus DZ twins – approximately 50% concordance

- 15-fold increased risk for 1st degree relatives (eg siblings)
  - Risk is ~6% through age 30 years
  - Risk increases in presence of susceptibility genes
  - Risk greater if father has type 1D – genetic imprinting?
  - Insulin gene – maternally imprinted

MHC Region – Chromosome 6p21



Predisposition to T1D is Better Determined by Haplotypes

- DRB1-DQB1 haplotypes more accurately determine T1D risk
- Testing for DQA1-DQB1 more precise
- High risk T1D haplotypes
  - DQA1*0501-DQB1*0201
  - DQA1*0301-DQB1*0302

Relative Increase (fold) in T1D Risk by Number of High Risk Haplotypes

	Number of High Risk DQA1-DQB1 haplotypes	
Ethnicity	Two	One
Caucasians	16	4
African Americans	45	7
Asians	11	4

Absolute T1D Risk (to age 30) by Number of High Risk Haplotypes

	Number of High Risk DQA1-DQB1 Haplotypes		
Ethnicity	Two	One	Zero
Caucasians	2.6%	0.7%	0.2%
African Americans	3.1%	0.5%	0.1%
Asians	0.2%	0.1%	0.02%

Absolute T1D Risk for Siblings of Affected Individuals

	Number of High Risk DQA1-DQB1 Haplotypes		
	Two	One	Zero
Risk of developing T1D	25%	8.3%	1%

Genome Screens for T1D

IDDM1	6p21	IDDM13	2q34-q35
IDDM2	11p15	IDDM15	6q21
IDDM3	15q26	IDDM17	10q25
IDDM4	11q13	IDDM18	5q31-q33
IDDM5	6q25-q27	PTPN22	1p13
IDDM6	18q21		8q24
IDDM7	2q31	VDR, INFγ	12q12-qter
IDDM8	6q27-qter		16p11-p13
IDDM9	3q21-q25		16q22-q24
IDDM10	10p11-q11		17q24-qter
IDDM11	14q24-q31	TGFβ1	19p13-q13
IDDM12	2q33		Xp11

IDDM2

- Insulin (*INS*) gene
- Chromosome 11p15, OMIM: 176730
- Variable number of tandem repeats (VNTR) in regulatory region
  - Class I: 26-63 repeats – increased risk
  - Class II: ~80 repeats
  - Class III: 141-209 repeats
  - Relative increase in risk ~2-fold with two class I alleles (compared to 0 class I alleles)
- Class I is associated with lower mRNA in the thymus – may reduce tolerance to insulin and its precursors
- *Class III associated with protection*

IDDM12 – CTLA4

- Cytotoxic T Lymphocyte Associated-4 (CTLA-4) – induces T cell apoptosis

- Chromosome 2q33, OMIM: 123890
  - ICOS and CD28 flank

- Encodes a T cell receptor that plays are role in T cell apoptosis
  - A49G polymorphism (Thr17Ala)
  - Relative increase in risk ~ 1.2

- Dysfunction of *CTLA-4* is consistent with development of T1D – survival of self reactive T cells ?

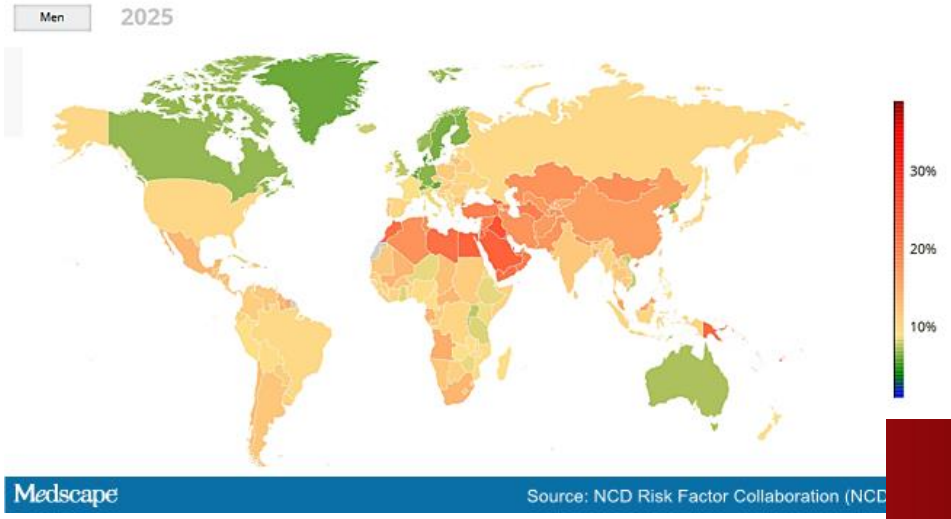
PTPN22

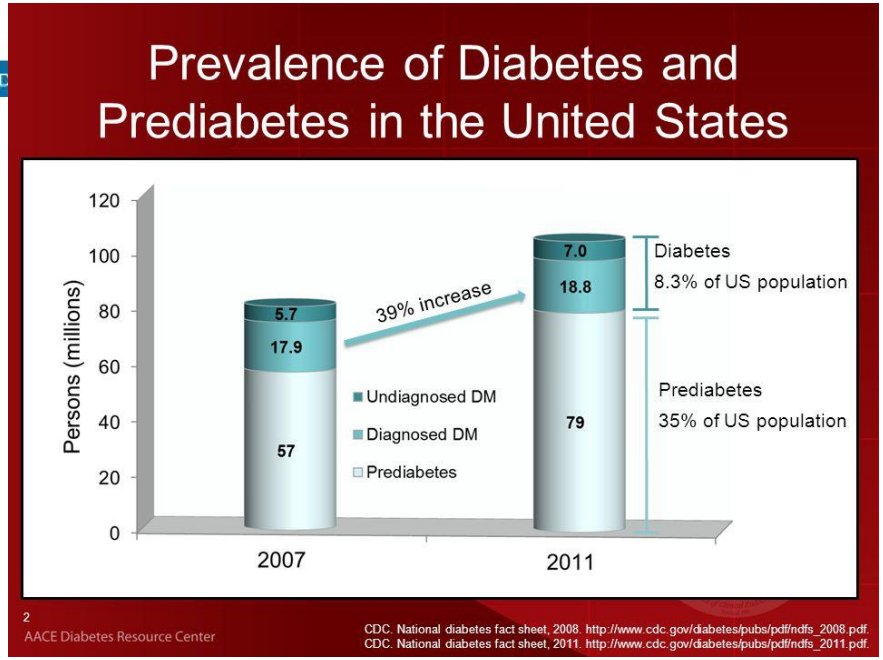
- Lymphoid specific tyrosine phosphatase (LYP)
- Chromosome 1p13, OMIM: 600716
- Encodes a LPY that is important in negative T-cell activation and development
  - C858T polymorphism (Arg620Trp)
  - Relative increase in risk ~ 1.8
- May alter binding of LYP to cytoplasmic tyrosine kinase, which regulates the T-cell receptor signaling kinases

Genetics and Prevention of T1D

- Type 1 diabetes cannot be prevented
- Ethical concerns regarding genetic testing for T1D, especially in children
- Lifestyle changes during early age may help prevent onset in individuals with the disease predisposition

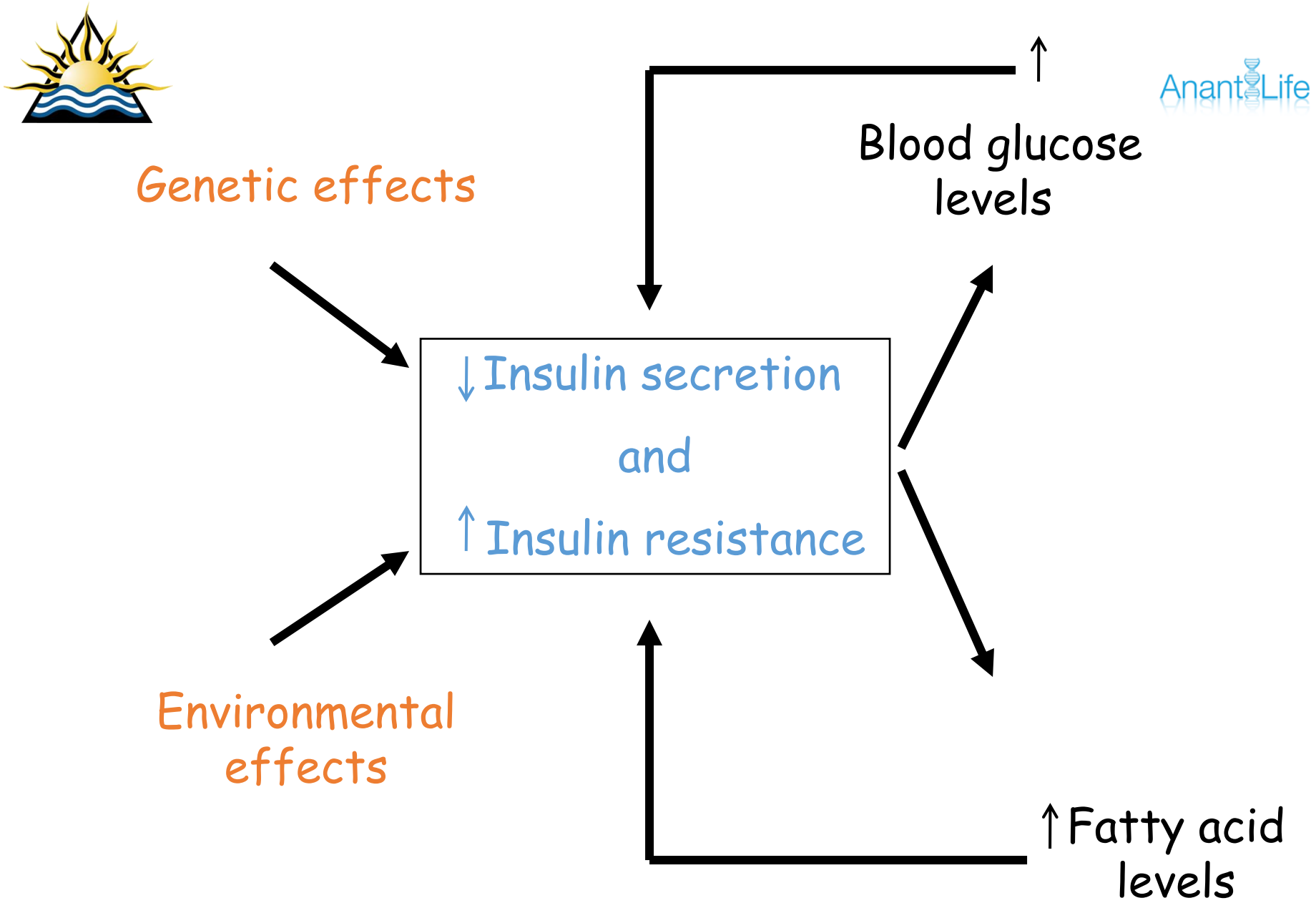
Type 2 Diabetes (T2D)





Type 2 Diabetes

- Is group of genetically heterogeneous metabolic disorders that cause glucose intolerance
  - Involves impaired insulin secretion and insulin action
- ~90% of individuals with diabetes have T2D
- Considerations
  - Onset generally after 40 years
  - May be treated with diet / oral medications / physical activity
  - T2D individuals may be asymptomatic for many years
  - Associated with long-term complications
- Polygenic and multifactorial
  - Caused by multiple genes that may interact
  - Caused by genetic and environmental risk factors (obesity, diet, physical activity)



From McIntyre and Walker, 2002

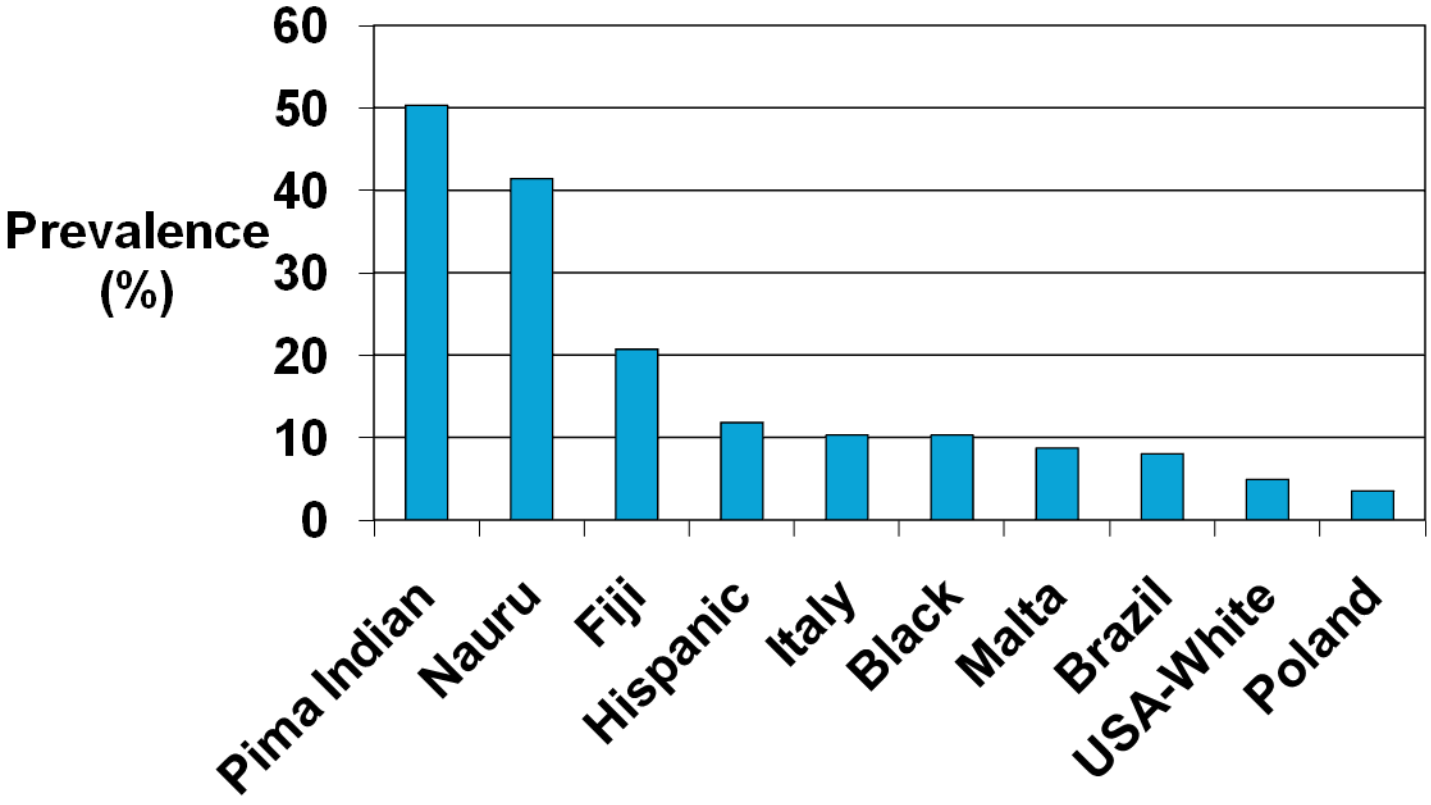
Thrifty Genotype

- Had a selective advantage
- In primitive times, individuals who were ‘metabolically thrifty’ were
  - Able to store a high proportion of energy as fat when food was plentiful
  - More likely to survive times of famine
- In recent years, most populations have
  - A continuous supply of calorie-dense processed foods
  - Reduced physical activity
- These changes likely explain the rise in T2D worldwide

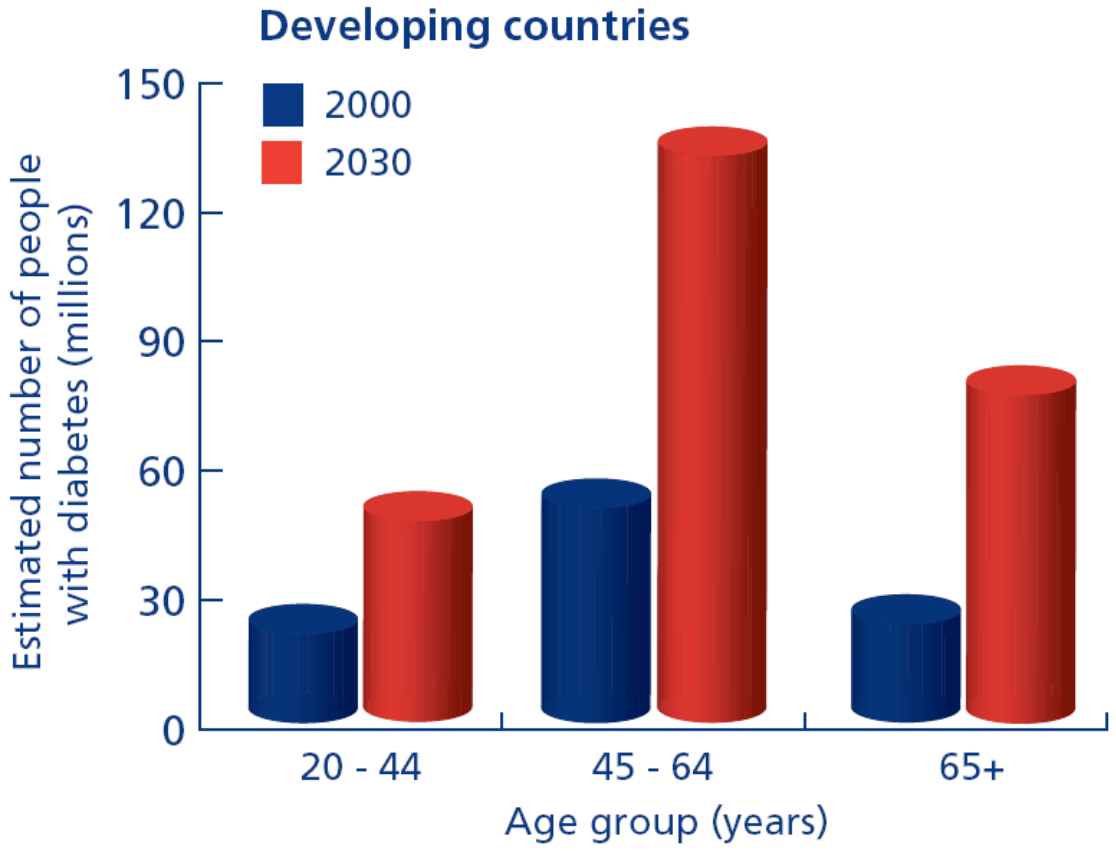
Revised Classification Criteria for T2D

- Fasting plasma glucose
  - ≥ 7.0 mmol/L
  - ≥ 126 mg/dl
- Random blood glucose
  - ≥ 11.1 mmol/L
  - ≥ 200 mg/dl

