

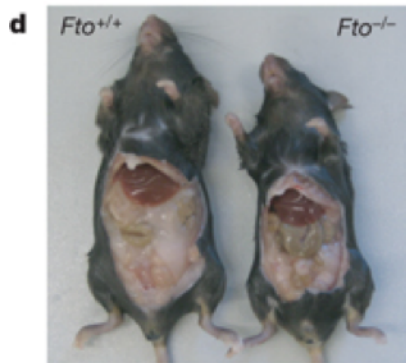


An Integrated Genetic Approach to Metabolic and Dietary Health.

Dr. Penny Kendall-Reed, ND



Why we can't all eat the same diet?



- ❑ Normal vs Variant FTO.
- ❑ 20-week-old mice:
- ❑ Same diet, exercise and sleep patterns



Metabolic Genes

- ❑ FTO rs9939609
- ❑ MC4R rs17782313
- ❑ ADIPOQ rs17366568
- ❑ ADIPOQ rs17300539
- ❑ ADRB2 rs1042714
- ❑ PPARg rs1801282



FTO rs9939609

- ❑ Normal Allele = T Variant Allele = A
- ❑ Regulates ghrelin, leptin and adiponectin.
- ❑ Can stimulate dopaminergic activity in the Ventral Tegmental Area.
- ❑ Increased synaptic firing and wiring for Feeding Seeking Behaviours.

❑ *Abisaid et al 2006 and 2011, Addict Biol 2001 Jan;16(1):82-91, Citri and Malenka, 2008:, Nicoll, 2017*



FTO A Allele

- ❑ Lowered metabolic rate.
- ❑ Increased risk of obesity by 1.7%
- ❑ Increased adipogenesis – IRX3 and IRX5
- ❑ Gene expression turned on with saturated fats, simple carbohydrates and/or increased caloric intake.



MC4R rs17782313

- ❑ Normal Allele = T Variant Allele = C
- ❑ Melanocortin 4 receptor on the hypothalamus.
- ❑ Regulates satiety vs hunger.
- ❑ Ghrelin >> increases NPY and AgRP = hunger.
- ❑ Leptin >> increases α -MSH and inhibits NPY = satiety.



MC4R C Allele

- ❑ Heterozygote increases obesity and BMI by 8%.
- ❑ Homozygote variant increases obesity and BMI by 43%.
- ❑ Increased insulin resistance by 14% especially with sugars and saturated fats.
- ❑ Variants have significant increase in weight with antidepressants and antipsychotics.

- ❑ *Hinley et al, Prog Mol Biol Transl Sci. 2013;114:147-91*
- ❑ *Chambers JC, P et al, (Jun 2008). Nature Genetics 40 (6): 716–8.)*





MC4R – can't stop eating!



ADIPOQ

- ❑ Regulates insulin sensitivity.
- ❑ Regulates serum glucose levels.
- ❑ Regulates fatty acid oxidation.
- ❑ Decreases inflammation.

❑ *Nat Med.* 2001 Aug; 7(8): 941-6



ADIPOQ rs17366568

- ❑ Normal Allele=G Variant Allele= A
- ❑ Variants have decreased production of adiponectin **during weight loss.**
- ❑ Increased production of adiponectin when following genetic diet.
- ❑ Variants have increased weight, BMI, diabetes and sugar cravings.

