B12 – What the Genes!

PART 5: GENES INVOLVED IN B12 SYNTHESIS

Methylation polymorphisms

- Numerous polymorphisms of genes are involved in methylation pathways
- Folate, B-12, and methionine in these pathways have complex gene-environment interactions which affect DNA methylation, gene expression, and a variety of clinical outcomes (Jacob 2000)
- Important to note: Folate provides the one-carbon units required for purine and thymidylate syntheses and for methylation of a wide variety of essential biological substances, including phospholipids, proteins, DNA, and neurotransmitters (Stover, 2009)

Methylation polymorphisms

- In the activated methyl cycle, folate, as *N*5-methyltetrahydrofolate, supplies a methyl group to convert homocysteine to methionine, which is then converted to the universal methyl donor, *S*-adenosylmethionine (Ragsdale, 2008)
- Although nutrients other than folate supply or transport methyl groups (methionine, choline, and vitamin B-12)
- Only folate is capable of ***de novo generation of one-carbon groups*** (Jacob 2000)
- Remember B12 and Folate must hold hands together and JUMP in

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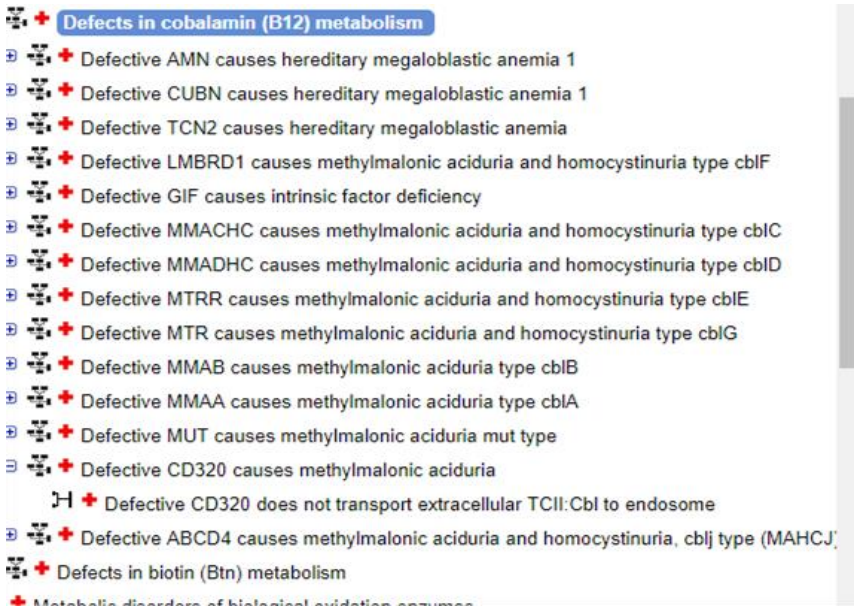

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Defective MMADHC causes methylmalonic aciduria and homocystinuria type cblD

Defective AMN causes hereditary megaloblastic anemia 1

Defective CD320 causes methylmalonic aciduria

Defective MTR causes methylmalonic aciduria and homocystinuria type cblG

Defective MTRR causes methylmalonic aciduria and homocystinuria type cblE

Defective MMAB causes methylmalonic aciduria type cblB

Defective GIF causes intrinsic factor deficiency

Defective LMBRD1 causes methylmalonic aciduria and homocystinuria type cblF

Defective CUBN causes hereditary megaloblastic anemia 1

Defective TCN2 causes hereditary megaloblastic anemia

Defective ABCD4 causes methylmalonic aciduria and homocystinuria, cblj type (MAHCJ)