T2D Prevalence - Americas

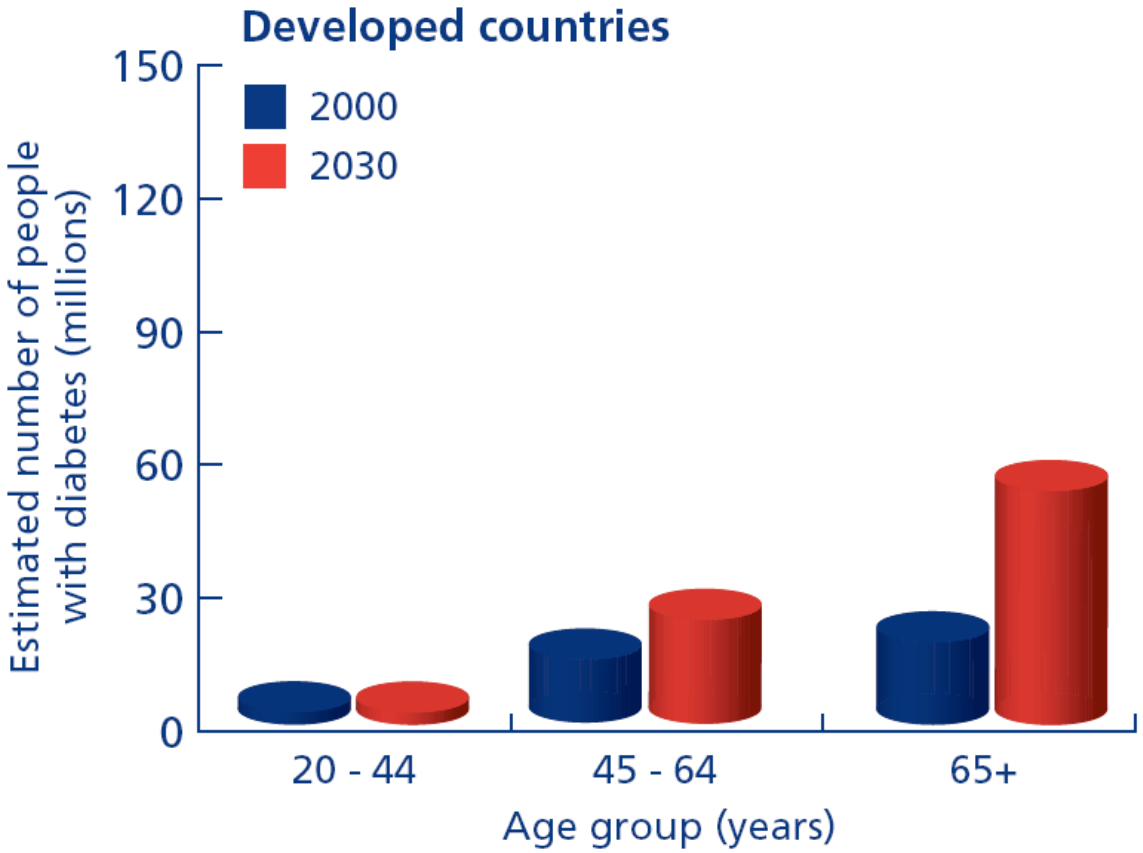


Estimated Number of Adults with Diabetes – Developing Countries



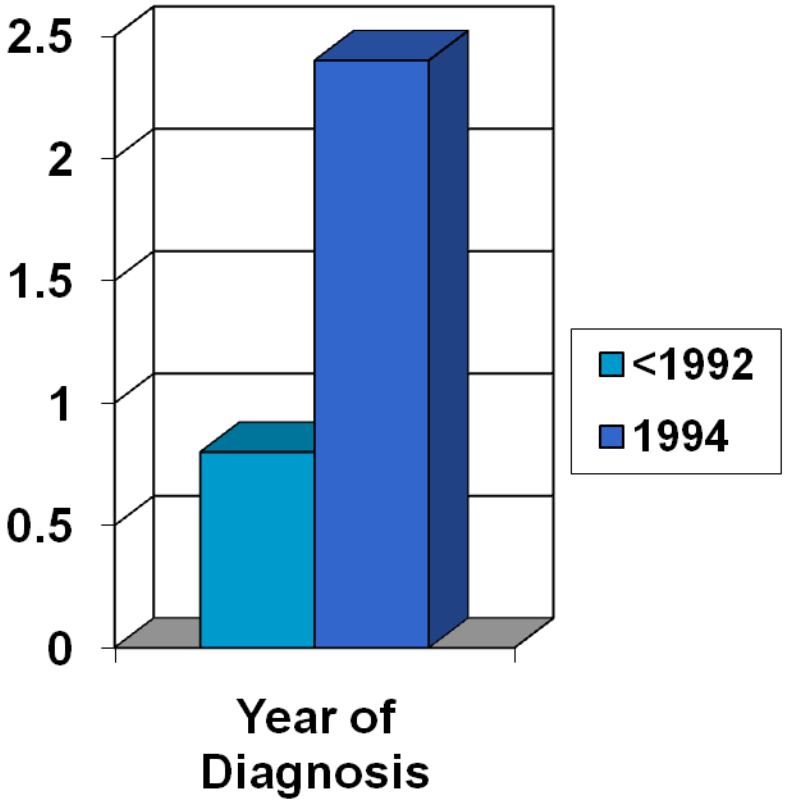
www.who.int/diabetes/actionnow/en/diabprev.pdf

Estimated Number of Adults with Diabetes – Developed Countries



www.who.int/diabetes/actionnow/en/diabprev.pdf

Increase in T2D in Children



- Most T2D children were females from minority populations (incidence per 100,000 children)
- Mean age at onset was around puberty
- Many had a family history of T2D

Environmental Risk Factors in T2D

- Obesity
  - Increases risk of developing T2D
  - Defined as:
    - $\geq$ 120% of ideal body weight
    - Body mass index (BMI) $\geq$ 30 k / m^2
  - Likely related to the increase in T2D
    - ~80% newly diagnosed cases due to obesity
  - Higher association with abdominal or central obesity
    - Assessed by measuring the waist-to- hip ratio

Environmental Risk Factors in T2D

- Physical Activity
  - Lack - Increases risk of developing T2D
  - Even 30 mins a day reduces risk
  - Exercise
    - Controls weight
    - Improves glucose and lipid metabolism
    - Is inversely related to body mass index
  - Lifestyle interventions (diet and exercise) decreased risk of progression of impaired glucose tolerance to T2D by ~60%
  - Genetic programs may have higher efficacy

Genetics and T2D

- Individuals with a positive family history are about 2-6 times more likely to develop T2D than those with a negative family history
  - Risk ~40% if T2D parent; ~80% if 2 T2D parents
- Higher concordance for MZ (upto 60-90%) versus DZ twins
- Has been difficult to find genes for T2D
  - Late age at onset
  - Polygenic inheritance
  - Multifactorial inheritance

Finding Genes for T2D

- Candidates selected because they are involved in
  - Pancreatic beta cell function
  - Insulin action / glucose metabolism
  - Energy intake / expenditure
  - Lipid metabolism

- Genome wide screens
  - Nothing is assumed about disease etiology

- Genome wide association studies
  - Current approach based on thousands of cases and controls

To date over 50 genes have been identified

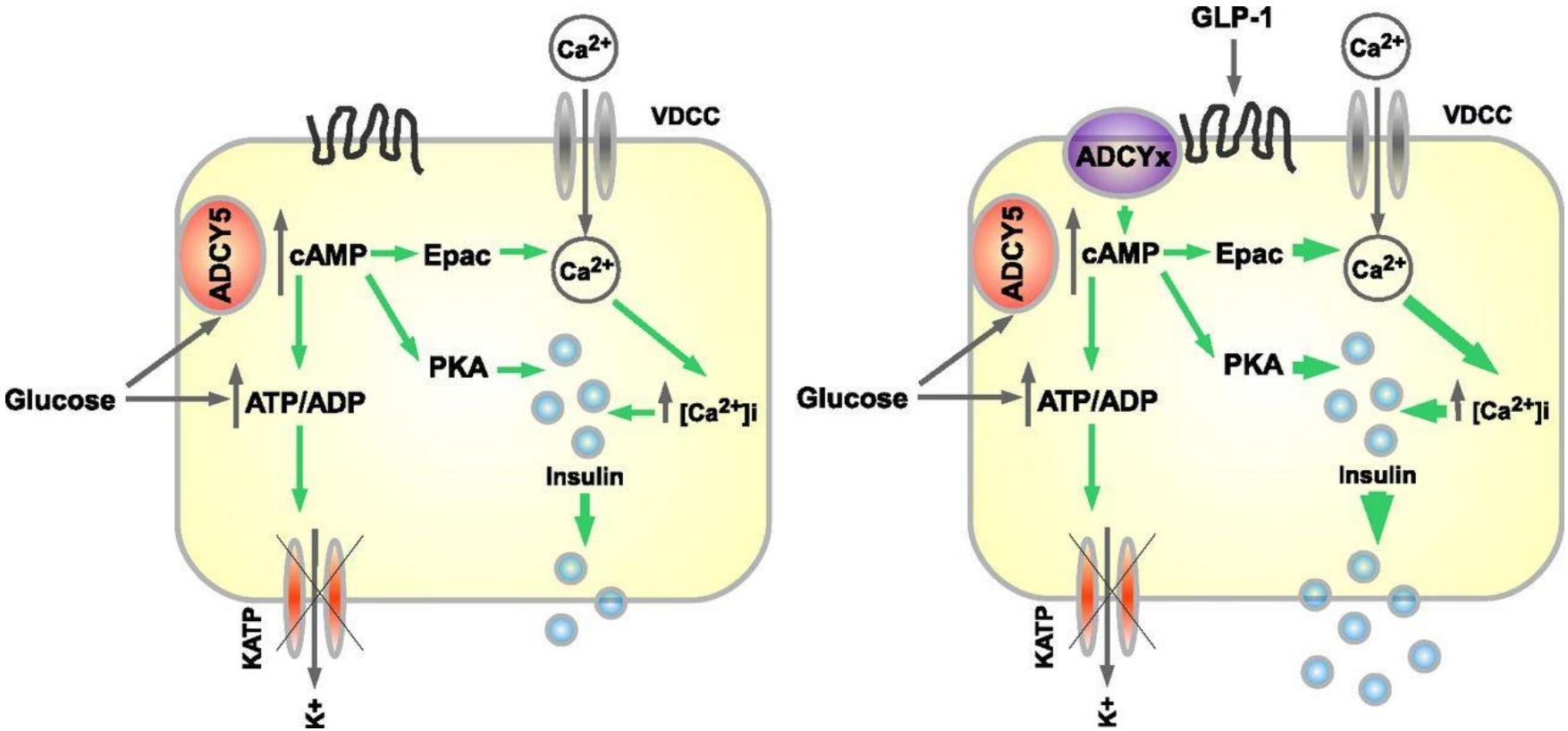
Challenges in Finding Genes

- Inadequate sample sizes
  - Multiplex families
  - Cases and controls
- Difficult to define the phenotype
- Reduced penetrance
  - Influence of environmental factors
  - Gene-gene interactions
- Variable age at onset
- Failure to replicate findings
- Genes identified have small effects

ADCY5

- Encodes for adenylate cyclase 5 – cAMP generation from ATP which plays role in signaling
- Single nucleotide polymorphisms (SNPs) within the ADCY5 gene, encoding adenylate cyclase 5, are associated with elevated fasting glucose and increased type 2 diabetes (T2D) risk.
- These mutations impact ADCY5 activity which compromises function of beta islet cells.
- rs11708067-A risk allele contributes to type 2 diabetes by disrupting an islet enhancer, which results in reduced ADCY5 expression and impaired insulin secretion.

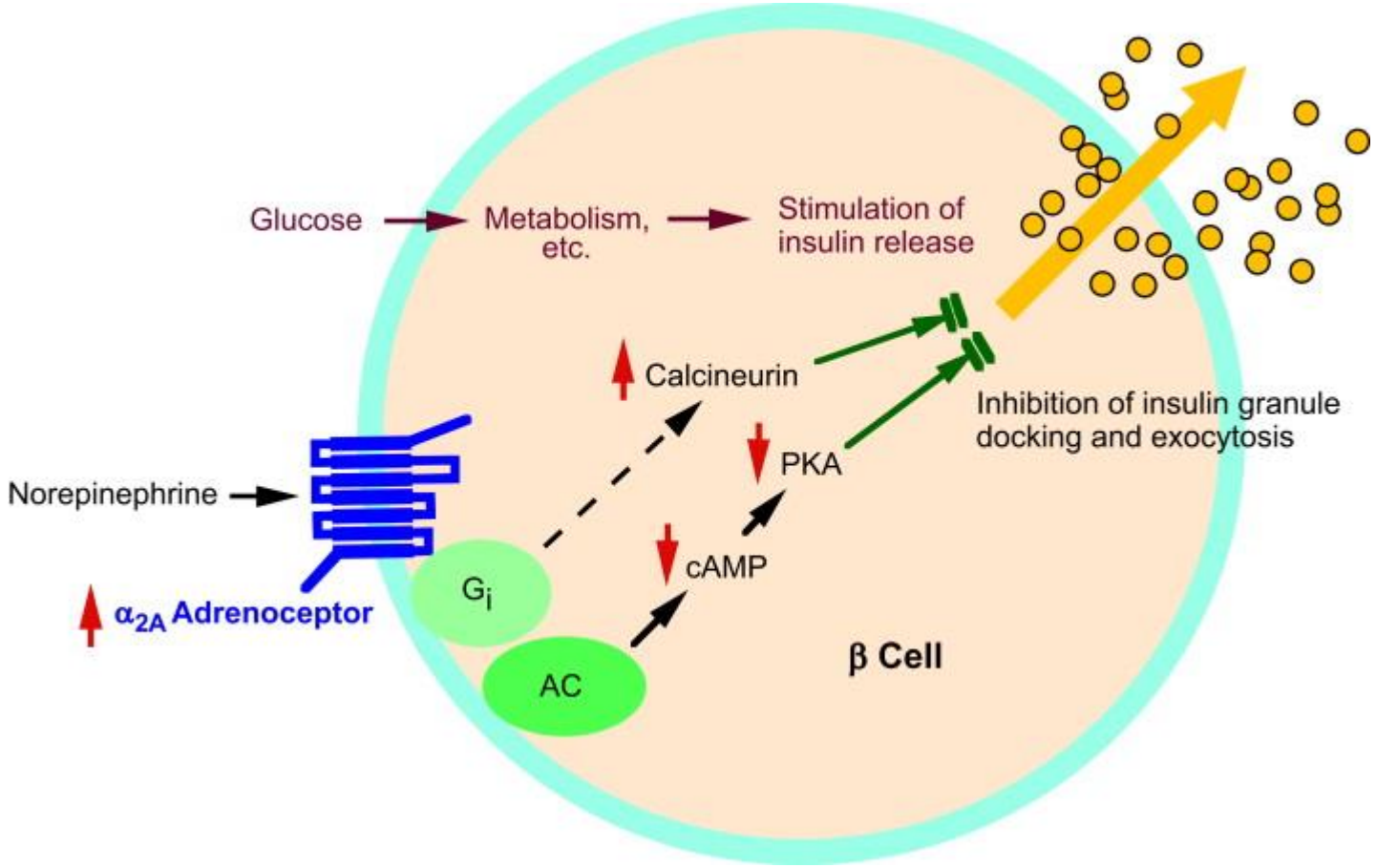
ADCY5


Ca2+
VDCC
ADCY5
cAMP
Epac
Ca2+
PKA
Glucose
ATP/ADP
[Ca2+]i
Insulin
KATP
K+
GLP-1
Ca2+
VDCC
ADCYx
ADCY5
cAMP
Epac
Ca2+
PKA
Glucose
ATP/ADP
[Ca2+]i
Insulin
KATP
K+

ADRA2A

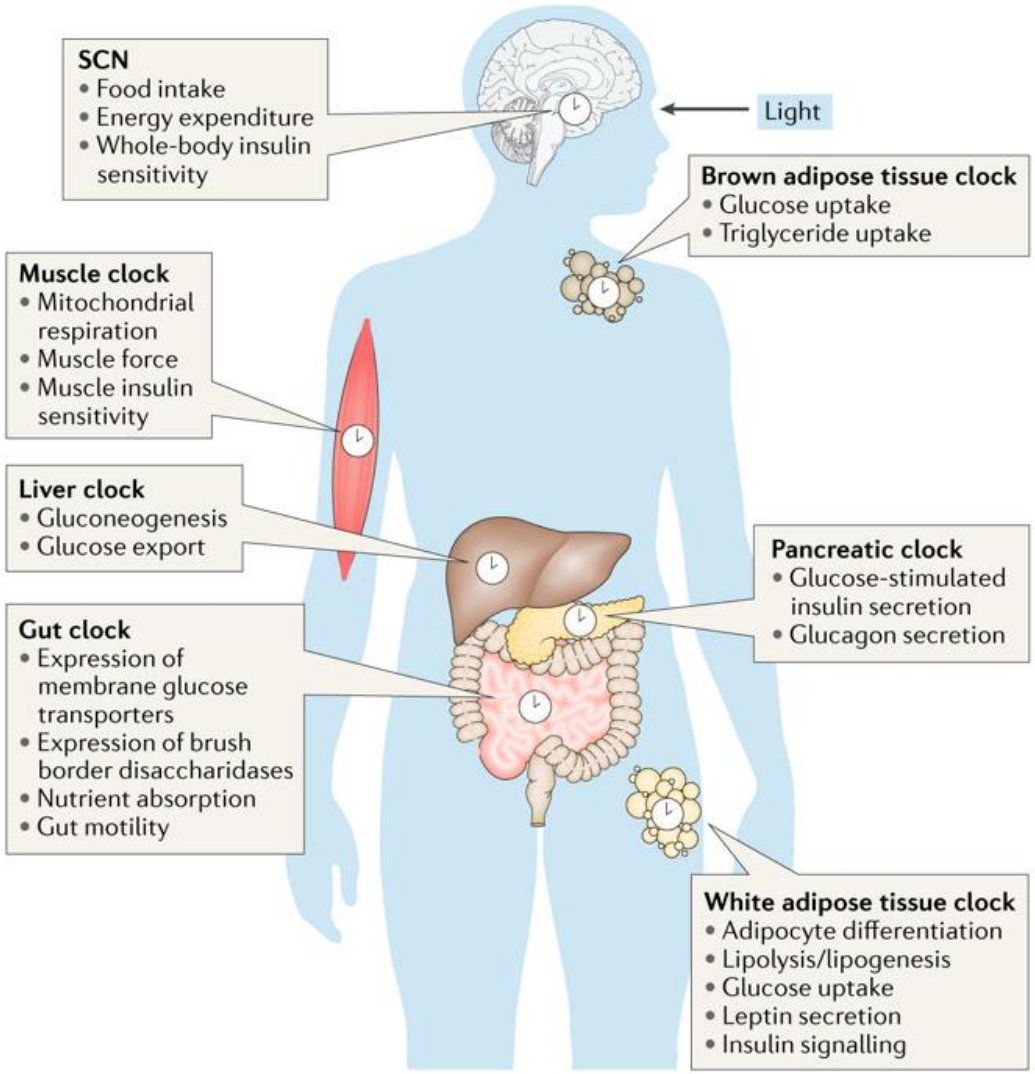
- α2-adrenergic receptor, encoded by ADRA2A gene, is a G-coupled receptor regulating an unusually wide range of central nervous system signalling pathways and metabolic functions
- α2A adrenoceptors play a central role in mediating inhibition of insulin release following treatment with α2-adrenoceptor agonists or stimulation of sympathetic pancreatic nerves
- AA genotype of rs553668 in ADRA2A might be a genetic risk factor that increases T2D susceptibility in Europeans

ADRA2A


Glucose
Metabolism, etc.
Stimulation of insulin release
Calcineurin
PKA
Inhibition of insulin granule docking and exocytosis
Norepinephrine
cAMP
G_i
AC
α_{2A} Adrenoceptor
β Cell

CIRCADIAN CLOCK AND DIABETES

SCN – Suprachiasmatic Nuclei – Region in Hypothalamus which regulates circadian clock



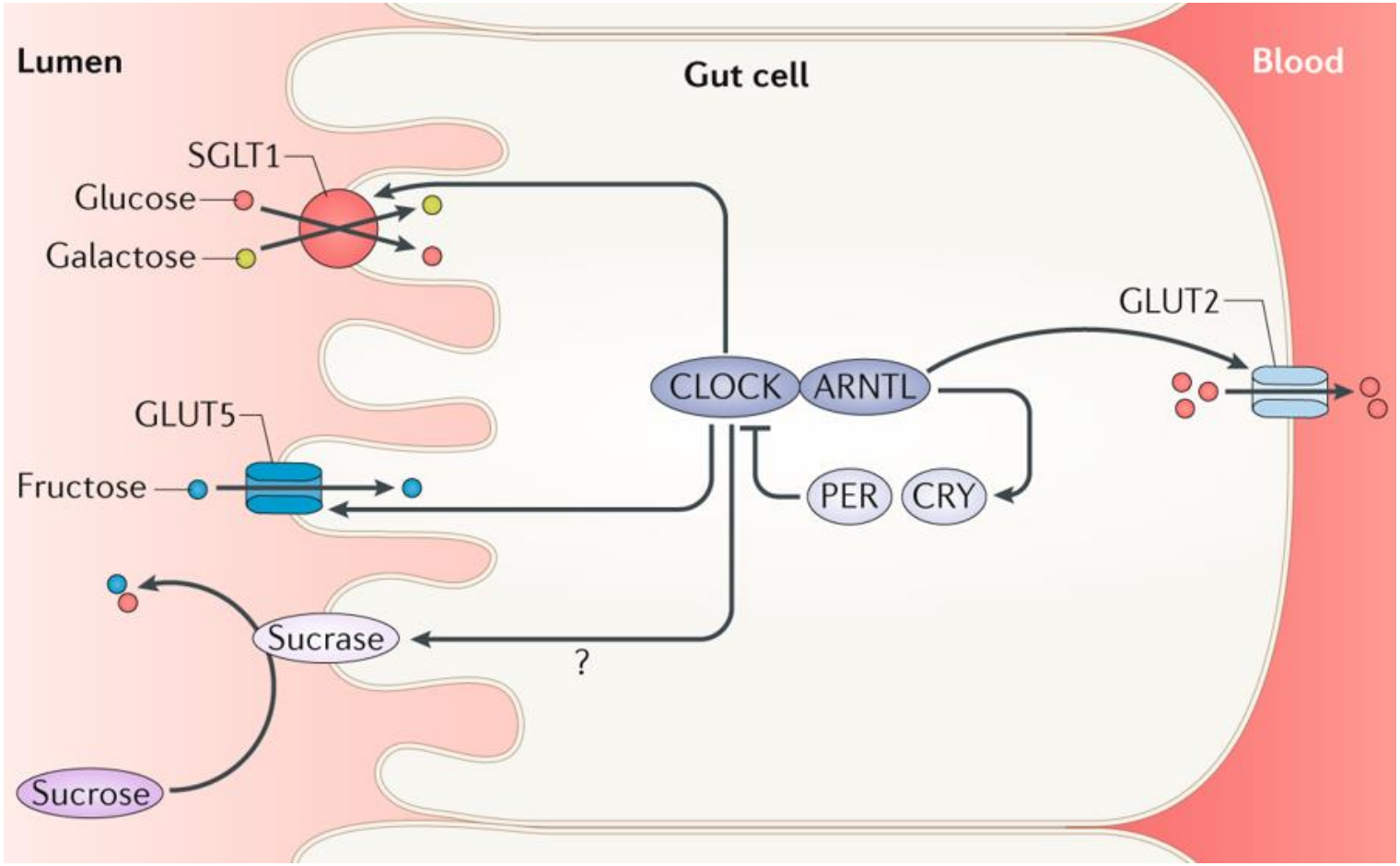
CRY2

- Flavin adenine dinucleotide-binding protein that is a key component of the circadian core oscillator complex, which regulates the circadian clock.