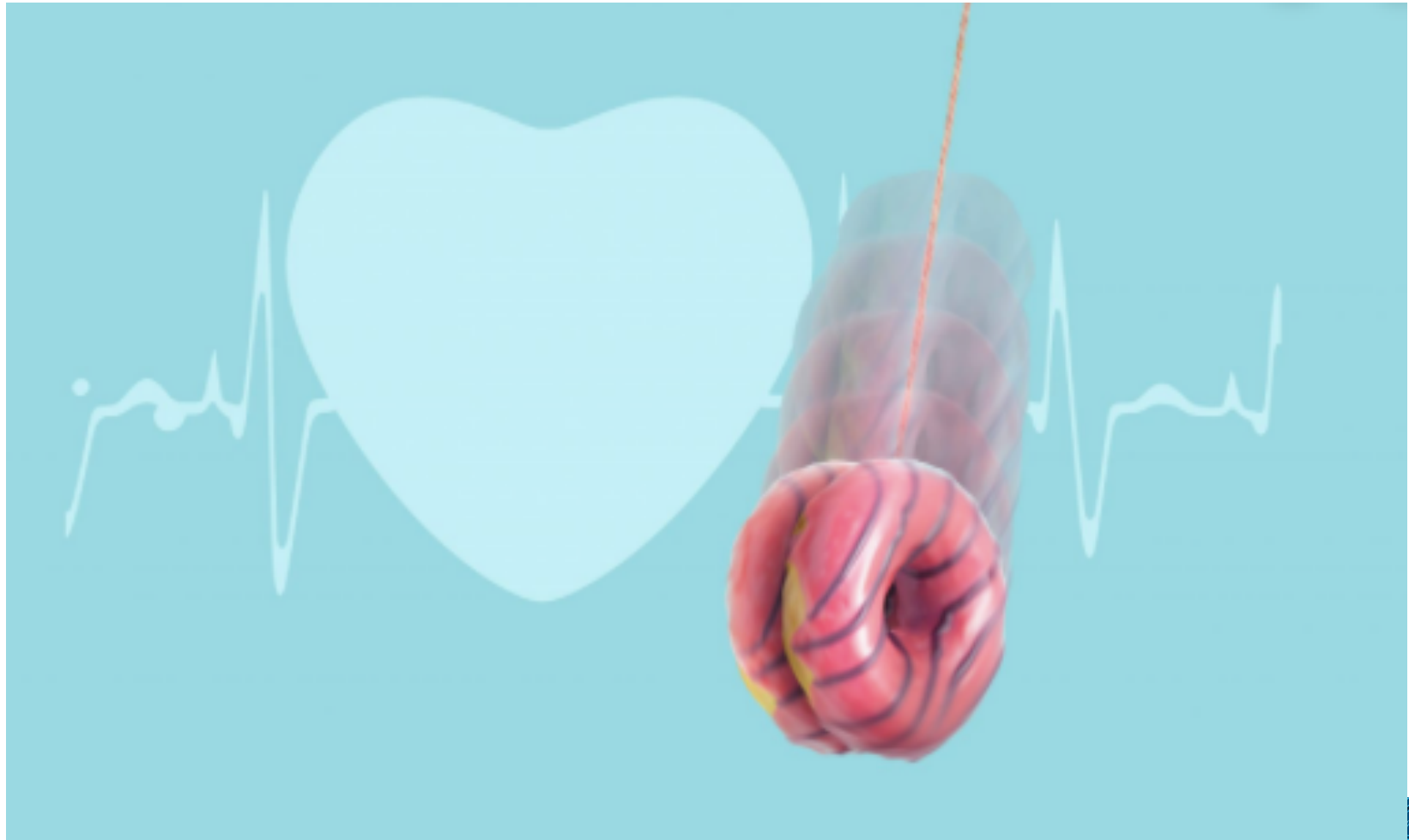
❑ *Hormone and Metabolic Research. 2009; 41: 55-61.*



ADIPOQ rs17300539

- ❑ Normal Allele = A Variant Allele = G.
- ❑ Variants have decreased production of adiponectin **when cheating or during weight maintenance.**
- ❑ Increased production of adiponectin when not following genetic diet.
- ❑ Yoyo dieter!





ADRB2 rs1042714

- ❑ Normal Allele = C Variant Allele is G
- ❑ Beta-2 adrenergic receptor- wide distribution.
- ❑ Binds stress hormones regulating food cravings, mood, response to diet and exercise, BMI, lipogenesis and anxiety.