Defective MMAA causes methylmalonic aciduria type cblA

Defective MUT causes methylmalonic aciduria mut type

Defective MMACHC causes methylmalonic aciduria and homocystinuria type cblC

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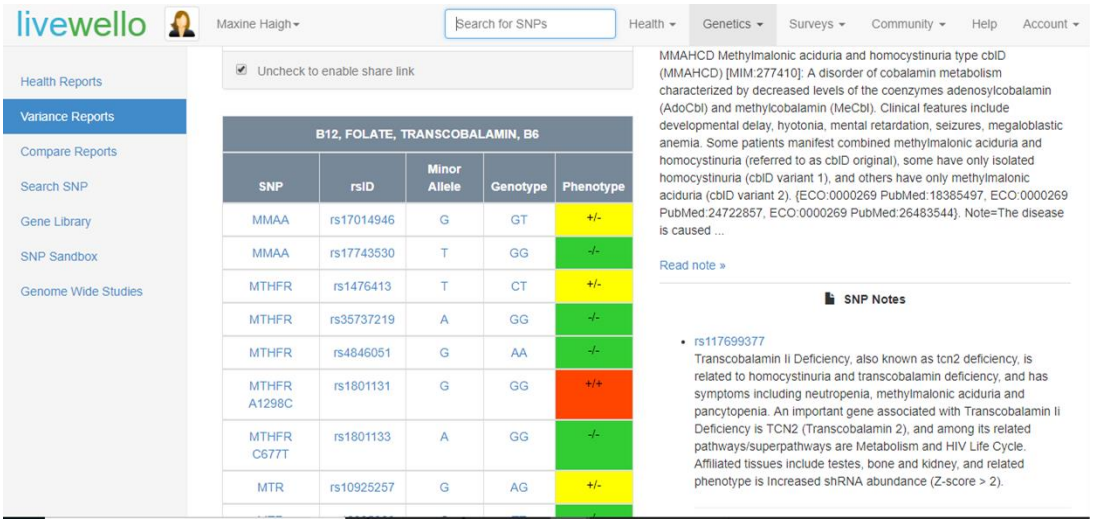
Gene Reports



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Cubilin receptor

- Also known as Intrinsic Factor-Cobalamin Receptor encoded by CUBN
- Cubilin protein and aminonless (AMN) protein forms a Cubam complex which helps in vitamin B12 absorption
- Recognizes the IF-B12 complex and AMN helps inreceptor mediated endocytosis. Co-transporter protein having 3623 amino acids - transportation requires calcium

(Grasbeck, 2006; Grasbeck & Kantero, 1959)(Krzemien, Turczyn, Szmigielska, & Roszkowska-Blaim, 2015)

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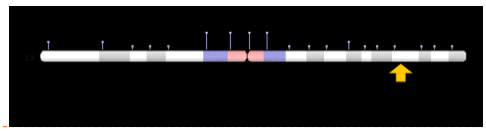
FUT2



- The official name of this gene is "fucosyltransferase 2 FUT2 is the gene's official symbol.
- **Associated Health Conditions:**
  - People with **GG** genotype are at **reduced risk** of Vitamin B12 levels
  - People with **AA** genotype are at **reduced risk** of Folate pathway vitamin levels

https://ghr.nlm.nih.gov/gene/FUT2#

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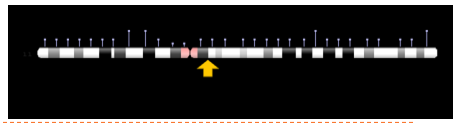
GIF



- A member of the cobalamin transport protein family.
- Encodes a glycoprotein secreted by parietal cells of the gastric mucosa and is required for adequate absorption of vitamin B12.
- Intrinsic factor deficiency
- Hereditary intrinsic factor deficiency (IFD): Autosomal recessive disorder characterized by megaloblastic anemia
- Also known as :IF, IFMH, INF, TCN3

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GIF

- IF deficiency may be due to defect in GIF gene or GIF antibodies.
- Juvenile cobalamin deficiency (JCD) potentially fatal megaloblastic anaemia in western world is due to GIF mutation (Tanner et al., 2005)
- Identification of such mutations in different type of populations allows for quick and easy genetic testing in a disease that is difficult to diagnose but easy to treat.

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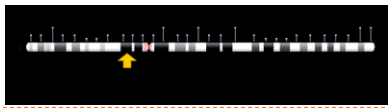
MUT



- The *MUT* gene provides instructions for making an enzyme called methylmalonyl CoA mutase active in mitochondria
- Methylmalonyl CoA mutase is responsible for a particular step in the breakdown of several protein building blocks
- (amino acids), specifically isoleucine, methionine, threonine, and valine.
- The enzyme also helps break down certain types of fats (lipids) and cholesterol

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MUT

- Then, working with a compound called adenosylcobalamin (AdoCbl), which is a form of vitamin B12, methylmalonyl CoA mutase converts methylmalonyl CoA to a compound called succinyl-CoA
- Other enzymes break down succinyl-CoA into molecules that are later used for energy.
- This defect allows methylmalonyl CoA and other toxic compounds to build up in the body's organs and tissues, causing the signs and symptoms of methylmalonic acidemia.