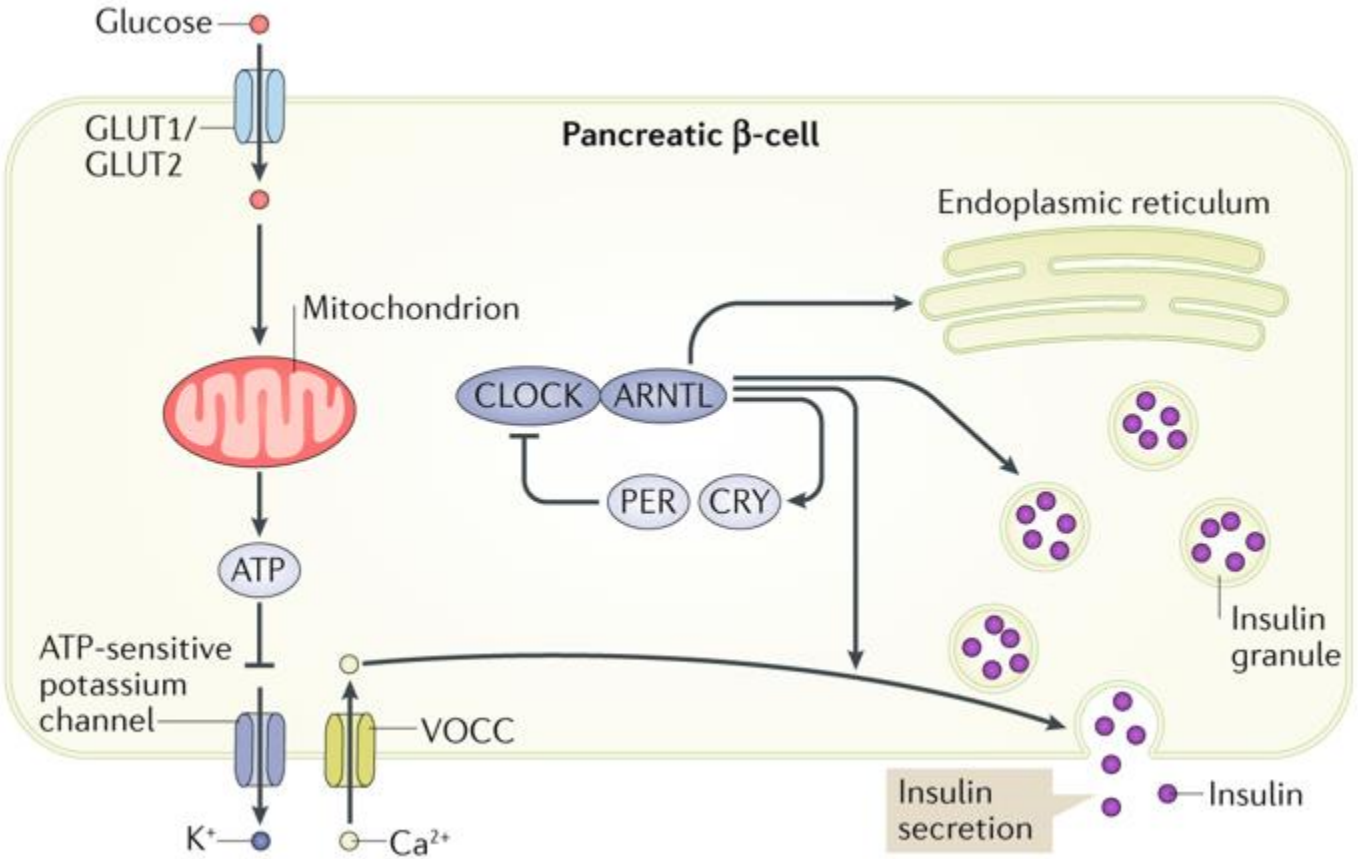
- Cry2 is a cryptochrome – a protein that is responsive to light.

- Mutations in Cry2 have been associated with T2D.

CRY2 AND GUT CELLS



CRY2 AND ISLET CELLS



CRY2 MUTATIONS

- Mutations associated with T2D

- CRY2 may represent an important molecular switch in hepatic lipid and glucose metabolism favoring triglyceride synthesis at the expense of gluconeogenesis, possibly by channeling intermediary metabolites (e.g., glycerol 3-phosphate) from gluconeogenesis to esterification with fatty acids/triglyceride synthesis.

FADS1

- The protein encoded by this gene is a member of the fatty acid desaturase (FADS) gene family. Desaturase enzymes regulate unsaturation of fatty acids through the introduction of double bonds between defined carbons of the fatty acyl chain.
- Desaturates omega-3 and omega-6 polyunsaturated fatty acids at the delta-5 position, catalyzing the final step in the formation of eicosapentaenoic acid (EPA) and Arachidonic acid
- FADS1 mutations impact proinsulin levels and are associated with an increased risk of T2D
- FADS1 mutations are also associated with risk of coronary artery disease in T2D patients

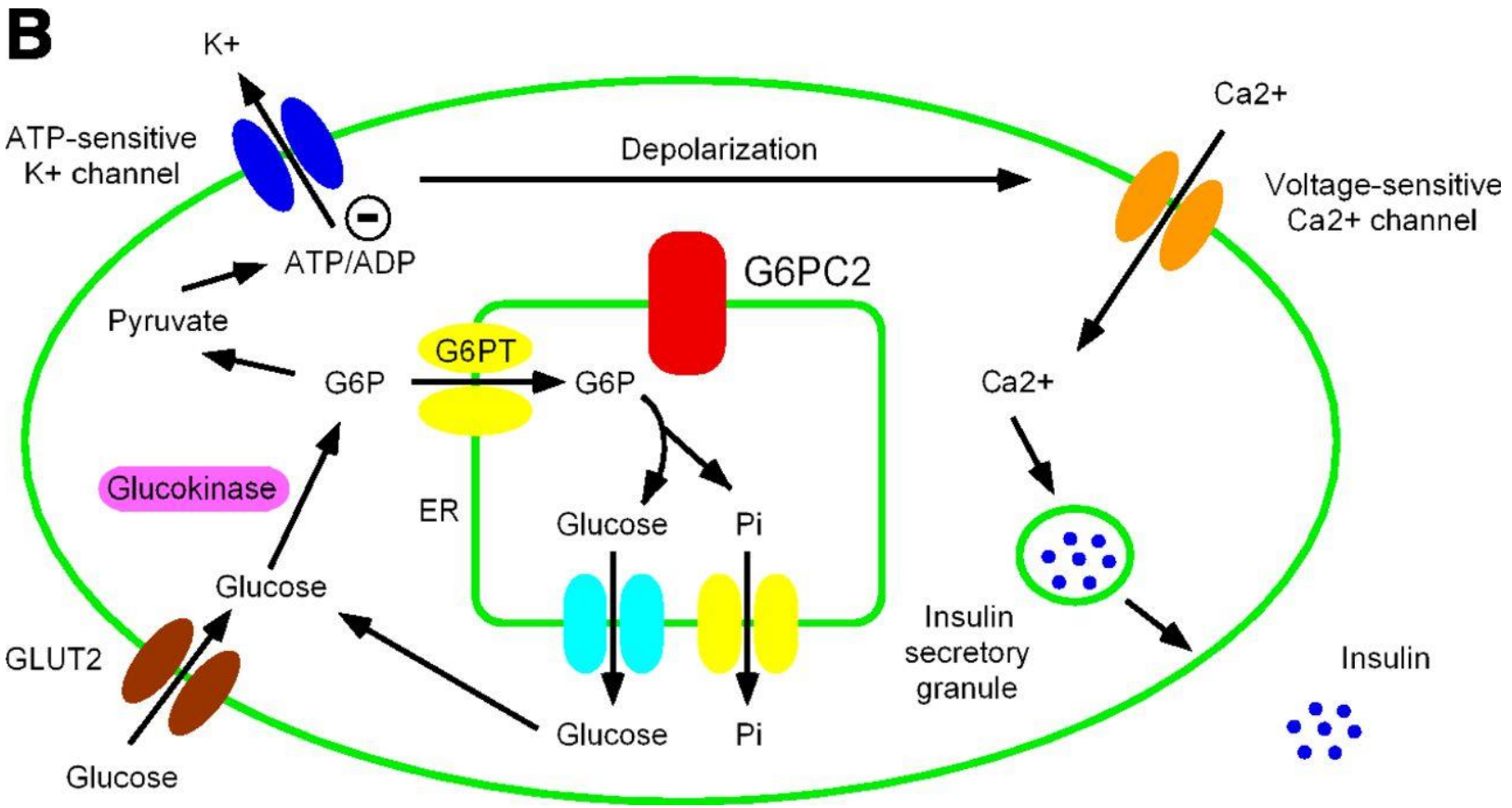
FADS1 and potential mechanism

- Reduction in FADS1 activity promotes liver inflammation
- Reductions induces monocytic differentiation to M1 macrophages
- Inflammatory cascade regulation?
- Inflammation is associated with T2D

G6PC2

- G6PC2 encodes an islet-specific, endoplasmic reticulum–resident glucose-6-phosphatase catalytic subunit.
- Hydrolyses Glucose-6-phosphate to glucose
- A Negative Regulator of Glucose-Stimulated Insulin Secretion
- Mutations in G6PC2 may impact insulin production and are associated with T2D

G6PC2


B
K+
ATP-sensitive
K+ channel
ATP/ADP
Depolarization
Ca2+
Voltage-sensitive
Ca2+ channel
G6PC2
Pyruvate
G6PT
G6P
G6P
Ca2+
Glucokinase
ER
Glucose
Pi
Glucose
Insulin
secretory
granule
Insulin
GLUT2
Glucose
Glucose
Pi
Glucose

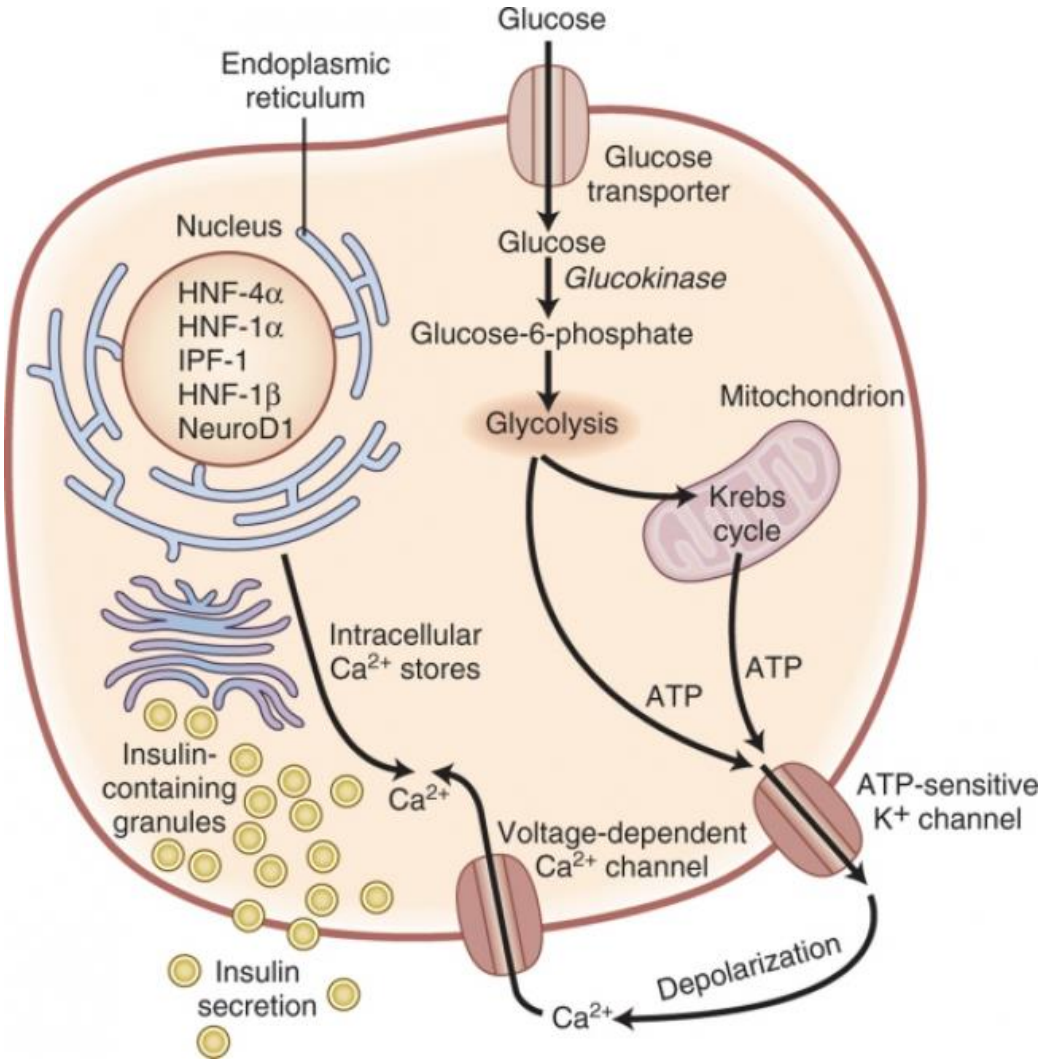
GCK

- Glucokinase (GCK) is a gene which plays an important role in recognising how high the blood glucose is in the body.
- Acts as the “glucose sensor” for the pancreas, so that when the blood glucose rises, the amount of insulin produced also increases. This means that the blood glucose does not become too high if glucokinase is functioning normally.
- GCK variants can lead to increases in blood glucose and affected people may be diagnosed with diabetes

GCK – Mature Onset Diabetes

- Mature Onset Diabetes of the Young (before 25 yrs)
- Heterozygous inactivating mutations cause mild fasting hyperglycaemia, the hallmark of GCK-MODY
- Rare homozygous inactivating mutations result in more severe hyperglycaemia presenting as permanent neonatal diabetes mellitus (PNDM).
- Other GCK mutations result in oversecretion of insulin and present with hyperinsulinemic hypoglycaemia.

GCK


Glucose
Endoplasmic reticulum
Glucose transporter
Nucleus
Glucose
Glucokinase
HNF-4α
HNF-1α
IPF-1
HNF-1β
NeuroD1
Glucose-6-phosphate
Mitochondrion
Glycolysis
Krebs cycle
Intracellular Ca2+ stores
ATP
ATP
Insulin-containing granules
Ca2+
ATP-sensitive K+ channel
Voltage-dependent Ca2+ channel
Depolarization
Insulin secretion
Ca2+

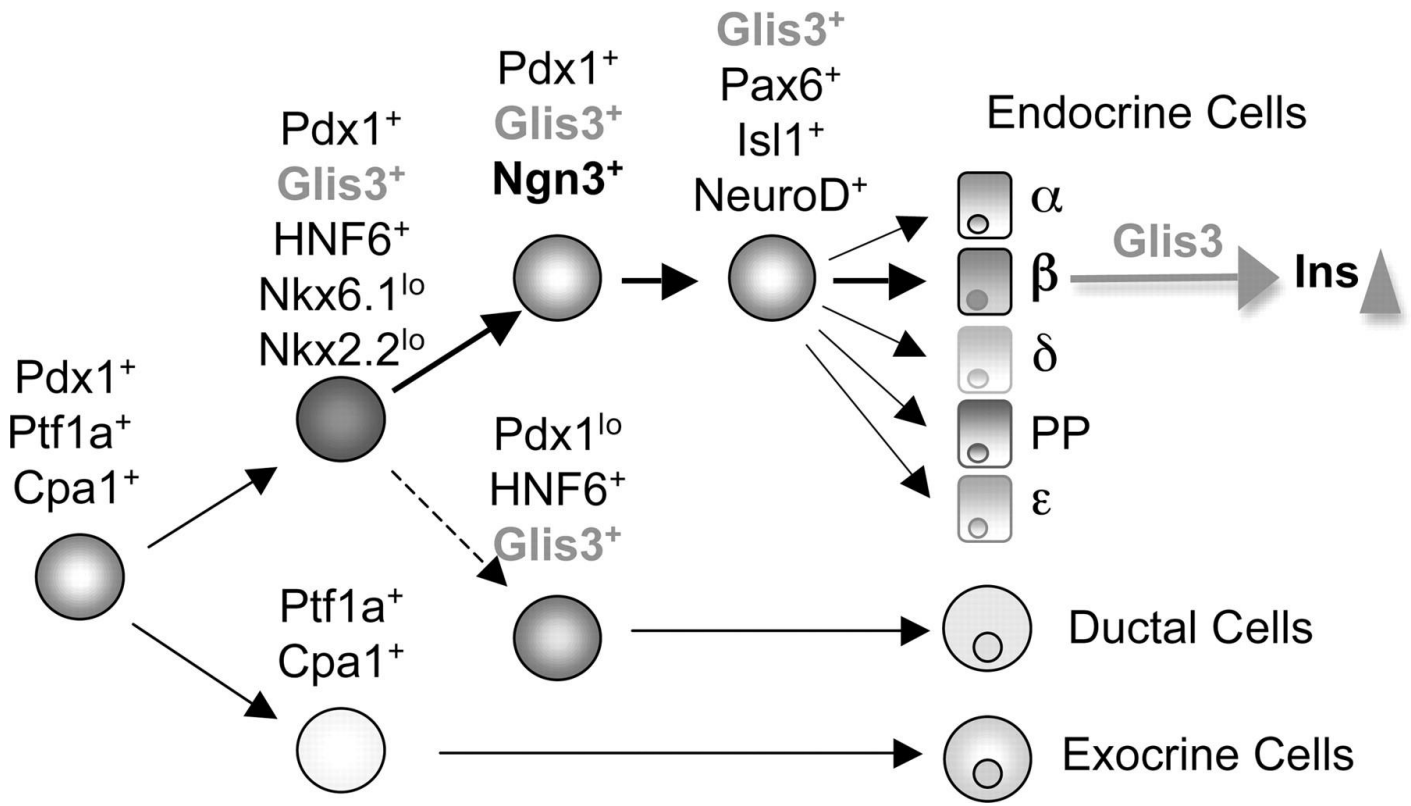
GCKR

- Pancreatic islets and the liver contain a regulatory protein (glucokinase regulatory protein, GCKR), which inhibits GCK in an allosteric manner with respect to glucose concentration by forming an inactive heterodimer.
- GCKR is needed to prevent continuous insulin production
- GCKR-/- mice have impaired sugar control
- GCKR variants associated with T2D – dysregulation of glucose/insulin axis – impaired insulin production due to heightened GCKR activity

GLIS3

- Acts as both a repressor and activator of transcription
- Specifically involved in the development of pancreatic beta cells, the thyroid, eye, liver and kidney.
- Serves as a transcriptional regulator of insulin
- Mutations associated with T2D

GLIS3


Pdx1+
Ptf1a+
Cpa1+
Pdx1+
Glis3+
HNF6+
Nkx6.1lo
Nkx2.2lo
Pdx1+
Glis3+
Ngn3+
Glis3+
Pax6+
Isl1+
NeuroD+
Endocrine Cells
α
β
δ
PP
ε
Glis3
Ins
Pdx1lo
HNF6+
Glis3+
Ptf1a+
Cpa1+
Ductal Cells
Exocrine Cells