❑ *Metabolism 2007 Jun;56(6):757-65.*

❑ *Physio Behav 2008 May 23;94(2):219-30*



ADRB2 G Allele

- ❑ Increased sensitivity to carbohydrates and sugars.
- ❑ Decreased weight loss with endurance exercise.
- ❑ Increased production of inflammatory cytokines.
- ❑ Altered leptin production.

❑ *Appl. Physiology, Nutrition Metabolism* Mar 2016; 41(3)

❑ *Pharmacogenet Genomics* 2010 Jan;20(1):64-69.



PPAR γ rs1801282

- ❑ Normal Allele = C Variant Allele = G
- ❑ Peroxisome proliferator-activated receptor gamma in adipose tissue.
- ❑ Regulates insulin sensitivity, serum glucose and fat metabolism.
- ❑ Regulates endothelial inflammation and reduces atherosclerosis .
- ❑ Impacts the production of inflammatory cytokines TNFa and IL6.
- ❑ *Gene. 2012 Dec 15; 511(2): 404-10.*
- ❑ *Diabetes. 2002 Aug; 51(8): 2341-2347.*



PPAR γ rs1801282

- ❑ Master Regulator of adipocyte biology.
- ❑ Modifies transcription of numerous genes involved in glucose and lipid metabolism.
- ❑ Involved in fat cell differentiation >> development of adipocyte precursor cells.



PPAR γ G Allele

- ❑ Variant allele but not the risk allele.
- ❑ Improved insulin sensitivity.
- ❑ Decreased risk of diabetes and heart disease.
- ❑ *Worse on high carbohydrate and high saturated fat diet.
- ❑ **Higher risk of complications in patients that develop diabetes.**
- ❑ **Increased weight gain if the individual becomes overweight.**



PPAR γ C Allele

- ❑ Normal Allele but the risk allele
- ❑ Higher BMI
- ❑ Increased risk of diabetes.
- ❑ Worse on high carbohydrate and high saturated fat diet.
- ❑ Fewer health benefits from exercise compared to GG.



Comparative Integration

❑ FTO A/A

❑ MC4R T/C

❑ ADIPOQ (wl)-A/G

❑ ADIPOQ (m) – G/G

❑ ADRB2 – C/C

❑ PPARG – C/C

❑ FTO – T/T

❑ MC4R – T/T

❑ ADIPOQ (wl) – A/A

❑ ADIPOQ (m) – G/G

❑ ADRB2- C/G

❑ PPARg – G/G



Case Study 1

- ❑ 53-yr-old female gained 32 lbs. over the past 5 years, with large food cravings for sweets and fats.
- ❑ Had always struggled with weight, but if she really reduced her caloric intake, she could loose some.
- ❑ NOT THIS TIME!
- ❑ 3 meals, no snacks, lean protein, balanced whole grains, no simple sugars and low saturated fats.



Case Study 1

- ❑ FTO A/A – low adiponectin, high ghrelin, leptin instability.
- ❑ MC4R T/C – increased ghrelin and leptin instability.
- ❑ ADIPOQ(wl)-A/G – lower adiponectin.
- ❑ ADIPOQ (m) – G/G – really low adiponectin if deviates
- ❑ ADRB2 – C/C – normal stress response
- ❑ PPARG – G/G – variant allele but not the risk allele



Case Study 1

- ❑ Dolichos biflorus, Piper Betle and Acetyl L-Carnitine combo:
 - 2 caps BID 30 mins to 1 hour before lunch and dinner for 8 weeks.
 - Intermittent Fasting with 3 cycles of FMD to start.



Case Study 1

- ❑ She started dropping 2.5 lbs weekly until she had lost 38 lbs.
- ❑ Reduced her Metabolic combo to 1 week out of every 3 weeks (smaller rotation due to multiple genes).
- ❑ Kept her on Intermittent Fasting and rotated in FMD (fasting mimicking diet) 3 times a year.
- ❑ 7 years later she has maintained her weight loss, has no food cravings and controls her weight if she indulges.