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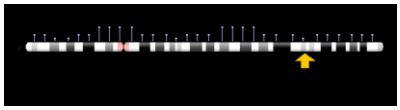
MMAA



- The *MMAA* gene provides instructions for making a protein that is involved in the formation of a compound called adenosylcobalamin (AdoCbl).
- AdoCbl, which is derived from vitamin B12 (also called cobalamin), is necessary for the normal function of an enzyme known as methylmalonyl CoA mutase.

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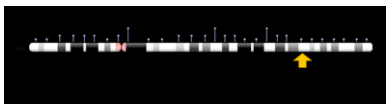
MMAB



- The *MMAB* gene is instrumental in the formation of a compound called adenosylcobalamin (AdoCbl)
- AdoCbl, which is the normal function of another enzyme known as methylmalonyl CoA mutase.
- This enzyme helps break down certain proteins, fats (lipids), and cholesterol.

https://ghr.nlm.nih.gov/gene/MMAB#

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MMAB

- Once vitamin B12 has been transported into mitochondria
- MMAB enzyme converts cob(I)alamin to AdoCbl.
- Studies suggest that this enzyme may also deliver AdoCbl to methylmalonyl CoA mutase.
- At least 25 mutations in the *MMAB* gene have been found to cause methylmalonic acidemia

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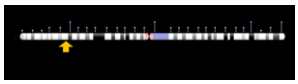
MMACHC



- The *MMACHC* gene also provides instructions for making a protein that helps convert vitamin B12 (also called cobalamin) into one of two molecules, adenosylcobalamin (AdoCbl) or methylcobalamin (MeCbl).
- This enzyme converts the amino acid homocysteine to another amino acid, methionine.
- The body uses methionine to make proteins and other important compounds.

https://ghr.nlm.nih.gov/gene/MMACHC

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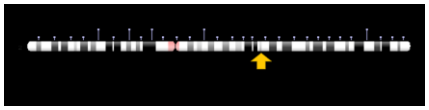
MMADHC



- The official name of this gene is "methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria." This gene provides instructions for converting vitamin B12 (also called cobalamin) into one of two molecules, adenosylcobalamin (AdoCbl) or methylcobalamin (MeCbl).
- AdoCbl is required for the normal function of an enzyme known as methylmalonyl CoA mutase. This enzyme helps break down certain protein building blocks (amino acids), fats (lipids), and cholesterol.
- AdoCbl is called a cofactor because it helps methylmalonyl CoA mutase carry out its function. MeCbl is also a cofactor, but for an enzyme known as methionine synthase. This enzyme converts the amino acid homocysteine to another amino acid, methionine.

https://ghr.nlm.nih.gov/gene/MMADHC#

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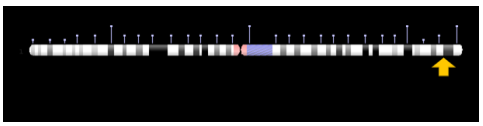
MTR



- The official name of this gene is "5-methyltetrahydrofolate-homocysteine methyltransferase."
- The MTR gene provides instructions for making an enzyme called methionine synthase.
- Specifically, methionine synthase carries out a chemical reaction that converts the amino acid homocysteine to another amino acid called methionine.

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MTRR

- The body uses methionine to make proteins and other important compounds
- As we have discussed to function properly, methionine synthase requires methylcobalamin (a form of vitamin B12) and another enzyme called methionine synthase reductase, which is produced from the MTRR gene.

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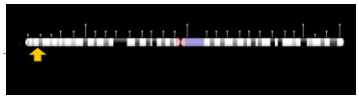
MTHFR (The most popular kid on the block)

- The *MTHFR* gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase.
- Methylenetetrahydrofolate reductase is important for a chemical reaction involving forms of the vitamin folate (also called vitamin B9).
- Specifically, this enzyme converts a molecule called 5,10-methylenetetrahydrofolate to a molecule called 5-methyltetrahydrofolate.

https://ghr.nlm.nih.gov/gene/MTHFR#



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MTHFR

- Mutations may impair the function of the enzyme, and some cause the enzyme to be turned off (inactivated).
- Other mutations lead to the production of an abnormally small, nonfunctional version of the enzyme.
- Without functional methylenetetrahydrofolate reductase, homocysteine cannot be converted to methionine. As a result, homocysteine builds up in the bloodstream, and the amount of methionine is reduced.