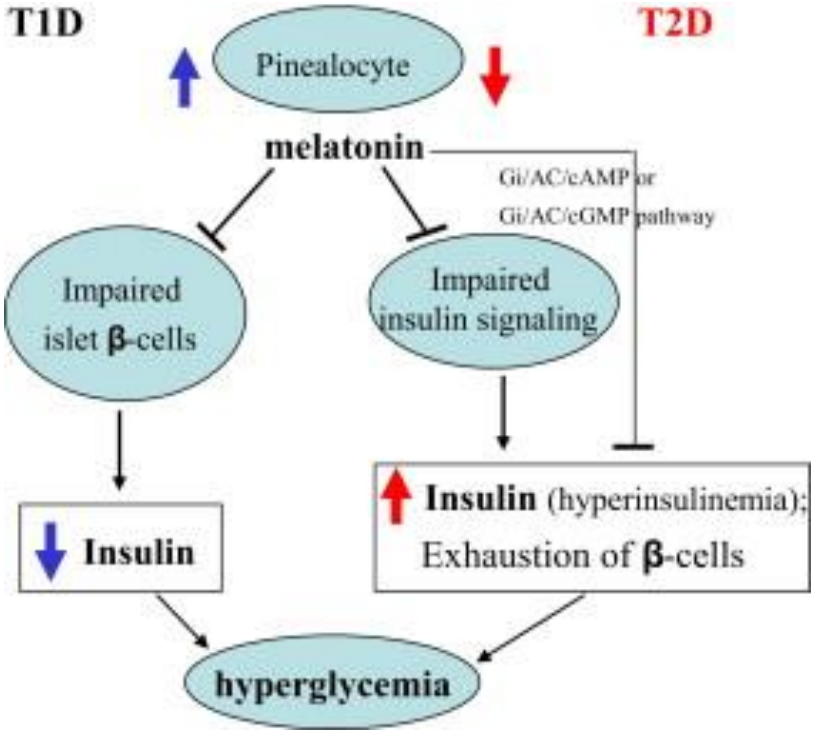
MADD

- MAP kinase-activating death domain protein is an enzyme that in humans is encoded by the MADD gene
- It's a gene that induces apoptosis
- Plays a critical role in glucose-induced insulin release from β-cells and that its functional disruption can cause type 2 diabetes.
- IG20/MADD can act as a guanosine triphosphate exchange protein for Rab3A and Rab27A which play critical roles in glucose-stimulated insulin release from β-cells
- Loss in MADD activity can impair glucose stimulated insulin production

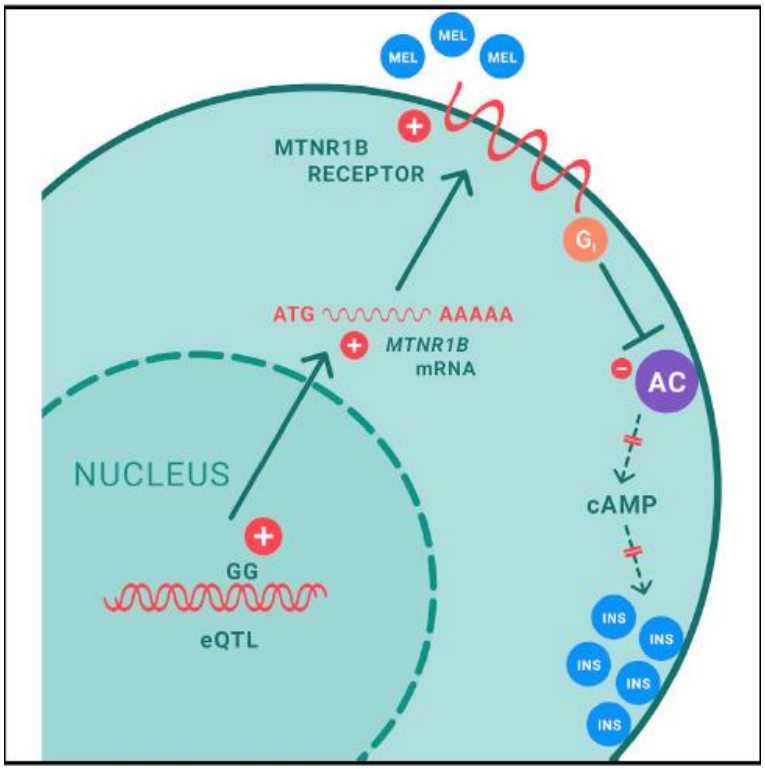
MTNR1B

- This gene encodes one of two high affinity forms of a receptor for melatonin (regulates wake and sleep cycles), the primary hormone secreted by the pineal gland.

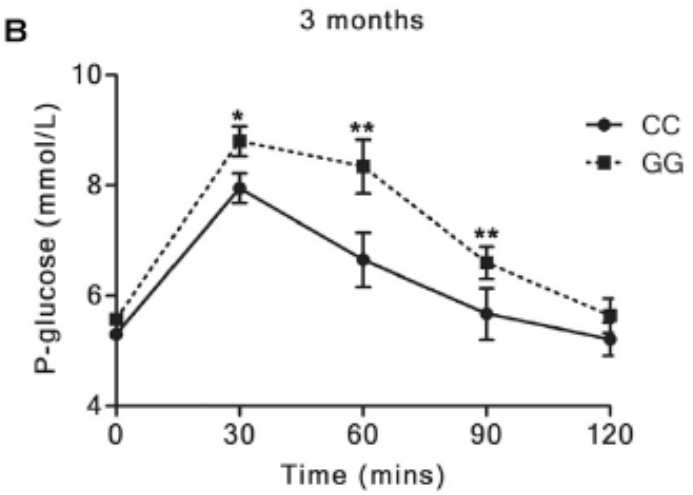
- Mutations in MTNR1B impact responsiveness to melatonin which associates with risk of T2D.



MTNR1B mutations and diabetes



- G allele of rs10830963 is the risk allele



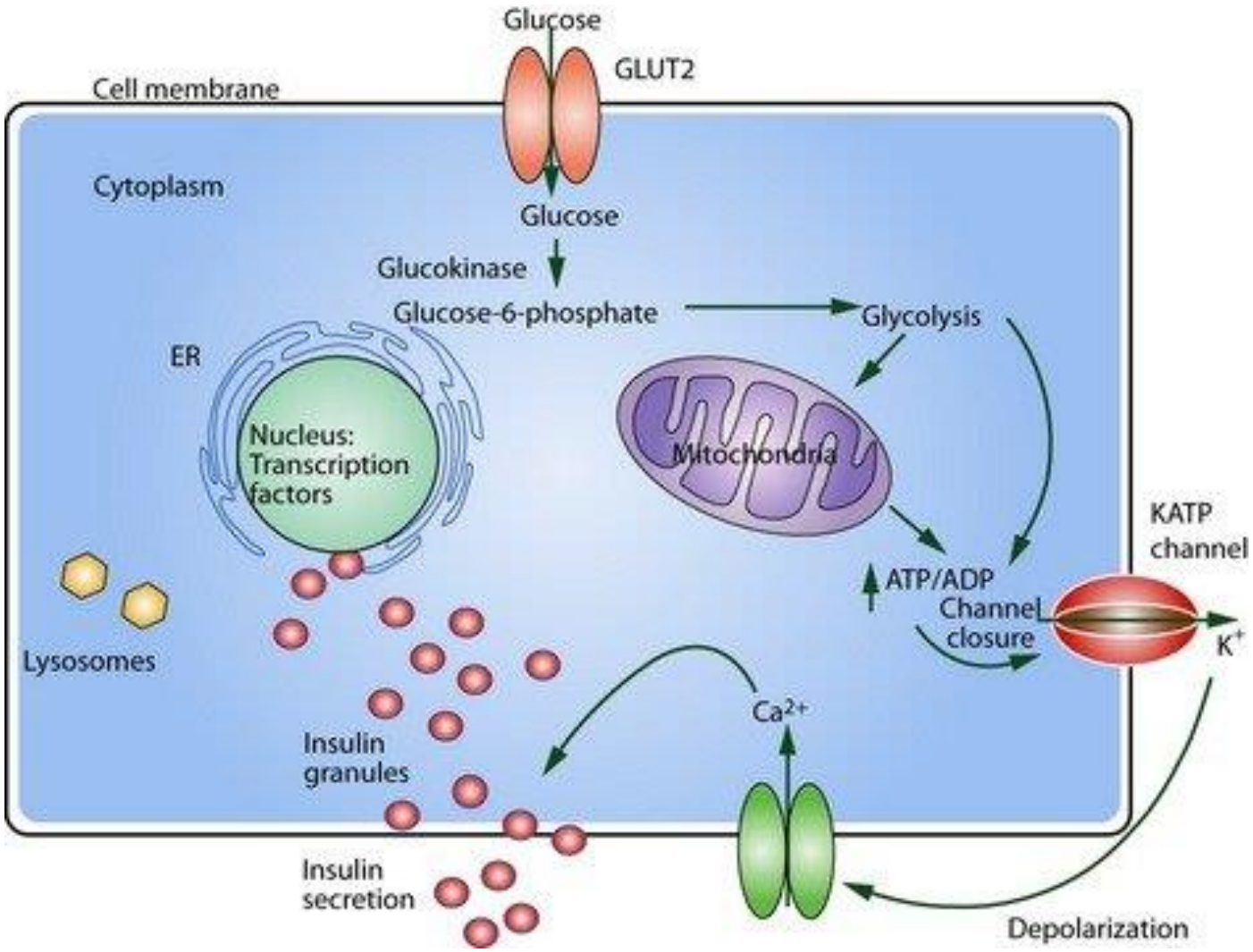
PROX1

- PROX1 encodes a key transcription factor (TF) involved in the development of tissues, such as endothelial lymphatic vessels, liver, retina, and pancreas
- Expression of PROX1 seems to occur in the specification and proliferation of pancreatic progenitor cells
- Lack of Prox1 activity prevents pancreas development and affects the organ's cellular structure
- Mutations associated with T2D
- Suppression of PROX1 activity inhibits glucose-stimulated insulin secretion

SLC2A2

- Encodes for Glucose Transporter GLUT2
- Mutations associated with T2D due to dysregulation of glucose induced insulin production
- Mutations may also impact beta islet differentiation
- Risk with some mutations may be amenable to moderate to vigorous exercise

SLC2A2


Glucose
GLUT2
Cell membrane
Cytoplasm
Glucose
Glucokinase
Glucose-6-phosphate
Glycolysis
ER
Nucleus:
Transcription
factors
Mitochondria
KATP
channel
ATP/ADP
Channel
closure
K+
Lysosomes
Ca2+
Insulin
granules
Insulin
secretion
Depolarization

TCF7L2

- Transcription factor 7-like 2 (chromosome 10q25)
  - Related to impaired insulin release of glucagon-like peptide-1 (islet secretagogue), reduced β-cell mass or β-cell dysfunction
    - Stronger among lean versus obese T2D
  - 10% of individuals are homozygous have 2-fold increase in risk relative to those with no copy of the variant
  - Responsive to sulfunynlureals not metformin
  - Estimated relative risk ~ 1.4

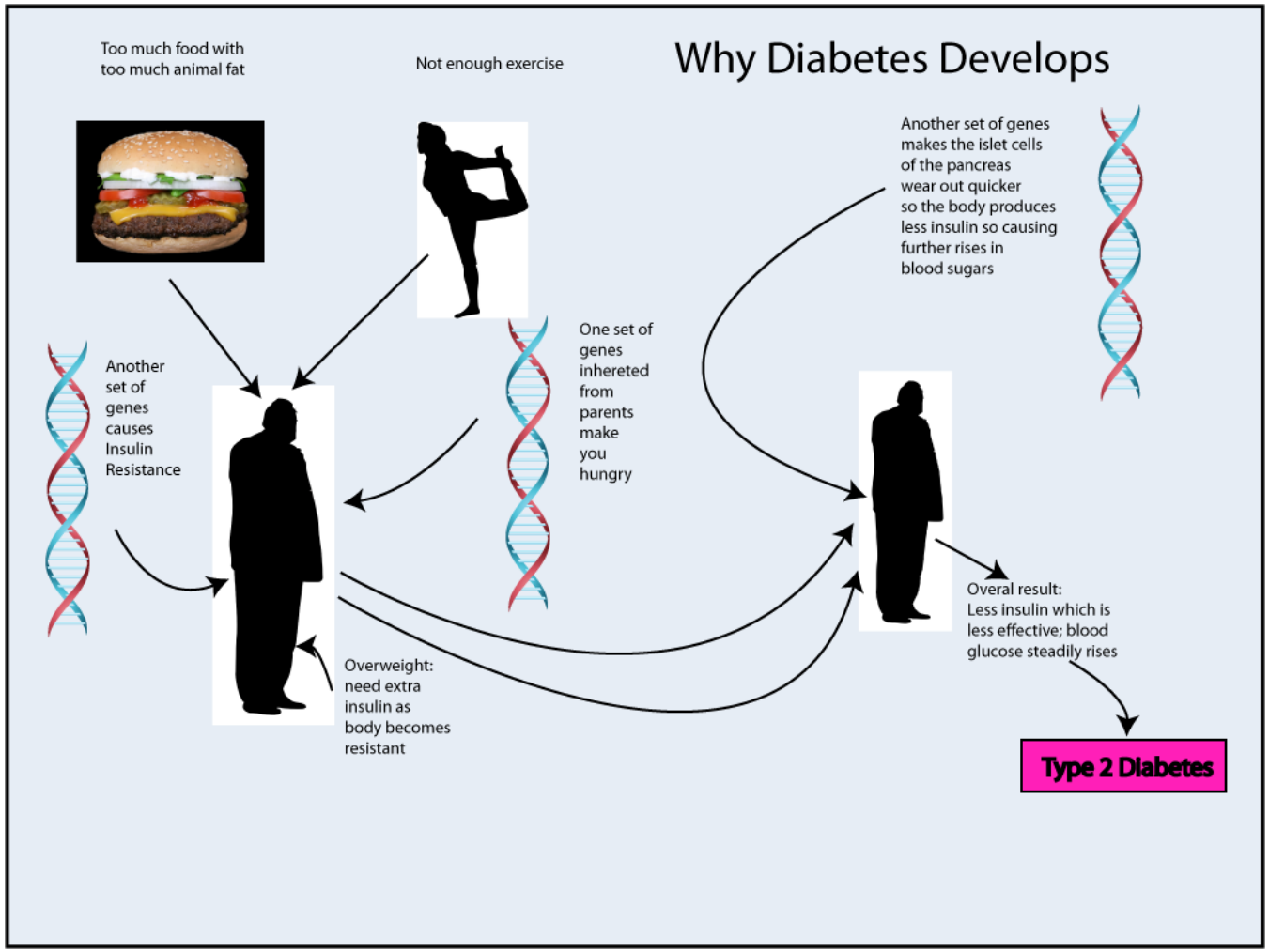
T2D Genes are Drug Targets

- Several genes discussed are the targets of drugs used routinely in the treatment of T2D
  - Pharmacogenetic implications
  - Response to oral agents may be related to one's genotype
  - Genetic testing may
    - Identify individuals at high risk for T2D
    - Guide treatment regimens for T2D
  - Individualize therapy

Genetics and Prevention of T2D

- T2D is preventable
  - Maintaining age-appropriate body weight
  - Physical activity
- New genes will provide insight to etiology
- Public health messages may have a greater influence on genetically susceptible
- Will genetic testing prevent T2D?
  - Knowledge of one's genetic risk will lead to behavior modifications

HOW DOES GENETICS MODULATE DIABETES RISK?



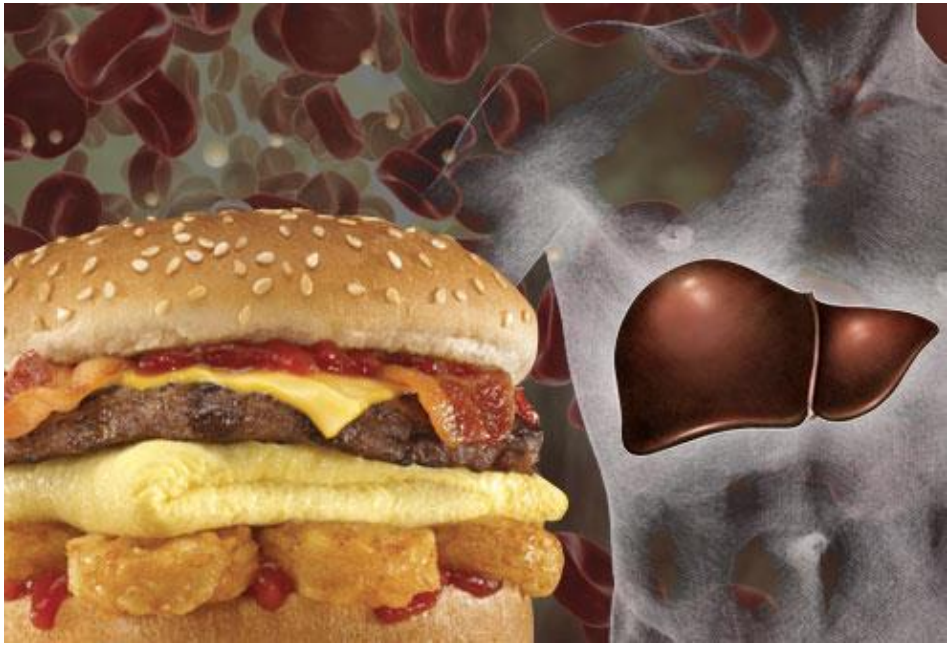
Genetics of T2D

METABOLIC ISSUE	GENE	YOUR GENOTYPE	GENE	YOUR GENOTYPE
Blood sugar	ADCY5	AG	GLIS3	AC
	ADRA2A	GG	MADD	AA
	CRY2	CC	MTNR1B	CC
	FADS1	TT	PROX1	TT
	G6PC2	CC	SLC2A2	AT
	GCK	GG	TCF7L2	CC
	GCKR	TT		

- If at risk then need to develop DNA based nutrition and exercise plan to reduce sugar intake, carbohydrate intake and controlling weight along with offering a fitness plan to maximize the efficacy of the fitness regimen.

Cholesterol

- Cholesterol is a fatty substance manufactured in the liver and is carried throughout the body in the bloodstream.