Case Study 2

- ❑ 31-year-old female who graduated med school 2 years ago.
- ❑ She was very stressed during school, worse now.
- ❑ Sleep deprived – 5 hrs/night and wakes at 2:30 am.
- ❑ She has always been slim but gained 11 lbs in the past 4 years, no change in diet or exercise, then a rapid weight gain of another 13 lbs in 6 months.
- ❑ Blood sugars began to rise quickly.



Case Study 2

- ❑ FTO – T/T – normal hormonal response, fast metabolism.
- ❑ MC4R – T/T - normal hormonal response, fast metabolism
- ❑ ADIPOQ – A/A – normal adiponectin
- ❑ ADIPOQ – G/G – low adiponectin when cheating
- ❑ ADRB2- C/G – increased weight, gene blocking with stress
- ❑ PPARg – C/C- increased PPARg blocking metabolic genes and faster increase in weight.



Case Study 2

- ❑ Tryptic Decapeptide, L-Theanine combo:
 - 2 BID empty stomach for 4 weeks, then reduce to 1 BID empty stomach increasing as needed for stress.
- ❑ Resveratrol– 150 mg BID empty stomach for 8 weeks and then reduce to once per day.
- ❑ No change in diet.



Case Study 2

- ❑ She lost 8 lbs in the first month and 4 each of the following months until she had lost 27 lbs.
- ❑ 5 months later a big stressor hit and she did not increase her Decapeptide combo, she gained 3.5lbs.
- ❑ She returned, we increased it back to 2 BID for 4 weeks and the weight dropped again.



Dietary Genes - Carbohydrates

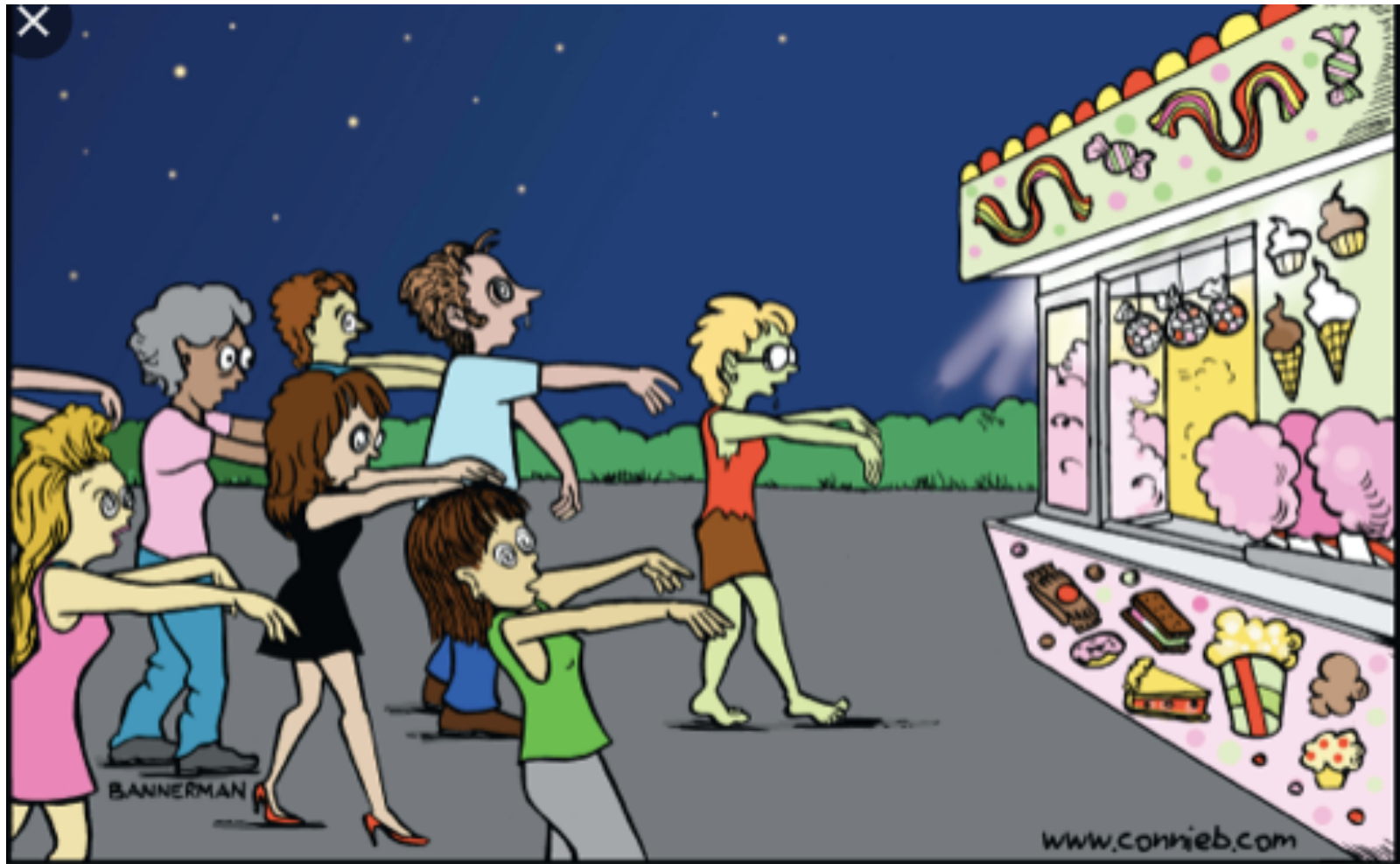
- ❑ TCF7L2 rs7093146
- ❑ IRS1 rs2943641
- ❑ GIPR rs2287019