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Haptocorrin

- Haptocorrin (HC) also known as transcobalamin-1 (TC-1) or R-protein is encoded by the TCN1 gene
- Glycoprotein - 433 amino acids and 30% carbohydrates.
- The essential function of haptocorrin is protection of the acid sensitive vitamin B12 while it moves through the stomach.
- 80% of the B12 in circulation is bound to HC, function of which is not known clearly (may be circulatory storage form).

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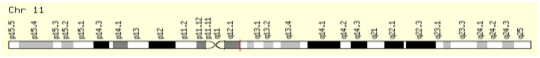
TCN1



- An important gene associated with Transcobalamin I
- Transcobalamin I Deficiency, also known as *cobalamin pseudodeficiency due to transcobalamin deficiency*, is related to some cancers
- This gene encodes a member of the vitamin B12-binding protein family. This family of proteins, alternatively referred to as R binders, is expressed in various tissues and secretions.
- This protein is a major constituent of secondary granules in neutrophils and facilitates the transport of cobalamin into cells

http://www.malacards.org/card/transcobalamin_i_deficiency

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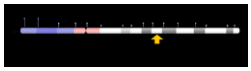
TCN2



The official name of this gene is "transcobalamin II." TCN2 is the gene's official symbol.

The TCN2 gene provides instructions for making a protein called transcobalamin (formerly known as transcobalamin II).

This protein transports cobalamin (also known as vitamin B12) from the bloodstream to cells throughout the body.

https://ghr.nlm.nih.gov/gene/TCN2

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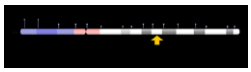
TCN2



- The transcobalamin-cobalamin complex binds to a receptor on the cell surface, which allows the complex to enter the cell.
- Transcobalamin releases cobalamin when the complex enters the cell and transcobalamin is broken down.
- Within cells, cobalamin helps certain enzymes carry out chemical reactions.

https://ghr.nlm.nih.gov/gene/TCN2

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TCN2

- In enterocyte B12 is liberated from IF and appears in blood bound to TC2 (holotranscobalamin) which carries B12 to various cells.
- 20% of total B12 is present in holotranscobalmin form which is supposed to be the form available for cellular uptake.
- Polymorphism in TCN2 gene (C776G, G1196A etc.) has been observed to reduce plasma TC II concentration and causes decrease in cellular availability of B12 and increased homocysteine levels.

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Homocystinuria

- A disorder of methionine metabolism, leading to an abnormal accumulation of homocysteine and its metabolites (homocystine, homocysteine-cysteine complex, and others) in blood and urine
- Homocystinuria is an inherited disorder in which the body is unable to process certain building blocks of proteins (amino acids) properly.

https://ghr.nlm.nih.gov/condition/homocystinuria#

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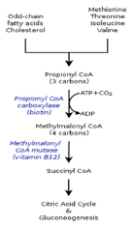
Methylmalonic Acidemia



- An autosomal recessive disorder of amino acid metabolism, involving a defect in the conversion of methylmalonyl-coenzyme A (CoA) to succinyl-CoA. Patients typically present at the age of 1 month to 1 year with neurologic manifestations, such as seizure, encephalop and stroke.
- The body is unable to process certain proteins and fats (lipids) properly.
- The effects of methylmalonic acidemia, which usually appear in early infancy, vary from mild to life-threatening. Affected infants can experience vomiting, dehydration, weak muscle tone (hypotonia), developmental delay, excessive tiredness (lethargy), an enlarged liver (hepatomegaly), and failure to gain weight and grow at the expected rate (failure to thrive).
- This condition occurs in an estimated 1 in 50,000 to 100,000 people

https://ghr.nlm.nih.gov/condition/methylmalonic-acidemia#

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Summary

- Methylmalonic acidemia
  - Mutations in the MUT, MMAA, MMAB, MMADHC, and MCEE genes cause methylmalonic acidemia.
- Homocystinuria
  - Mutations in the CBS, MTHFR, MTR, MTRR, and MMADHC genes cause homocystinuria.
- Methylmalonic acidemia with homocystinuria
  - MMACHC, MMADHC, LMBRD1, ABCD4, or HCFC1.

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