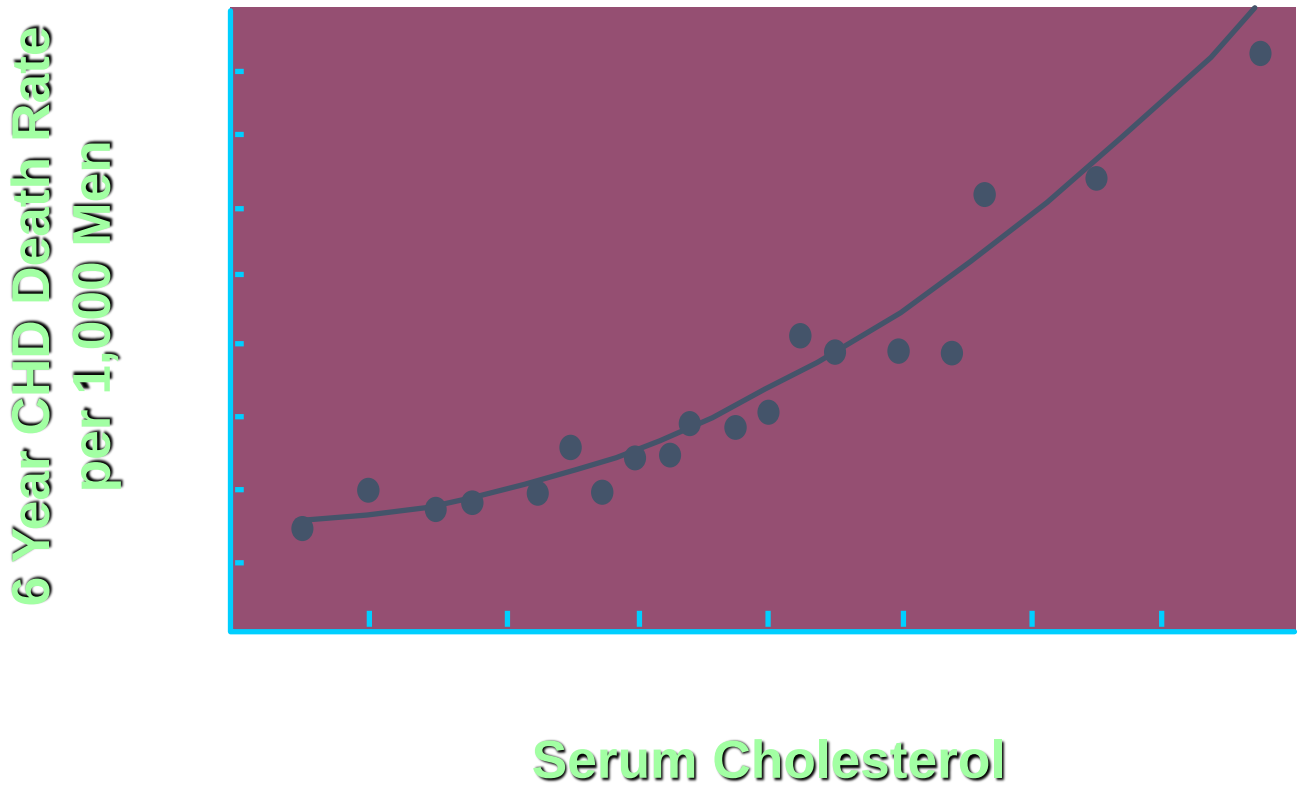
NORMAL CHOLESTEROL METABOLISM

- Synthesis
  - Endoplasmic reticulum of cells
  - Largest source is biliary secretion, not diet.
  - Normal absorption: 50%
  - For cholesterol to be absorbed it must:
    - undergo hydrolysis (de-esterification by esterases)
    - be incorporated into micelles
    - be taken up by cholesterol transporter
    - be re-esterified and incorporated into chylomicrons

Biological significance of cholesterol

- Cholesterol is an essential lipid constituent of cell membranes
- Cholesterol is a precursor of steroid hormones and of bile acids
- Intermediates of cholesterol biosynthesis are required to make vitamin D and for posttranslational modification of membrane proteins
- High plasma cholesterol promotes atherosclerosis

Serum Cholesterol and CHD in 361,662 U.S. Men



Martin M. Lancet 1986;11:933-936

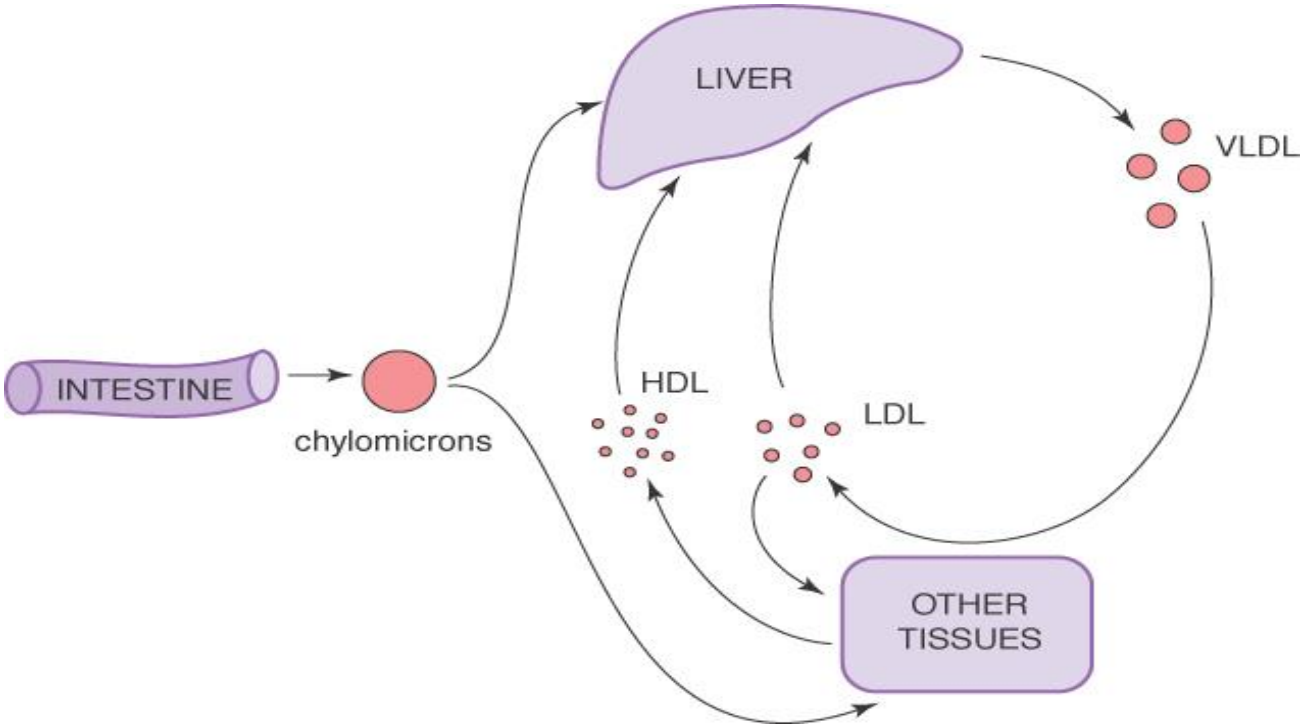
Processes that determine the cholesterol balance

- intestinal uptake of dietary cholesterol
- *de novo* cholesterol synthesis
- synthesis of steroid hormones from cholesterol
- synthesis of bile acids from cholesterol, and their biliary secretion
- biliary secretion of surplus cholesterol in unmodified form

Cholesterol synthesis

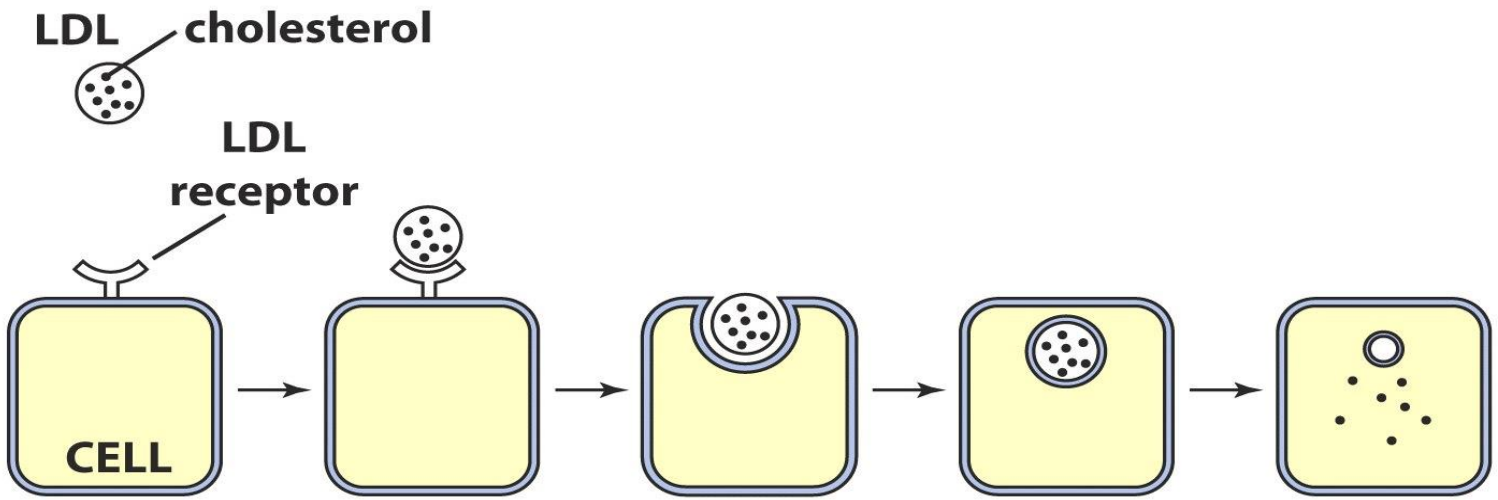
- Synthesis of cholesterol takes place in cytosol.
- The carbon skeleton of cholesterol is formed from acetyl CoA. The pathway of cholesterol biosynthesis has over 30 steps.
- The rate determining step of cholesterol synthesis and the major control point is the conversion of HMG-COA to mevolonic acid.
- Some intermediate steps of cholesterol synthesis are mevolonic acid— squalene— zymosterol—cholesterol.

Lipoprotein function



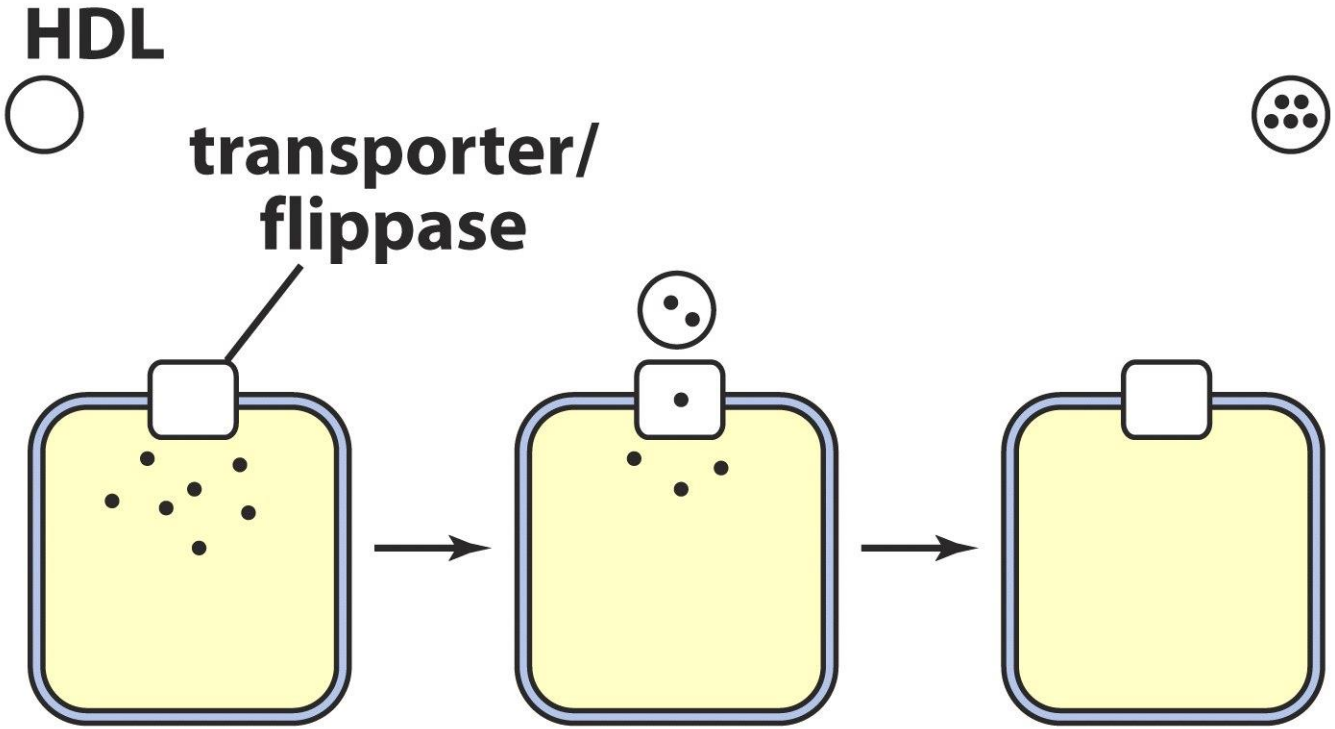
Chylomicrons, which are mostly lipid, transport dietary lipids to the liver and other tissues. Liver produces triacylglycerol-rich very- low- density lipoproteins (VLDL). As they circulate in the tissues, VLDL give up their triacylglycerol and become cholesterol-rich low- density lipoproteins (LDL), which are taken up by tissues. High Density Lipoproteins transport cholesterol from the tissues back to liver.

LDL



Cell can synthesize cholesterol as well as obtain it from circulating LDL. When LDL dock with LDL receptor on the cell surface, the lipoprotein-receptor complex undergoes endocytosis. Inside the cells, the lipoprotein is degraded and cholesterol enters the cytosol. Excess accumulation of cholesterol leads to atherosclerosis.

HDL



HDL are essential for removing excess cholesterol from cells. A transporter or flippase moves cholesterol from the cytosolic leaflet to the extracellular leaflet, from which it can diffuse into the HDL. Defects in the gene of the transporter cause **Tangier disease**, characterized by accumulations of cholesterol in tissues and a high risk of heart attack.

Why High Cholesterol Matters

- High cholesterol is one of the major risk factors for coronary artery disease, heart attacks, and strokes. It also appears to boost the risk of Alzheimer's disease.
- High cholesterol leads to a buildup of plaque that narrows the arteries. The most dangerous or rupture-prone plaques are caused by lesions that were less than 70% stenotic and not by those with the most severe narrowing.

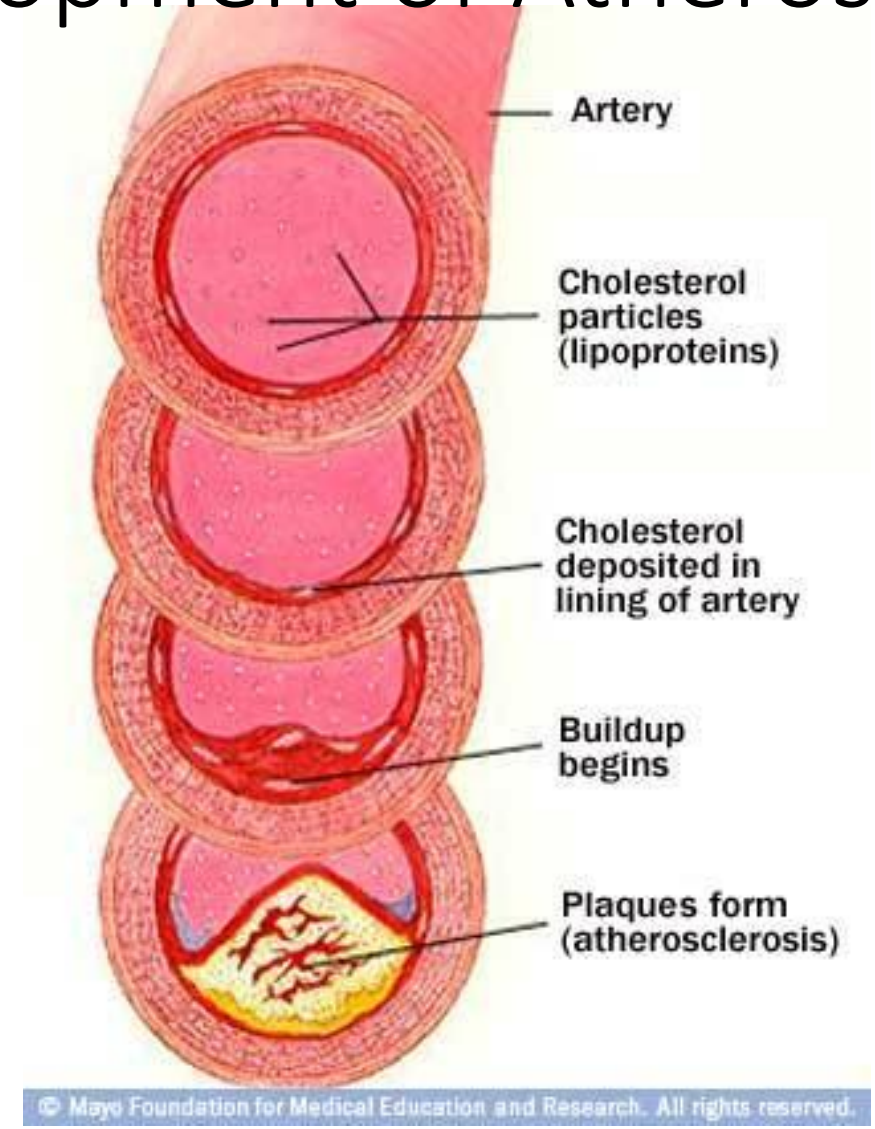
Prevalence

- About 50% of U.S. adults have an elevated total cholesterol level
- Majority of patients with atherosclerosis have some form of dyslipidemia
- 70-80% of individuals with dyslipidemia do not meet LDL cholesterol targets despite lipid therapy

Symptoms

- High cholesterol does not cause any symptoms.
- Too much cholesterol may lead to a buildup of plaque inside the arteries.
- This is known as atherosclerosis, a condition that causes narrowing of the space available for blood flow

Development of Atherosclerosis



Atherosclerosis

- Leading cause of morbidity and mortality in the U.S.
- Accounts for more than 1/3 of all deaths each year
- About 13 million Americans have coronary heart disease (CHD)
- Dyslipidemia (abnormal levels of fats in the blood) is the most prevalent and important modifiable risk factor for atherosclerosis

Total Cholesterol

- Total cholesterol measures the combination of LDL, HDL, and VLDL (very low density lipoprotein) in your bloodstream. VLDL is a precursor of LDL, the bad cholesterol.
- A total cholesterol score of under 200 mg/deciliter is considered healthy in most cases.

Low Density Lipoproteins

- Most of the cholesterol in the blood is carried by proteins called low density lipoproteins or LDL or the bad cholesterol
- LDL combines with other substances to clog the arteries.
- A diet high in saturated fats and trans fats tends to raise the level of LDL cholesterol.
- For most people, an LDL score below 100 is healthy, but people with heart disease may need to aim even lower

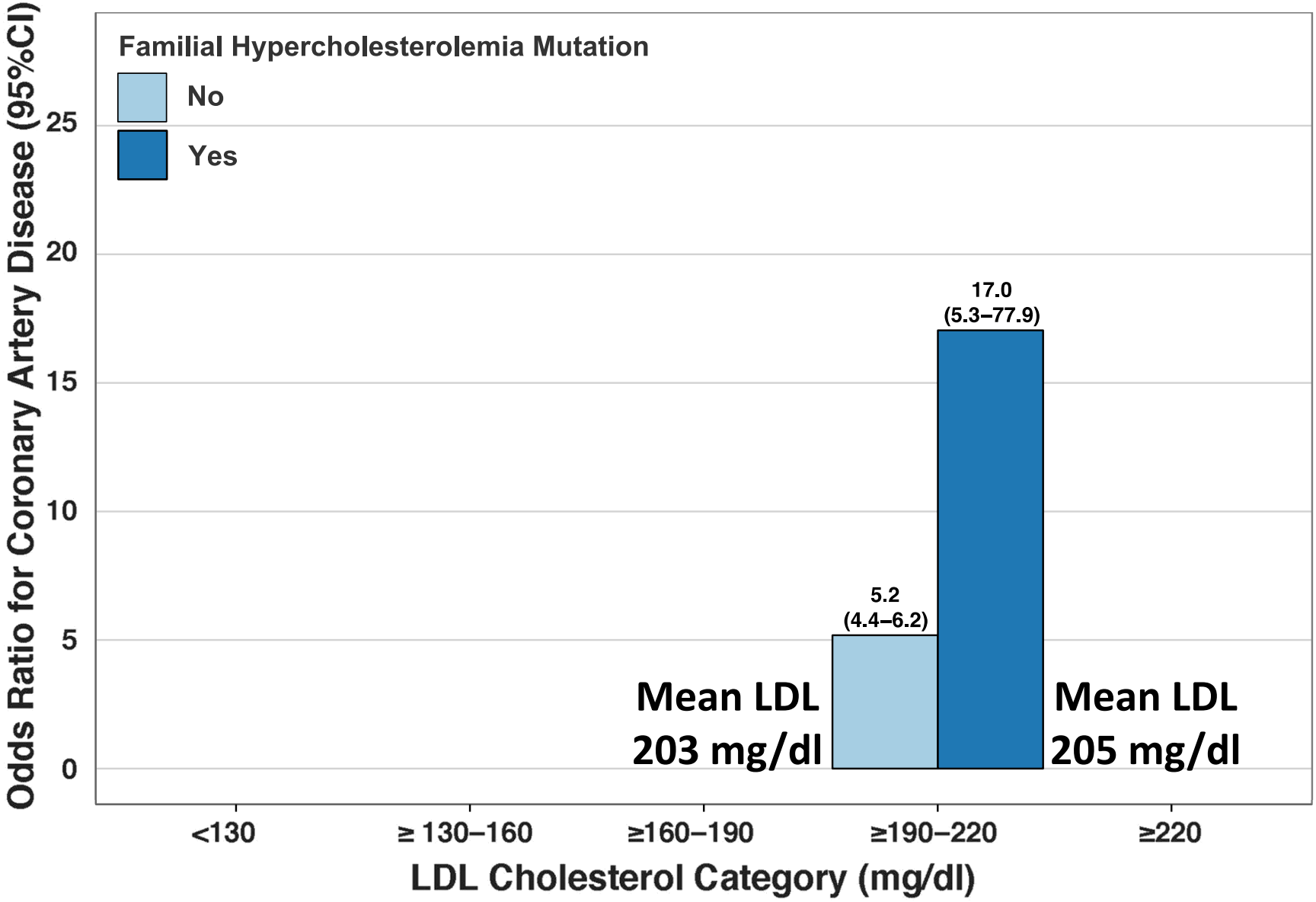
High-Density Lipoproteins

- Up to a third of blood cholesterol is carried by high-density lipoproteins or HDL or the good cholesterol.
- HDL helps remove bad cholesterol, preventing it from building up inside the arteries.
- The higher the level of HDL cholesterol, the better. People with too little are more likely to develop heart disease.