TCF7L2 rs7093146

- ❑ Normal Allele = C Variant Allele = T
- ❑ Transcription factor 7 like-2
- ❑ Alters the expression of other genes that control insulin production and sensitivity after the consumption of carbohydrates.
- ❑ Increased sugar cravings.





TCF7L2 T Allele

- ❑ Largest risk factor for glucose regulation and Type 11 diabetes.
 - Homozygote variants increased risk by 2-fold.
 - Heterozygotes increased risk by 1.4-fold.
- ❑ Involved in the signaling pathways of glucose regulation between cells.
- ❑ *Nat Genet 2006 38(3):320-3*
- ❑ *J Nutri Biochem 2012 23(3):239-44*



IRS1 rs2943641

- ❑ Normal Allele = T Variant Allele = C
- ❑ Insulin receptor substrate 1, ligand to the insulin receptor>>>insulin signaling and glucose transport.
- ❑ Major protein that activated IGF-1 and P13K pathways.
- ❑ *Trends Endocrinol Metab.* 2006 Mar; 17(2): 72-8.
- ❑ *Nature.* 2009 Apr 9; 458(7239): 725-31.



IRS1 C Allele

- ❑ Increased risk of obesity, BMI and diabetes following carbohydrate consumption.
- ❑ Increased risk of colorectal, lung, prostate and breast cancers.
- ❑ Increased progression of the above cancers.

❑ *Nat Genet. 2009 Oct; 41(10): 1110-5.*



GIPR rs2287019

- ❑ Normal Allele = C Variant Allele = T
 - ❑ Gastric Inhibitory Polypeptide Receptor
 - ❑ Protein that binds to insulinotropic peptide receptors to regulate insulin and glucose after carbohydrate consumption.
 - ❑ Inhibits release of gastric acid and gastrin.
- ❑ *Am J Clin Nutr.* 2012 Feb; 95(2): 506-13.



GIPR T Allele

- ❑ Increased insulin following carbohydrates.
 - ❑ Increased gastric and intestinal inflammation.
 - False gluten sensitivity.
 - ❑ Increased obesity and diabetes.
- ❑ *Genes Nutr.* 2013 May; 8(3): 271-87.
- ❑ *Endocr J.* 2013; 60(8): 991-1000.