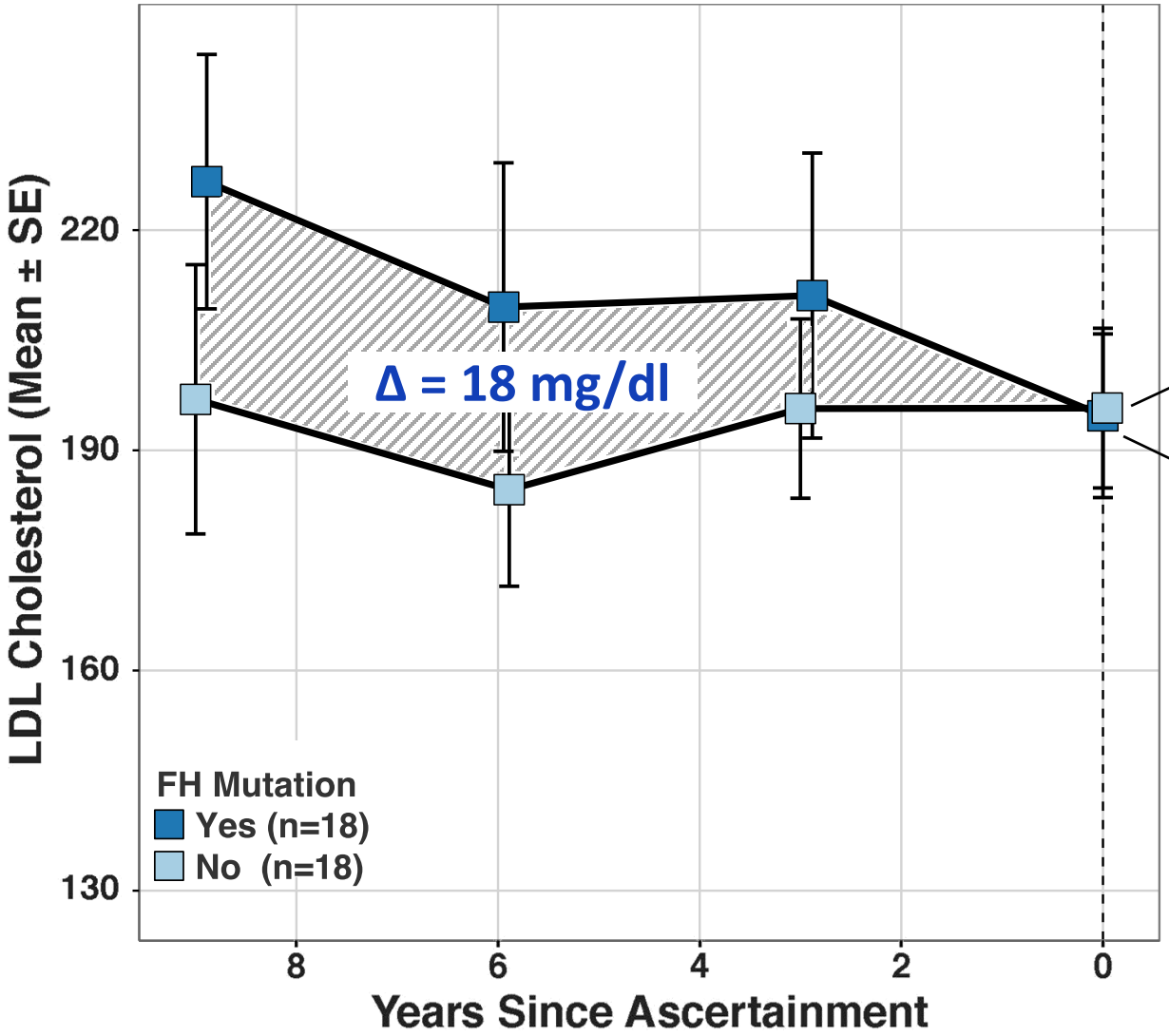
Familial Hypercholesterolemia

- Hypercholesterolemia is a condition characterized by very high levels of LDL cholesterol in the blood.
- People with hypercholesterolemia have a high risk of developing a form of heart disease called coronary artery disease.
- This condition affects about 1 in 500 people in most countries.
- Inherited forms of hypercholesterolemia resulting from mutations in the LDLR, APOB, or PCSK9 gene have an autosomal dominant pattern

Clinical Importance: For a Given Observed LDL, FH Mutation Carriers are at Increased Coronary Risk



Potential Mechanism: FH Mutation Carriers have Higher Cumulative Exposure to LDL Cholesterol



LDLR

- LDL Receptor is needed for efficient clearance of LDL (mostly in liver)
- Mutations that impact LDLR activity – increase the risk for elevated LDL

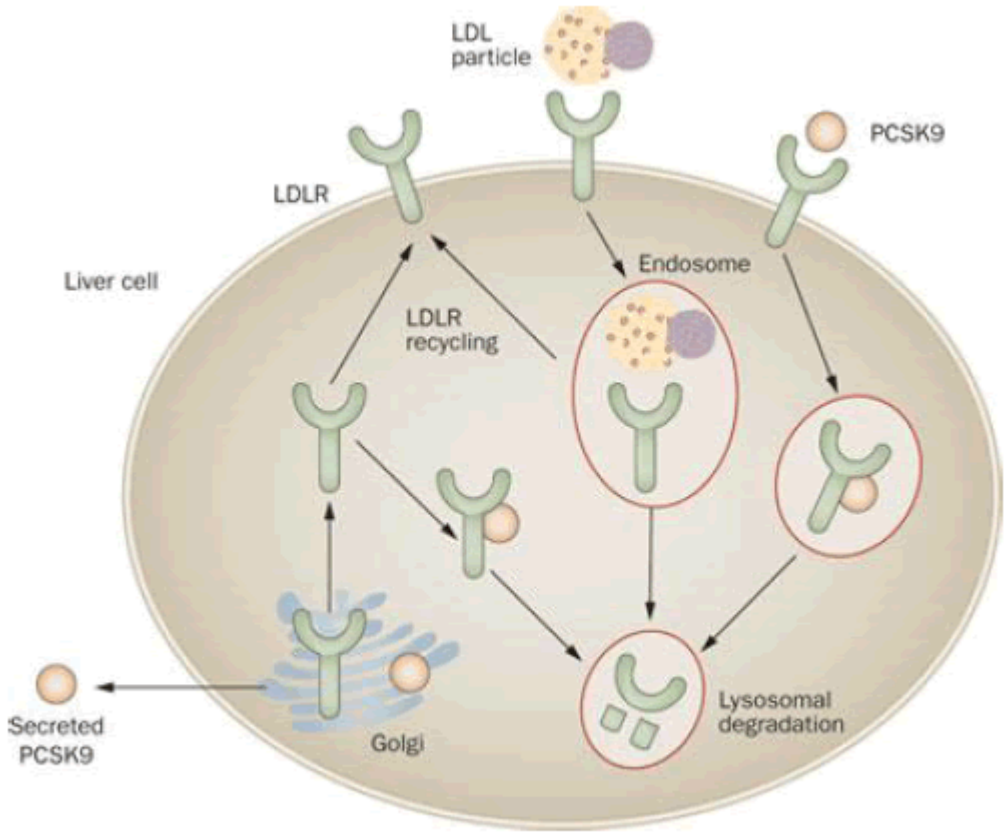


Figure 2: LDL receptors.

LDLR mutations

Table 1. Lipid and Lipoprotein Concentrations of Unrelated Persons

	Control Subjects[1] (n=203)	FH1[1] (n=112)	FH2[1] (n=36)	FH3 (n=31)
M/F	92/111	58/54	17/19	15/16
Age, y	41.1±14.5	40.0±13.6	40.1±15.1	36.7±12.5
TC, mmol/L	5.7±1.3	9.4±1.5	10.8±1.8[2]	9.4±1.4
LDL-C, mmol/L	3.8±1.2	7.7±1.4	9.0±1.6[2]	7.5±1.5
HDL-C, mmol/L	1.4±0.4	1.1±0.3	1.1±0.3	1.2±0.4
Triglycerides, mmol/L	1.8±1.5	1.3±0.6	1.6±0.6[3]	1.3±0.7

FH1, FH2, and FH3 indicate founder-related gene mutations in South African Afrikaners that affect the LDL receptor; FH, familial hypercholesterolemia; TC, total cholesterol; LDL-C, LDL cholesterol; and HDL-C, HDL cholesterol.

1. **Loss of function** variants in *LDLR*:
   a) Premature truncation (**nonsense**)
   b) Scramble the protein translation (**frameshift**)
   c) Alter the mRNA splicing process (**splice-site**)

APOB

- Apolipoprotein B
- Apolipoprotein B is the primary apolipoprotein of chylomicrons, VLDL, IDL, and LDL particles
- ApoB on the LDL particle acts as a ligand for LDL receptors in various cells throughout the body
- Loss of function mutations reduce LDL metabolism -> elevated risk

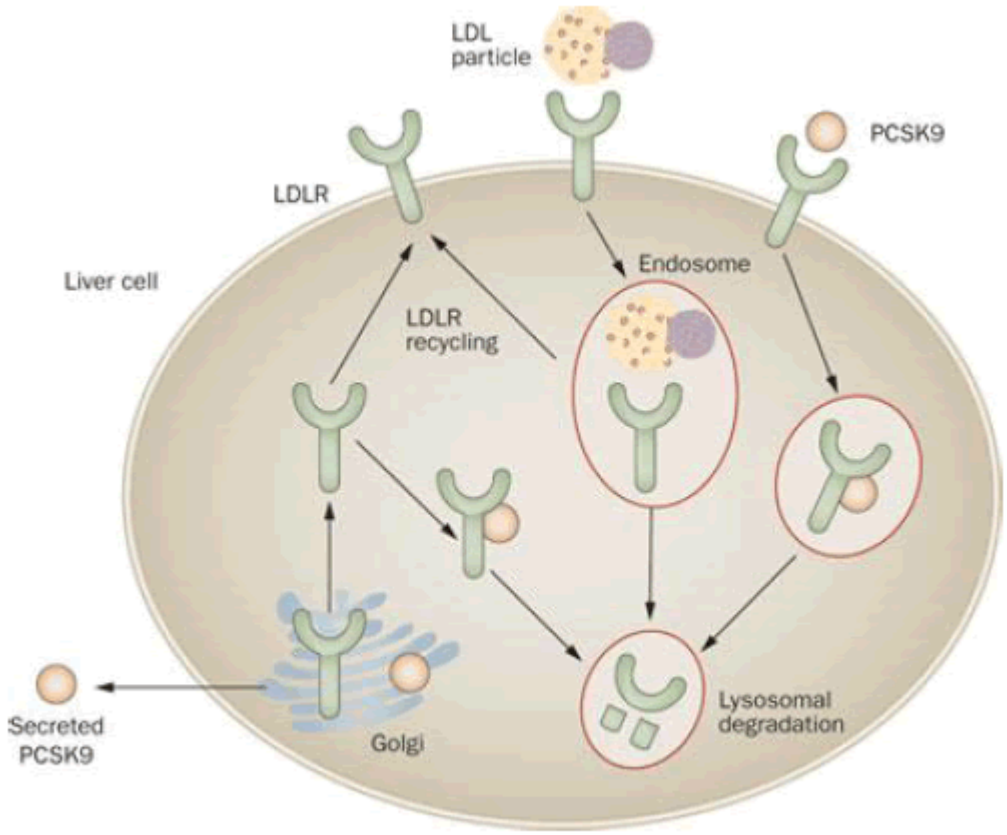
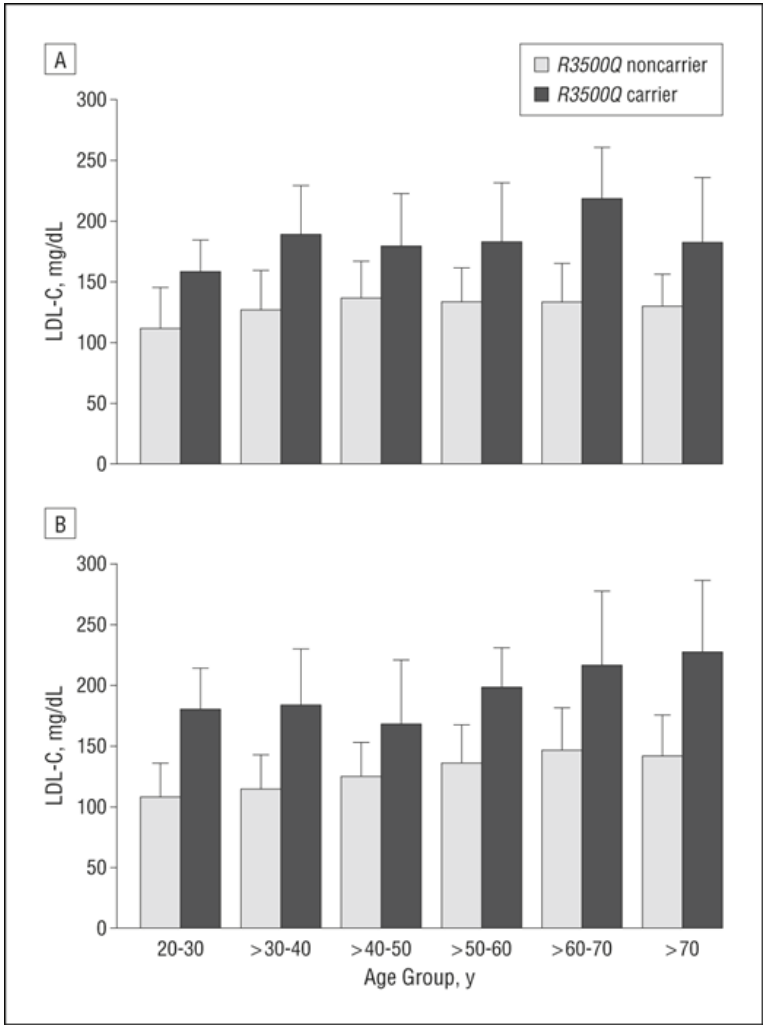
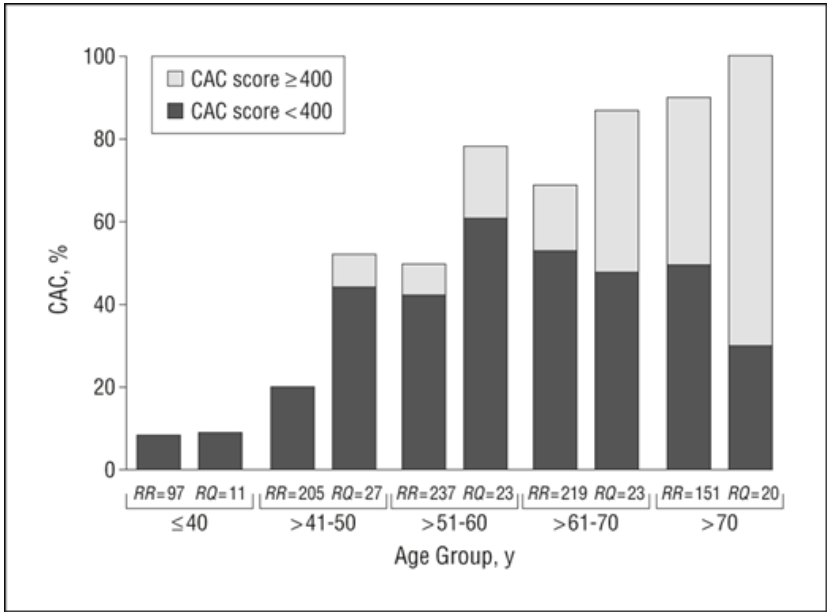


Figure 2: LDL receptors.