Comparative Integration

❑ TCF7L2 -C/C

❑ IRS1 – T/C

❑ GIPR – C/C

❑ FTO – A/A

❑ ADRB2 – G/G

❑ TCF7L2 – T/T

❑ IRS1 – T/T

❑ GIPR – C/T

❑ FTO – T/T

❑ ADRB2 – C/G



Case Study 3

- ❑ 48-year-old perimenopausal woman gained 27 lbs in 6 months with no change in diet or exercise.
- ❑ She had never been overweight in the past.
- ❑ Difficulties sleeping in the past year, waking at 2:00 am and again at 4:00 am.
- ❑ Dropped all sugars, starchy veggies, grains and fruits and gained more weight.



Case Study 3

- ❑ TCF7L2 - C/C – normal insulin response to carbs
- ❑ IRS1-T/C– slight increase insulin to carbs, increase CA risk.
- ❑ GIPR-C/C – normal insulin and GI inflammatory response to carbs.
- ❑ FTO – A/A – increased risk of obesity.
- ❑ ADRB2 – G/G – increased risk of obesity with stress.



Case Study 3

- ❑ Dolichos biflorus, Piper Betle and Acetyl L-Carnitine combo:
 - 2 caps BID 30 mins to 1 hour before lunch and dinner for 8 weeks and then rotate in 1 week every 6 weeks.
- ❑ Tryptic Decapeptide, L-Theanine combo:
 - 2 BID empty stomach for 10 weeks, then reduce to 1 BID empty stomach increasing as needed for stress.



Case Study 3

- ❑ Perimenopause had stimulated her variant ADRB2 gene which turned on her previously “quiet” FTO gene.
- ❑ Her weight gain had nothing to do with her diet – handled carbs well. Did not change her diet.
- ❑ 1 month later she had dropped 8 lbs, 4 months later she had dropped 33 lbs and has kept it off for the past 5 years.



Case Study 4

- ❑ 28-year-old male who moved out of his parents house a year ago.
- ❑ He gained 18 lbs in 2.5 months despite exercising 5 times a week.
- ❑ Increased simple carbs (pasta, rice) as they were easy to make and cheap.
- ❑ Had always eaten those foods in smaller quantities in the past and never had a weight issue.



Case Study 4

- ❑ TCF7L2 – T/T -increased insulin response to carbs
- ❑ IRS1 – T/T- increased insulin and cancer risk with carbs.
- ❑ GIPR – C/T- slight increase insulin and GI inflammation with carbs.
- ❑ FTO – T/T – normal fast metabolism.
- ❑ ADRB2 – C/G – increased obesity with stress.



Case Study 4

- ❑ Reduced Carbohydrates to 1 meal per day ½ the size of his protein.
- ❑ Eliminated completely sugars and fruits.
- ❑ No supplements



Case Study 4

- ❑ He lost on average 2 lbs a week until he had dropped 20 lbs then he didn't want to lose more.
- ❑ Added in magnesium and increased fluids to help combat "sugar withdrawal".
- ❑ Added in carb at a 2nd meal, still 1/2 the size of the protein, fruit and sugar on occasion.
- ❑ Has maintained his weight for the past 7 years.



Dietary Genes - Fats

- ❑ APOA2 rs5802
- ❑ FABP2 rs142649876
- ❑ FTO rs9939609



APOA2 rs5802

- ❑ Normal Allele = A or T, Variant Allele = G or C
- ❑ Apolipoprotein A2 influences several key enzymes in fat metabolism.
 - Cholesterol and fat transport
 - Glucose metabolism
- ❑ Increased obesity and BMI.
- ❑ Increased ghrelin.



APOA2 G or C Allele

- ❑ Variables only triggered in variants when consuming more than 22 grams of saturated fat per day.
- ❑ Increased BMI by 6.2% when consuming sat fats.
- ❑ Variables only triggered in heterozygotes when consuming more than 28 grams of saturated fat per day.