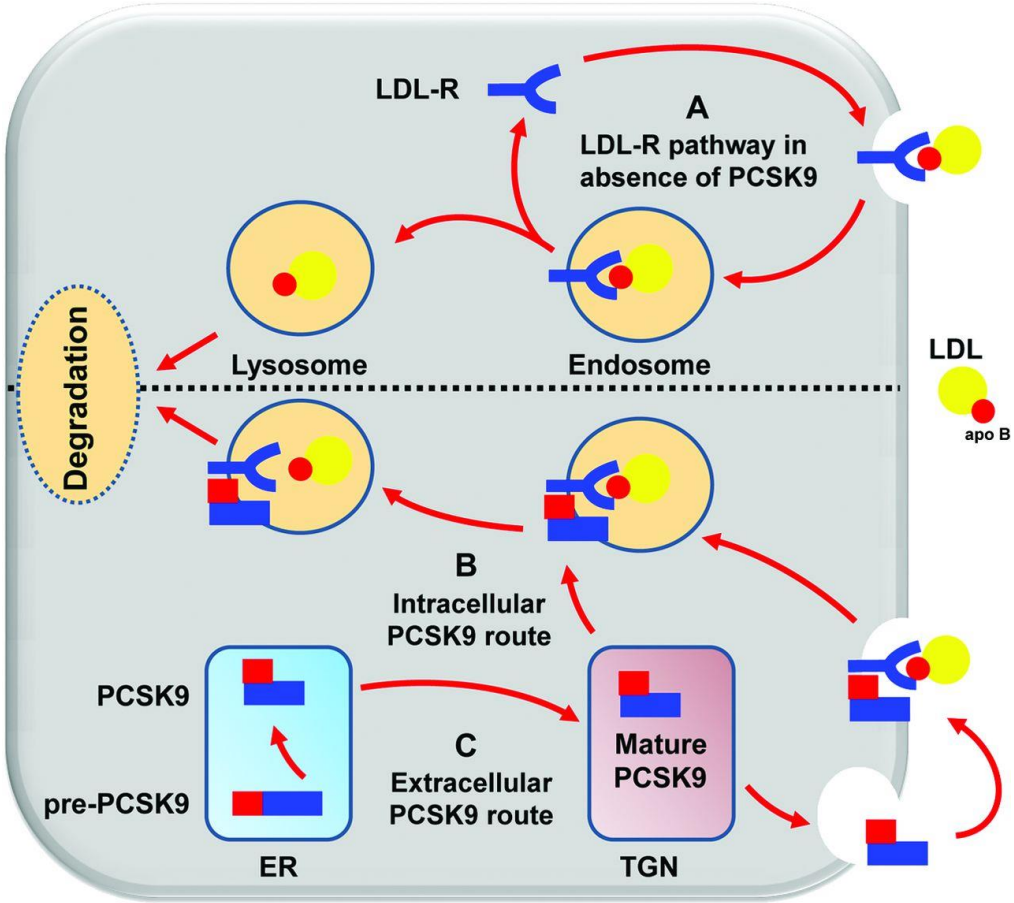
APOB MUTATIONS AND LDL



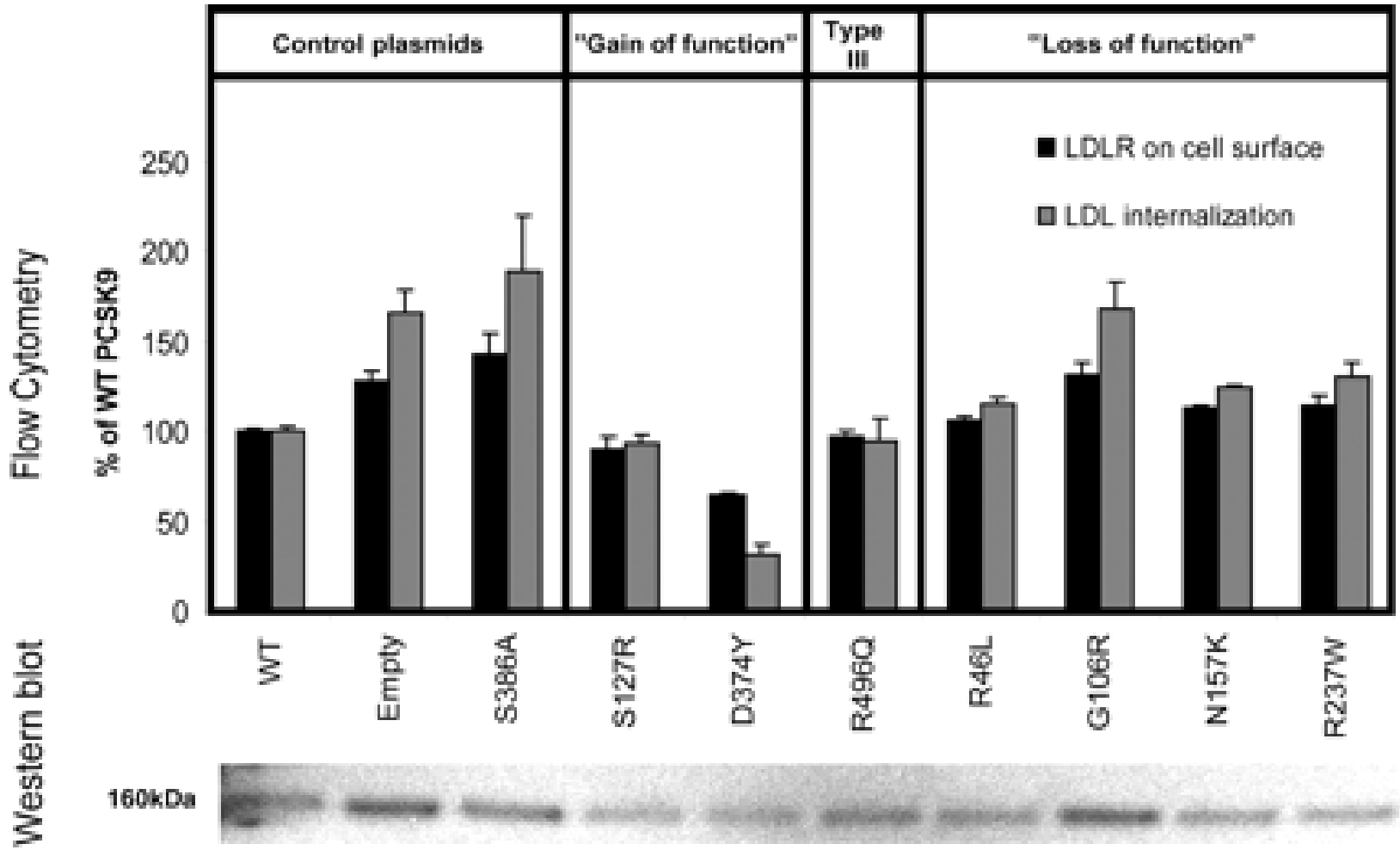


PCSK9

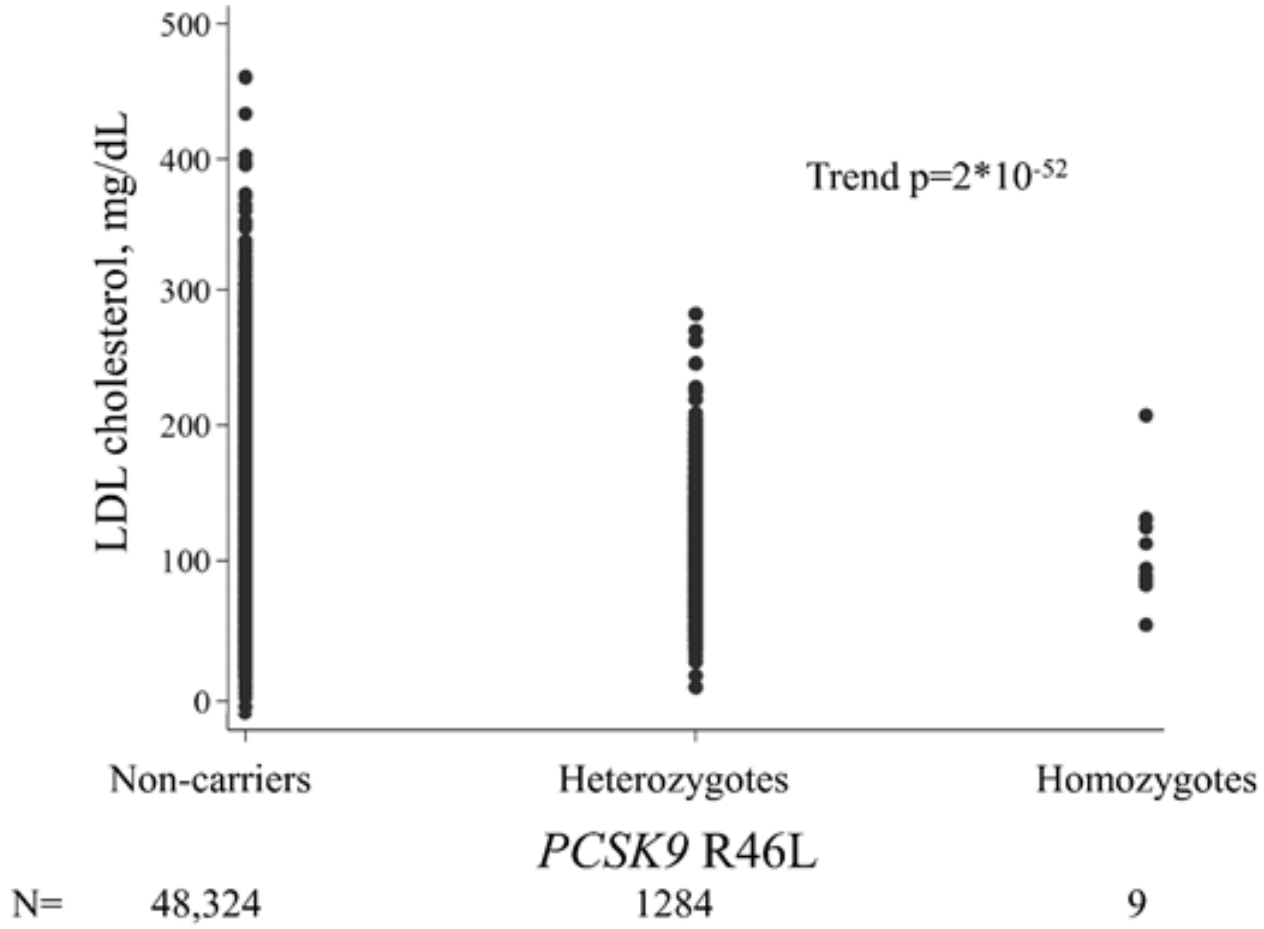
- The PCSK9 protein appears to control the number of low-density lipoprotein receptors, which are proteins on the surface of cells.
- These receptors play a critical role in regulating blood cholesterol levels.
- Increased PCSK9 increases LDL risk



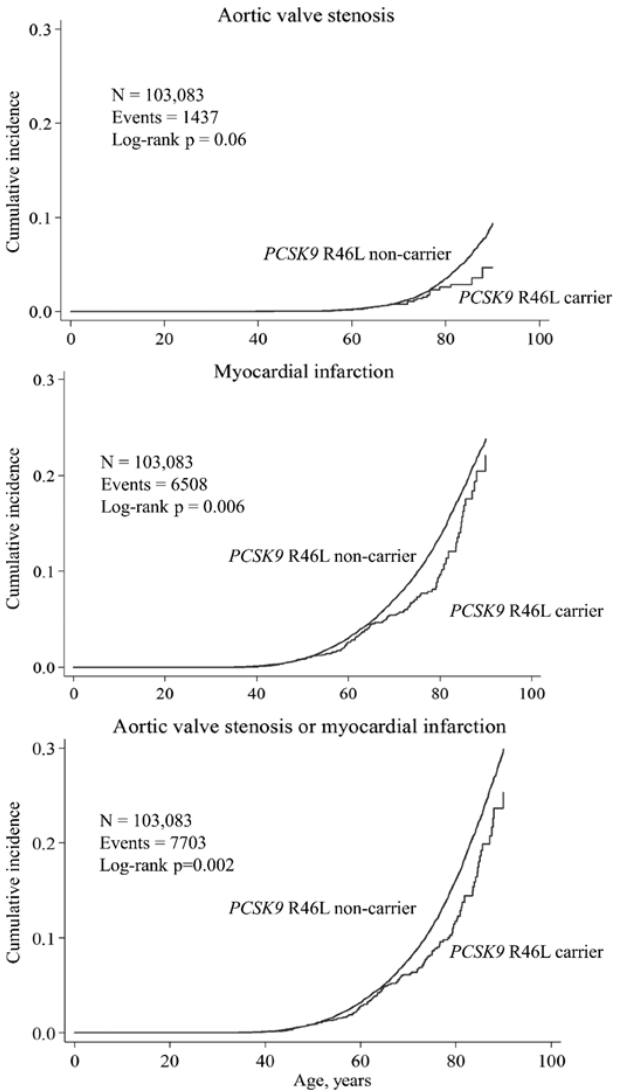
PCSK9 mutations and LDLR



PCSK9 mutations and cholesterol - LDL



PCSK9 mutations and cardiovascular health



Aortic stenosis is a narrowing of the aortic valve opening. Aortic stenosis restricts the blood flow from the left ventricle to the aorta and may also affect the pressure in the left atrium.

Myocardial infarction (MI), commonly known as a heart attack, occurs when blood flow decreases or stops to a part of the heart, causing damage to the heart muscle

IF AT RISK…

- Speak to your provider to learn whether your cholesterol levels have already been checked and how often testing should be repeated.
- Discuss ways to reduce your cholesterol with your provider. This may include certain medications as well as lifestyle modifications such as diet, exercise and quitting smoking.
- Consider completing a baseline electrocardiogram, a test that checks the electrical activity of the heart.

- Don’t smoke and avoid second-hand smoke
- Treat high blood pressure if you have it
- Eat foods that are low in saturated fat, trans fat, sodium (salt) and added sugars

- Be physically active
- Reach and maintain a healthy weight
- Control your blood sugar if you have diabetes

HDL – The underappreciated cholesterol

- Guidelines for dyslipidemia give little emphasis to treating low levels of HDL-C. Treating LDL-C is the primary target.

- The full benefits of increasing HDL-C have not been a major focus in clinical trials.

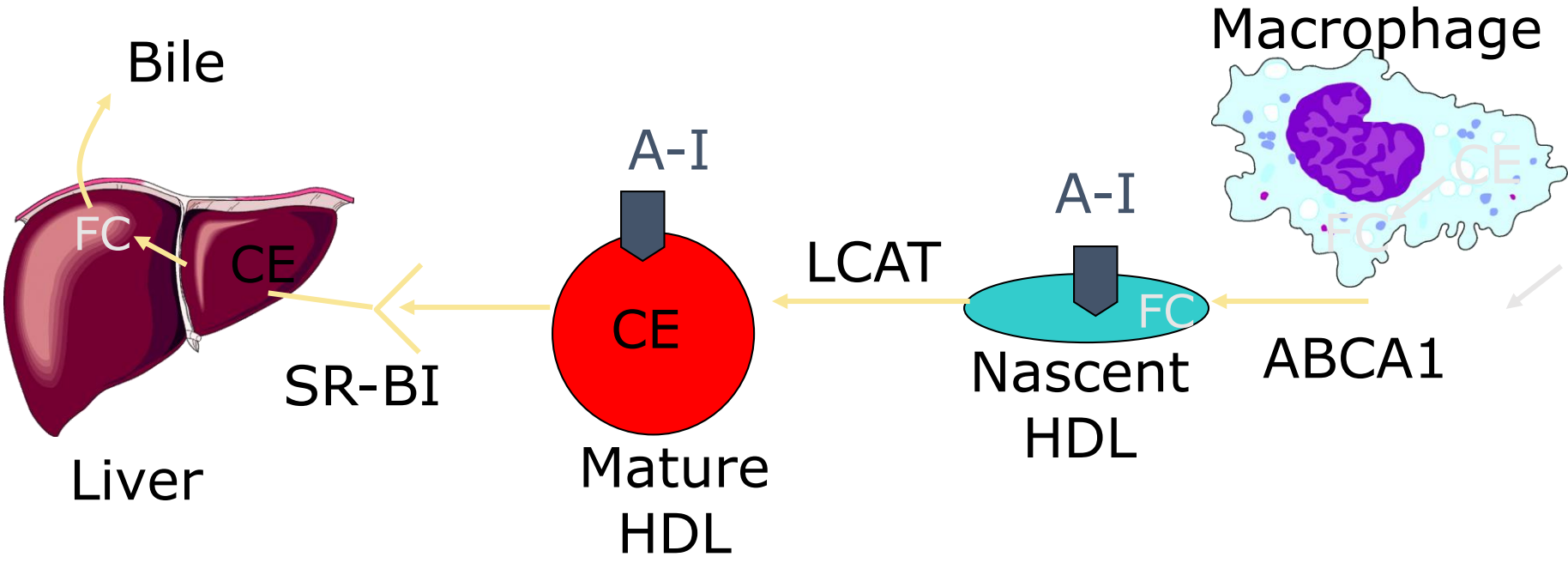
- Many providers are unaware of the benefits of raising HDL-C, and so put less effort into treating patients with low HDL-C levels.

What is HDL-C?

- High density lipoproteins are not contributors of atherosclerosis!

- High density lipoproteins:
  - inhibit the oxidation of low density lipoproteins
  - decrease adhesion molecules
  - decreases platelet activation
  - help remove the excess cholesterol deposited by LDLs from the arterial wall through reverse cholesterol transport.

Reverse Cholesterol Transport



ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I;
CE = cholesteryl ester; FC = free cholesterol;
LCAT = lecithin:cholesterol acyltransferase;
SR-BI = scavenger receptor class BI

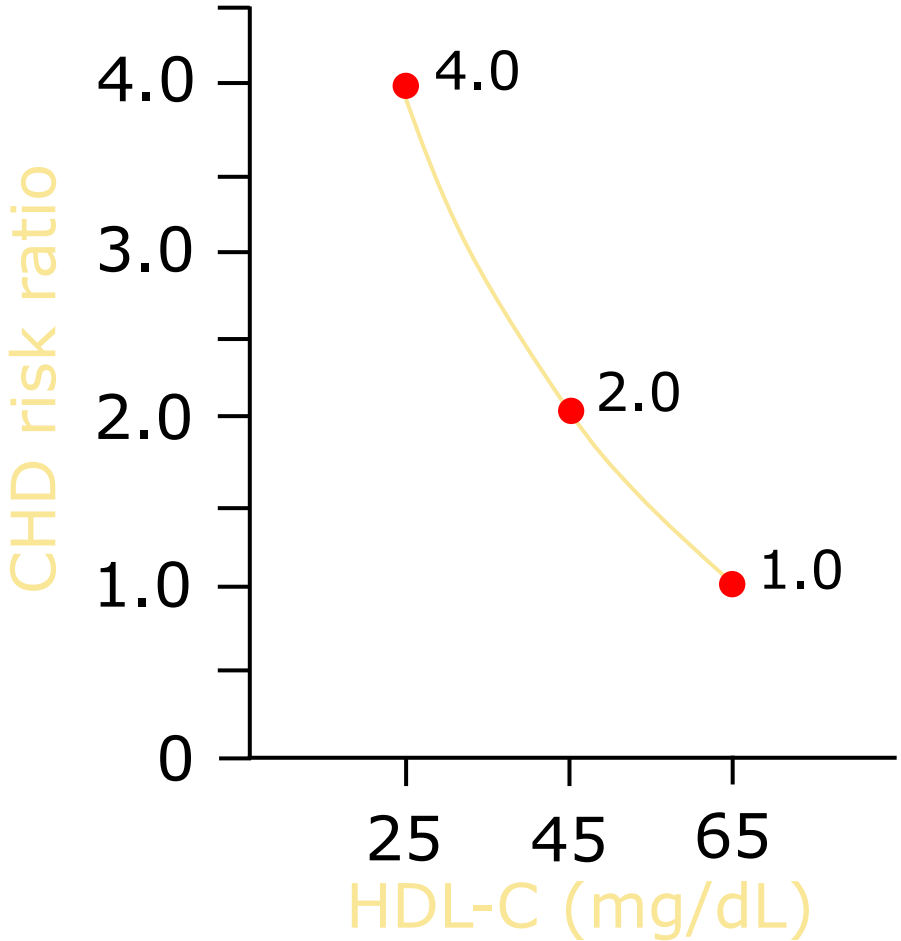
Why should you care about HDL-C?

- Independent of atherosclerosis or high levels of LDL-C, low HDL-C levels are a direct risk factor for CHD
  - This is true even when total cholesterol is normal <200 mg/dL
- Low HDL-C levels are especially dangerous in diabetics
  - 65% higher CHD death rate in diabetic men
  - Greater risk for atherosclerosis in diabetics

Why should you care about HDL-C?

- Low levels of HDL-C are associated with an increased risk for MI, restenosis after angioplasty, stroke, and sudden death
  - Men with low HDL-C are twice as likely to experience an MI as men with higher levels.
  - Women with low HDL-C are four to six times as likely to experience an MI as women with higher levels.

CHD Risk According to HDL-C Levels (Framingham Study)



Kannel WB. *Am J Cardiol* 1983;52:9B–12B.

Risk Reduction of CHD

- The risk for CHD decreases by 2-3% for every 1 mg/dL increase in HDL-C
  - Framingham Study
  - Helsinki Heart Study
    - increasing HDL-C reduced risk of CHD better than lowering LDL-C
  - Scandinavian Simvastatin Survival Study
    - patients with low HDL-C and high TG had greater risk reduction than those with high LDL-C on statin therapy

Risk Reduction

- Atherosclerotic plaque volume may be reduced by increasing HDL-C levels
- Increases in HDL-C decrease rate for coronary events
  - MI and death decreased by 22%
    - Vetrans Affairs cooperative studies program High-density Intervention Trial.

ABCA1 AND LOW HDL

- The ABCA1 gene belongs to a group of genes called the ATP-binding cassette family, which provides instructions for making proteins that transport molecules across cell membranes.
- The ABCA1 protein is produced in many tissues, with high amounts found in the liver and in macrophages
- ABCA1 mediates the efflux of cholesterol and phospholipids to lipid-poor apolipoproteins (apo-A1 and apoE), which then form nascent high-density lipoproteins (HDL).
- Reduced ABCA1 -> reduced HDL

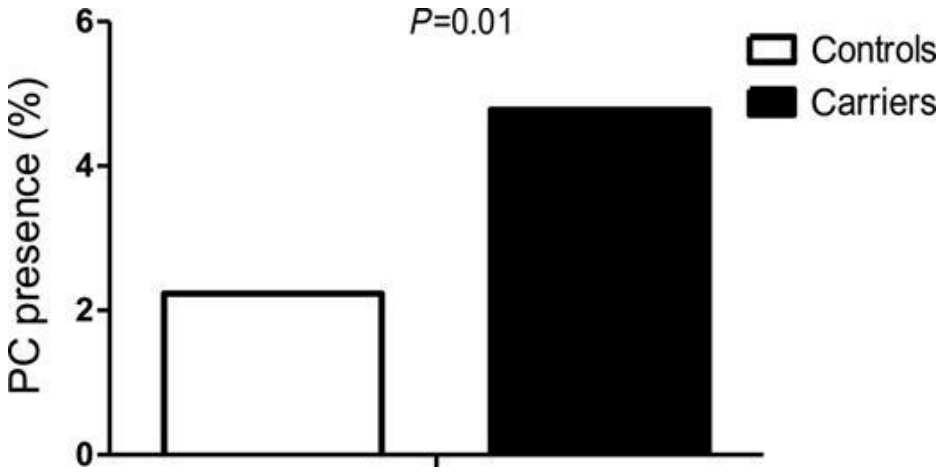
ABCA1 mutations & cardiovascular health

- Loss of function mutations associated with reduced HDL and increased plaques

Table 1

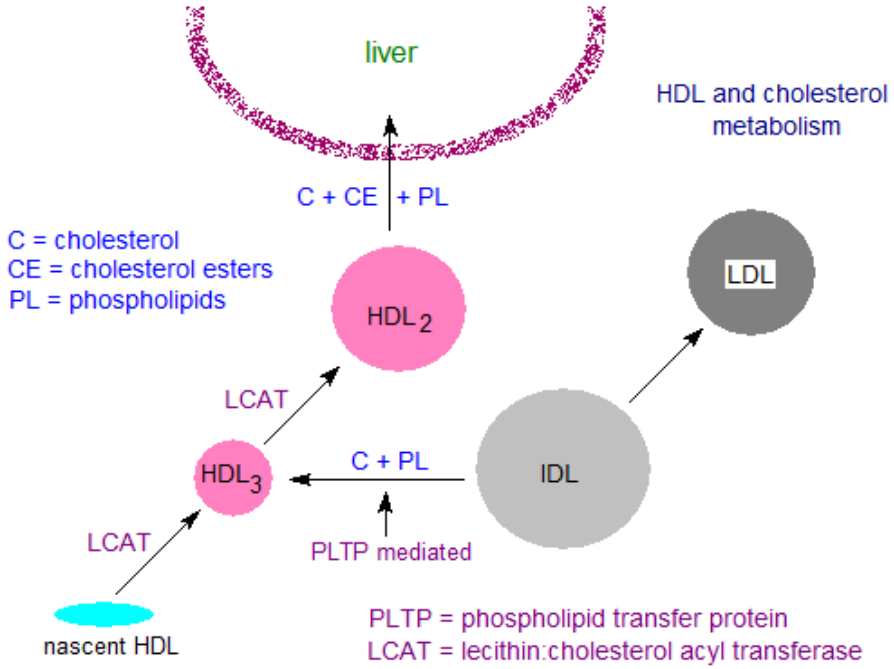
Characteristics in carriers of ATP-binding cassette transporter A1 gene mutations and controls