❑ Arch Intern Med_2009 Nov 9; 169(20): 1897-906



FABP2 rs142649876

- ❑ Normal Allele = G, Variant Allele = A
- ❑ Fatty Acid Binding Protein regulates the transportation of long chain fatty acids – especially saturated fats.
- ❑ Variant allele has twice the affinity for long chain fatty acids increasing their absorption.

❑ *J Cell Mol Med. 2014; 18(12): 2530-35.*



FABP2 A Allele

- ❑ Increased long chain FA absorption when consuming more than 53 grams of fat per day:
 - Increased FA oxidation
 - Increased insulin resistance
 - Increased diabetes risk.
 - *Lipids Health Dis.* 2015 Sep 29; 14: 121.
 - *Diabetes.* 1995 Oct; 44(10): 1239-42



Comparative Integration

❑ APOA2 – A/A

❑ FABP2- G/A

❑ FTO- T/T

❑ MC4R – T/T

❑ APOA2 – G/G

❑ FABP2 – G/A

❑ FTO – T/T

❑ MC4R- T/T



Case Study 5

- ❑ 24-year-old student started the bulletproof diet with a friend. She felt hungry and had increased food cravings on it but continued.
- ❑ Initially she lost 4 lbs. but then gained 13 lbs. over a 4-month period.
- ❑ Felt quite puffy and inflamed most of the time.
- ❑ Prior diet was balanced proteins to carbs with lower saturated fats.



Case Study 5

- ❑ APOA2 – G/G – very poor with saturated fats over 22 grams.
- ❑ FABP2- G/A – decreased response with saturated fats over 53 grams.
- ❑ FTO- T/T – fine with saturated fats, fast metabolism
- ❑ MC4R - T/T- fine with saturated fats, fast metabolism



Case Study 5

- ❑ Reduced her saturated fat intake to less than 22 grams per day.
- ❑ Dietary changes:
 - Removed all coconut oil and MCT oil.
 - Swapped peanuts, cashews and brazil nuts for almonds and walnuts.
 - Swapped regular fat dairy for organic fat free dairy (Greek yogurt or cottage cheese).
 - Reduced red meat to twice a week.



Why Keto is not for everyone.

❑ Saturated Fat - examples:

- 16 g/oz, in coconut oil or MCT
- 7.6 g/tbsp in butter
- 9.4 g/oz in dark chocolate
- 7 g/oz in hard goat cheese
- 1.1 g/oz in almonds (approx 30 almonds)
- 3 g in 12 walnuts.
- 6 g in half a fillet (200 g) of salmon.



Case Study 5

- ❑ Within 1 week she lost 3 lbs. and felt far less puffy.
- ❑ At the end of 6 weeks she had dropped 12 lbs.
- ❑ At the 10 week mark she had dropped 18 lbs. and felt great.
- ❑ Increased energy, no inflammation and no food cravings or hunger.



Case Study 6

- ❑ 33-year-old friend who did the bulletproof diet as well.
- ❑ Lost 23 lbs. over 2.5 months and felt great.
- ❑ Her mental and physical performance improved as did her sleep.



Case Study 6

- ❑ APOA2 – A/A – normal response to saturated fats.
- ❑ FABP2 – G/A – normal response to saturated fats.
- ❑ FTO – T/T- normal response to saturated fats and faster metabolism.
- ❑ MC4R- T/T- normal response to saturated fats and faster metabolism.



Case Study 6

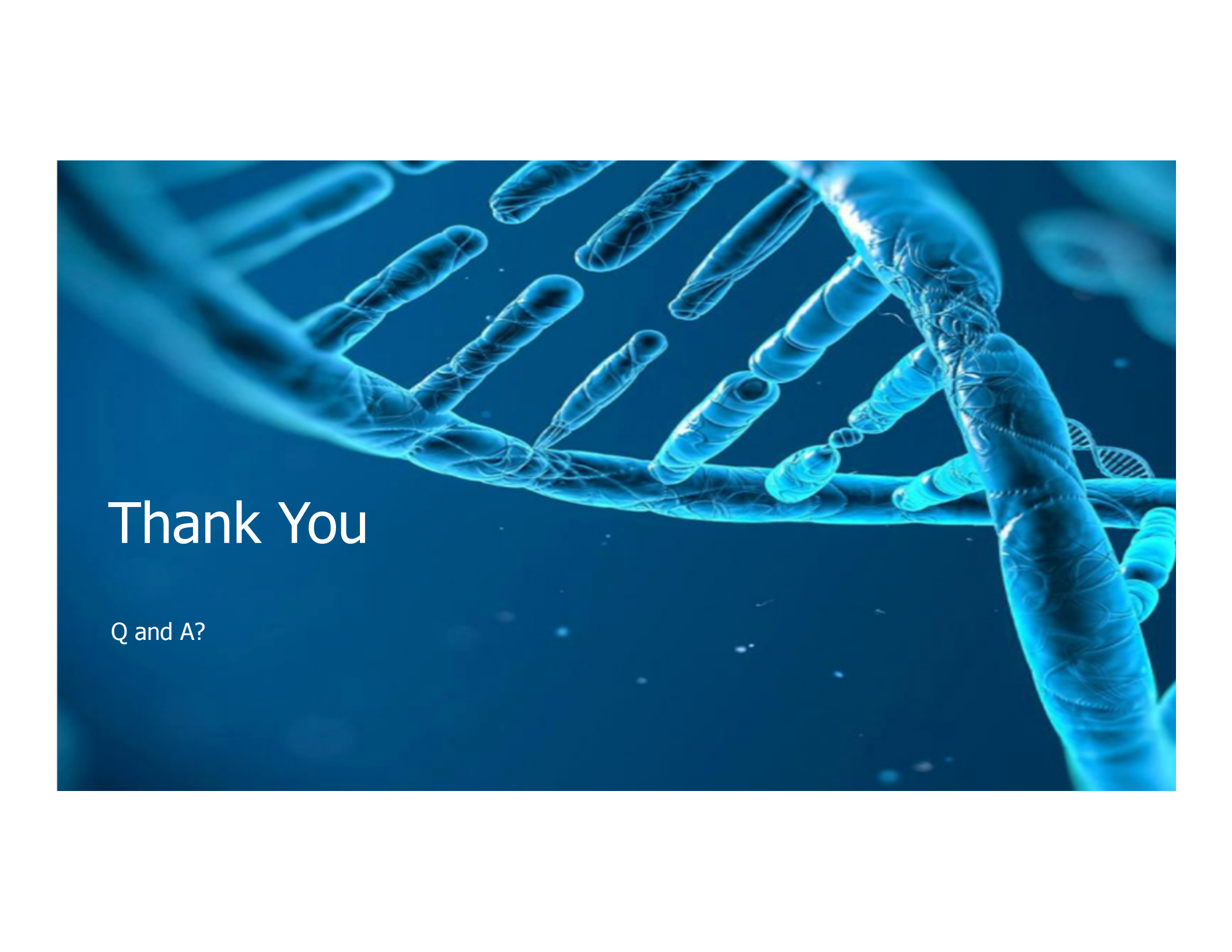
- ❑ She was designed for Bulletproof or Keto.
- ❑ She would have to exceed 53 grams of saturated fat a day to stimulate increased adipogenesis and inflammation.
- ❑ No changes needed.



Putting it all Together.

- ❑ Our body is a unit, when you change one area or pathway it will ultimately change another.
- ❑ Just because we have a gene, does not mean we are expressing it.
- ❑ Be sure not to turn on the adverse expression of a gene via turning on another gene.
- ❑ Know all the pieces of the puzzle and put them together.





Thank You

Q and A?