	ABCA1 mutation carriers (*n* = 36)	Controls (*n* = 36)	*P*-value
Lipid metabolism			
Total cholesterol (mmol/L)	4.35 ± 1.31	5.20 ± 1.09	0.004
LDL-cholesterol (mmol/L)	3.11 ± 1.04	3.41 ± 0.83	0.18
HDL-cholesterol (mmol/L)	0.84 ± 0.39	1.44 ± 0.44	<0.001
Triglycerides (mmol/L)	1.06 (0.78–1.39)	1.01 (0.68–1.40)	0.37
Apolipoprotein B (mg/dL)	120.79 ± 41.10	109.19 ± 26.64	0.19
Apolipoprotein A-I (mg/dL)	106.21 ± 43.15	156.74 ± 25.68	<0.001



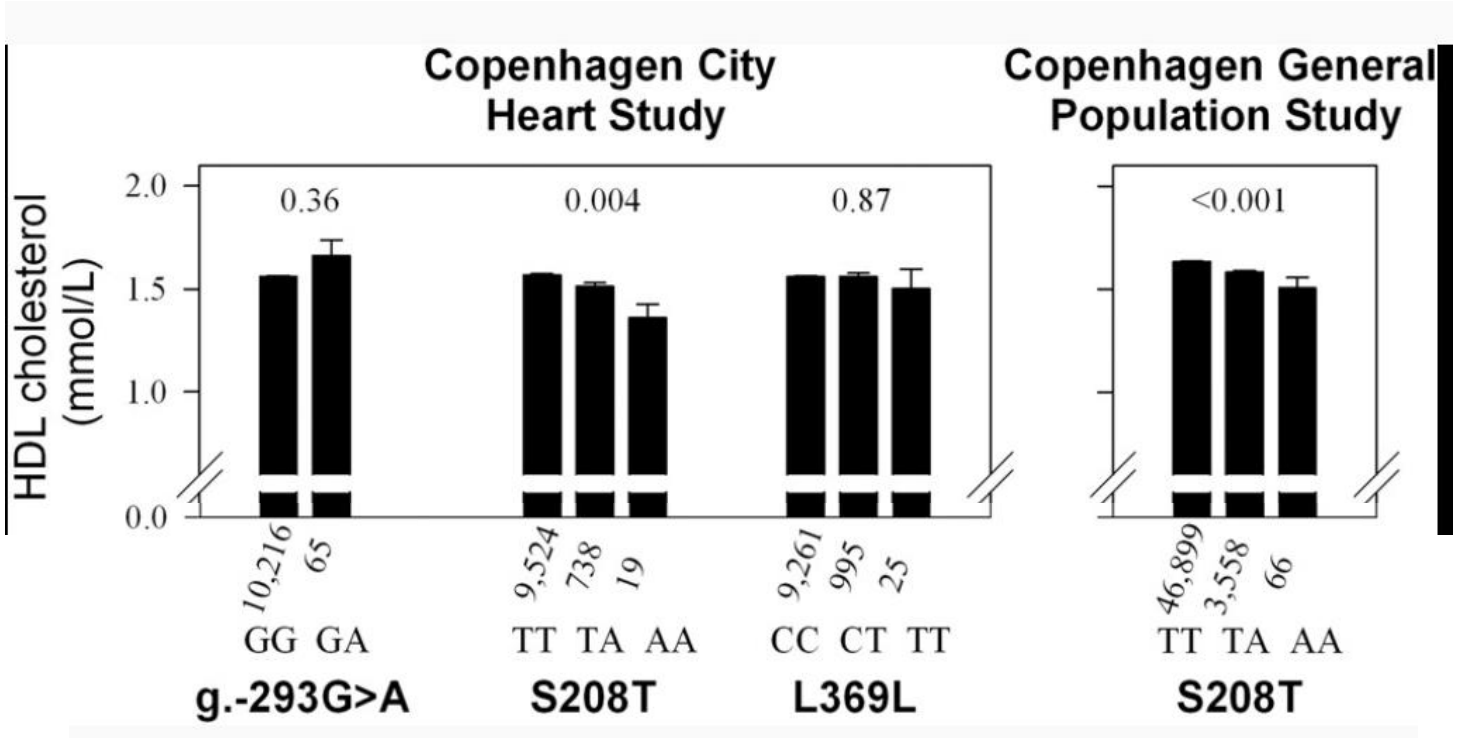
LCAT AND LOW HDL

- Lecithin:cholesterol acyltransferase (LCAT) is crucial to the maturation of high-density lipoprotein (HDL).
- Homozygosity for LCAT mutations underlies rare disorders characterized by HDL-cholesterol (HDL-c) deficiency while heterozygotes have half normal HDL-c levels.



LCAT AND LOW HDL

- Mutations that impact LCAT activity are associated with low HDL levels

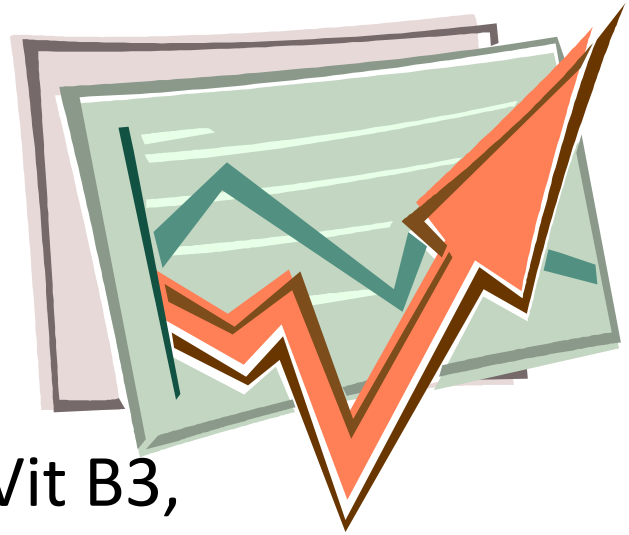


CETP AND LOW HDL

- Cholesteryl ester transfer protein
- Found in plasma, where it is involved in the transfer of cholesteryl ester from high density lipoprotein (HDL) to other lipoproteins.
- Mutations that decrease CETP activity associated with elevated HDL and vice-versa
- However, these mutations have also been associated with CVD
- Mechanism of how CETP regulates CVD not understood

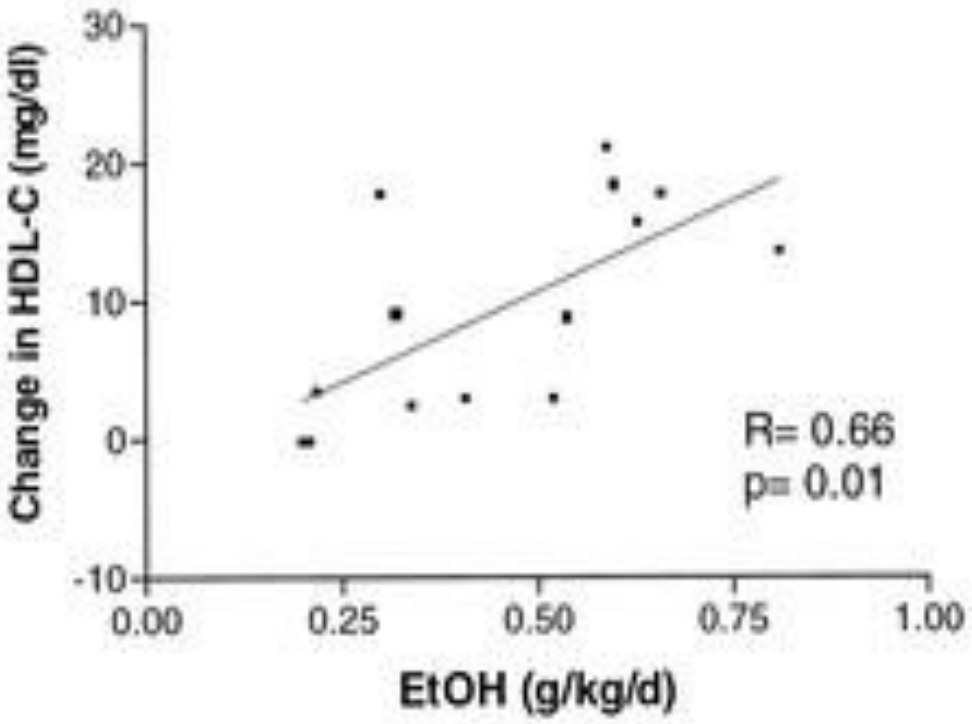
How can HDL-C be increased

- Lifestyle Changes
  - Smoking Cessation
  - Moderate Alcohol intake
  - Dietary Modification
  - Increased Physical Activity
- Current Pharmacology (Niacin – Vit B3, Statins)
- Developing Pharmacology



Lifestyle Changes

- Smoking Cessation
  - the relationship between smoking and low HDL-C is stronger in women compared to men
  - All patients should be advised to quit smoking
- Moderate Alcohol intake
  - moderate alcohol consumption = increases in HDL-C
  - increases HDL associated PON1 enzyme, which inhibits the oxidation of LDL and breaks down oxidized LDL



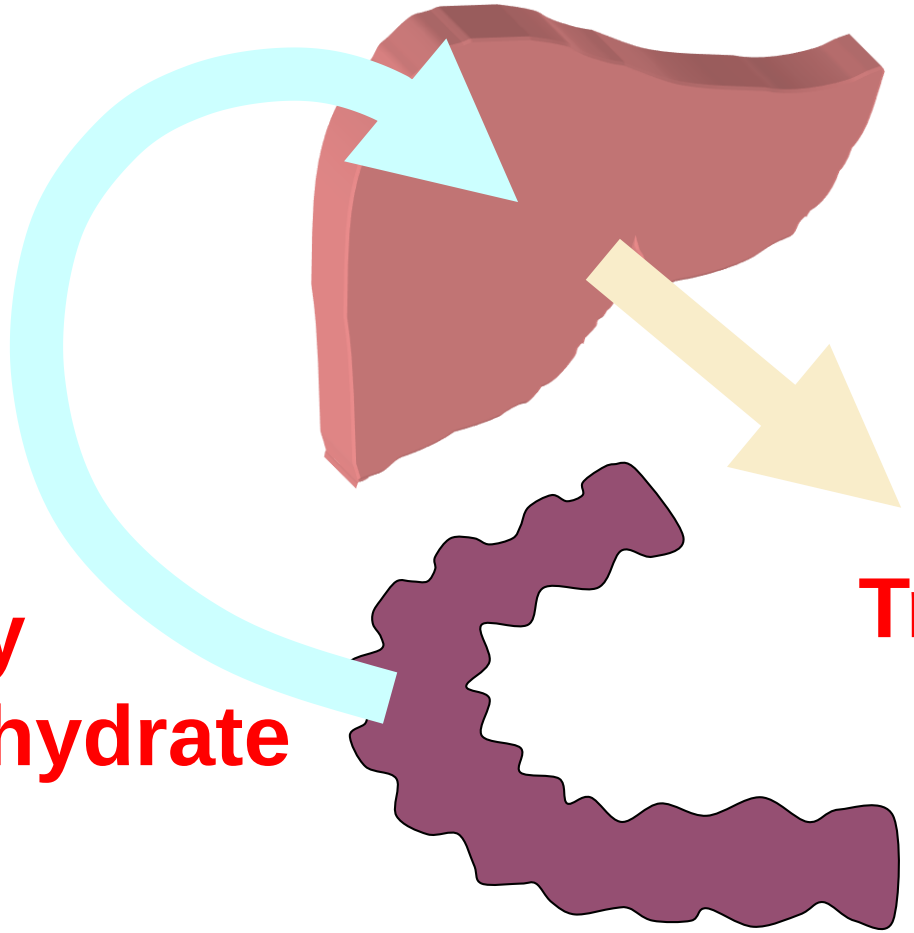
Lifestyle Changes

- Dietary Modification???
  - Dieting alone may lower LDL-C and triglycerides, but also lowers HDL-C levels
- Increase Physical Activity
  - Moderate intensity exercise significantly increases HDL-C levels.
- Results are best if diet and exercise are combined!

Triglycerides

- The body converts excess calories, sugar, and alcohol into triglycerides, a type of fat that is carried in the blood and stored in fat cells throughout the body.
- People who are overweight, inactive, smokers, or heavy drinkers and those who eat a very high carbohydrate diet tend to have high triglycerides
- A triglycerides score of 150 or higher puts you at risk for metabolic syndrome, which is linked to heart disease and diabetes.

Dietary Carbohydrate Increases VLDL Production



Triglycerides

Causes of high triglycerides in the general population

- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Excess alcohol intake
- Very high carbohydrate diets (>60% of energy)
- Other disease (diabetes, renal failure, nephrosis)
- Drugs: steroids, protease inhibitors, estrogen, etc
- Genetic factors

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

Triglycerides

Risk Classification of Serum Triglycerides

Normal <150 mg/dL

Borderline high 150–199 mg/dL

High 200–499 mg/dL

Very high ≥500 mg/dL

Triglycerides

- Publication of meta-analyses have shown that elevated triglycerides are in fact an ***independent risk factor*** for CHD

- This suggests that some triglyceride-rich lipoproteins (TGRLP) are atherogenic.

Triglycerides

- When triglyceride levels are ≥200 mg/dL, the presence of increased quantities of atherogenic remnant lipoproteins can heighten CHD risk substantially beyond that predicted by LDL cholesterol alone.
- This is why moderate elevation in triglyceride levels needs to be given increased clinical consideration.

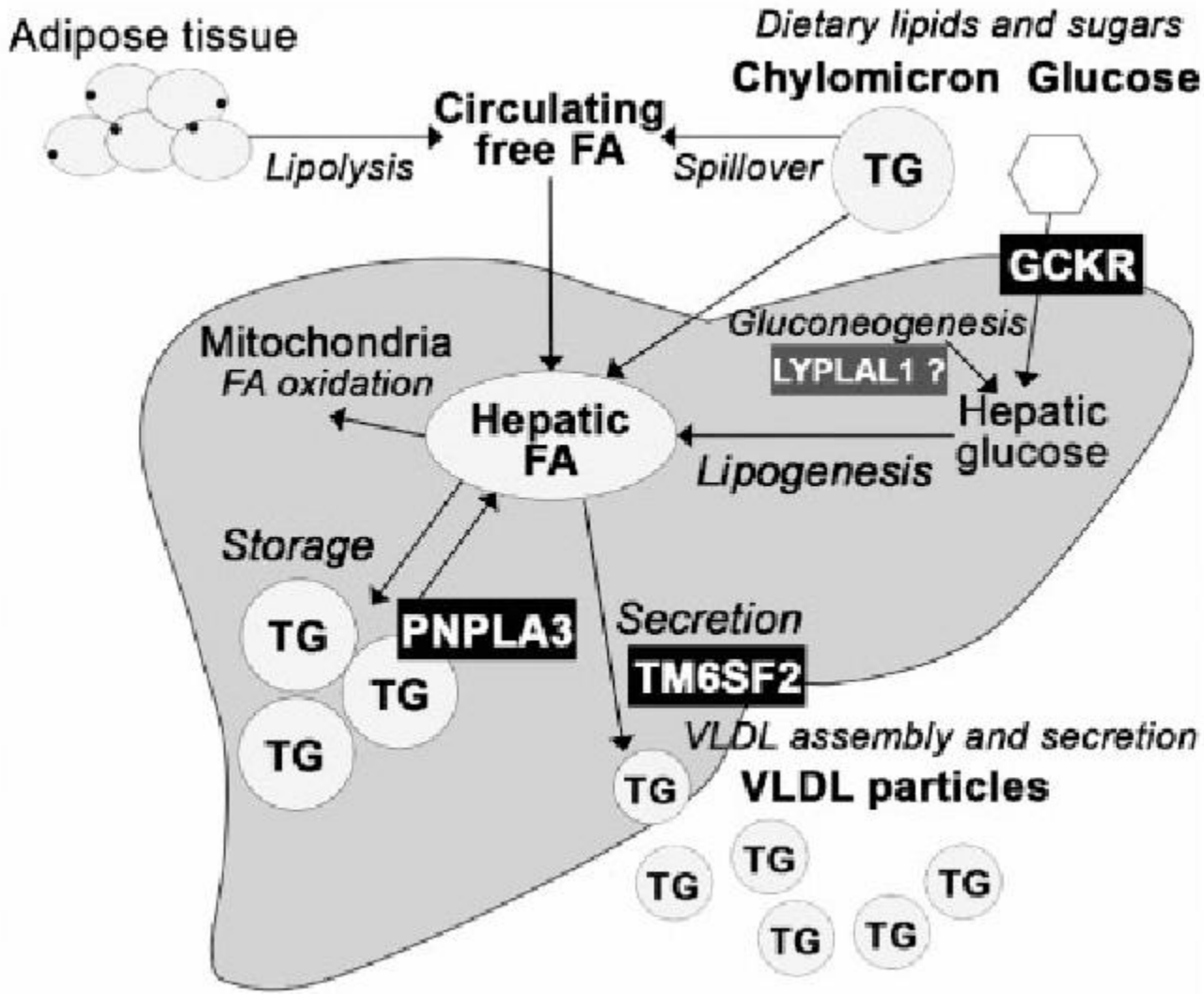
Triglycerides

- If triglycerides are very high (≥500 mg/dL), attention turns first to prevention of acute pancreatitis, which is more likely to occur when triglycerides are >1000 mg/dL.
- Triglyceride-lowering drugs (fibrate or nicotinic acid) become first line therapy; although statins can be used to lower LDL cholesterol to reach the LDL goal, in these patients

GCKR AND INCREASED TRIGLYCERIDES

- This gene encodes a protein belonging to the GCKR subfamily of the SIS (Sugar Isomerase) family of proteins.
- The gene product is a regulatory protein that inhibits glucokinase in liver and pancreatic islet cells by binding non-covalently to form an inactive complex with the enzyme
- Glucokinase is a key enzyme in glucose metabolism in the liver
- Glucokinase promotes glucose flux in liver

GCKR AND INCREASED TRIGLYCERIDES



GCKR AND INCREASED TRIGLYCERIDES

- Mutations that decrease GCKR activity
- Altered GCK regulation in liver is predicted to enhance glycolytic flux, promoting hepatic glucose metabolism and elevating concentrations of malonyl-CoA, a substrate for de novo lipogenesis which promotes triglyceride generation.

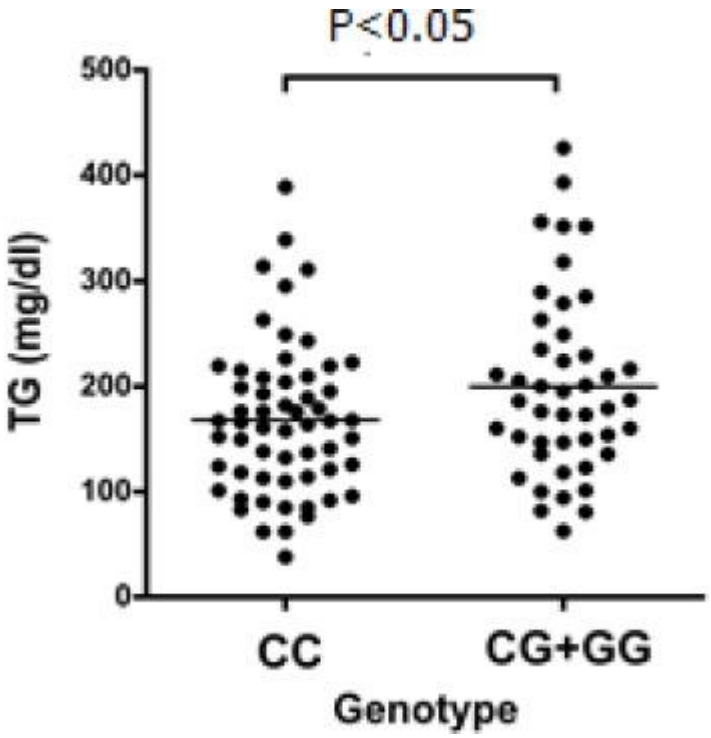
Table 2. Effects of *GCKR* rs1260326 on TG levels and glucose homeostasis parameters using the up-to-four repeated measurements over the 9-year follow-up study.

	Number of observations	*P* value	Δ% [95% CI]	Overall mean ± SD		
				CC	CT	TT
Fasting plasma triglycerides (mmol/l)						
add	13,955	**$1x10^{-4}$**	3.41 [1.68, 5.16]	1.12±0.87	1.19±0.97	1.21±0.73
dom		$1x10^{-3}$	4.24 [1.61, 6.94]			
rec		$1x10^{-3}$	5.00 [1.90, 8.19]			

ZNF259 AND INCREASED TRIGLYCERIDES

- Zinc finger protein ZPR1 is a protein that in humans is encoded by the ZNF259 gene.
- Deficiency of the zinc finger protein ZPR1 causes defects in transcription and cell cycle progression.

•Variants in this gene are associated with high triglycerides
•Mechanism not completely understood



IF SOMEONE HAS ELEVATED RISK…

- Personalize diet and exercise plan
- Incorporation of Omega 3 fatty acids, fiber and niacin (Vitamin B 3)
- Reduction in carbs and sugars, weightloss