Understanding SNPs

What is a SNP?

The acronym “SNP” stands for Single Nucleotide Polymorphism. It is not a snip of DNA; rather it’s a swap of one nucleotide on one of the rungs of the DNA ladder, at a particular location.

What is a Variant Report?

A Variant Report is a listing of Single Nucleotide Polymorphisms (SNPs), derived from the raw data results of 23andMe saliva testing, and generated via a software tool. The most comprehensive and well researched Variant Report can be obtained via MTHFRsupport.com, using Sterlings App. The Variant Report is organized into groups of SNPs, including Phase I and Phase II liver detoxification SNPs, IgE, IgA, and IgG SNPs, Methylation SNPs, Mitochondrial Electron Transport Chain SNPs, and others.

More Details:

Each SNP is associated with an “rs” number (e.g., rs4880), which represents a particular location (rung) on the DNA genome (ladder). Using the ladder analogy, a consecutive series of rungs provides a blueprint or code for generating a particular polypeptide (e.g., protein or enzyme). For example, the well-known MTHFR enzyme is encoded using a length of the DNA genome equivalent to thousands of rungs of the ladder, and is copied and subsequently used as the blueprint for building the MTHFR enzyme.

There are coding and non-coding parts (possibly signaling the coding portions) of the DNA genome. The segments that code verses the segments that do not, depend on the addition of a methyl group (think of the Great Oz toggling segments of the DNA on and off with a CH3 group called a methyl group) and histone winding (think garden hose wrapped around a portion of the DNA to “cover it up”). Our diets, environment, and habits affect toggling on/off via methyl groups and histone winding/unwinding of our DNA.

The DNA is subsequently expressed as its copied and then is used to build enzymes, receptors, and other polypeptides used by our bodies to run our biochemical machinery.
A little background (very simplified)…

The DNA genome is safely protected in the nucleus of each cell, where it remains as the blueprint for generating all polypeptides used in our body’s biochemical pathways. DNA is a Nucleic Acid made up of Nucleotides, where each nucleotide includes a Nucleobase, Deoxyribose (a pentose sugar) and a Phosphate group. The Nucleobases can be one of 4 possibilities; Adenine “A”, Guanine “G”, Cytosine “C” or Thymine “T”. Going back to our analogy ladder, there are two Nucleobases per ladder rung. Cytosine pairs with a Guanine, while Thymidine pairs with an Adenine.

Day in and day out, Messenger RNA moves into the nucleus, copies an unzipped segment (unzips right down the middle, length-wise) of the ladder, and carries the copied portion out of the nucleus with its Nucleotides. The copied portion is carried to a ribosome, outside of the nucleus but inside that particular cell. There are stop/start segments of DNA to signal where one enzyme blueprint starts and stops. Think hair comb with a spine handle and nucleotide teeth, extending perpendicular from the base.

The ribosomal (machinery) assists in selecting amino acids (beads), where three sequential Nucleotides (comb teeth) translate/code into one amino acid. For example, if the three sequential Nucleotides are G, G, T, then the resulting amino acid “bead” selected is glycine. If the next three sequential Nucleotides are T, C, T, then the ribosomal machinery selects a serine amino acid (next bead). The amino acids are derived from protein foods we eat, which in turn, depend on our GI’s ability to assimilated and digest them.

Through a series of complicated steps, the selected amino acids are strung together to form the polypeptide chain (necklace). If all goes well, a perfect polypeptide is formed, and that polypeptide goes off and does its thing (e.g., MTHFR enzyme). However, if an incorrect Nucleotide (SNP) translates into an incorrect amino acid (bead), then the resulting enzyme, receptor or carrier protein function is not optimal. The non-optimal function is the result of many things, but it’s typically due a shape change or impaired cofactor affinity for a vitamin or mineral that’s need for its operation. If you Google a particular enzyme, you will see that it looks like a ribbon (I analogized it to a beaded necklace) with curls and bends and docking sites for cofactors such as magnesium, vitamin B6, etc.). Each curl and bend and docking site is critical to its function.

Despite an incorrect amino acid selection due to a SNP in the DNA, the resulting polypeptide, with its alteration, is still utilized in its biochemical pathway to convert A into B. Due to the shape alteration, the conversion may be compromised; like a key that’s not quite right for a particular lock,
but with a bit of jiggling still works.

Going back to our MTHFR example, “A” would be 5,10 Methyl THF and “B” would be 5- MTHF. In the case of an MTHFR SNP, the conversion of 5,10 Methyl THF and “B” to 5- MTHF would be slowed.

If the MTHFR SNP comes from one parent, it operates at slower speed in its conversion of 5,10 Methyl THF to 5- MTHF, and is referred to as a heterozygous SNP. If the same SNP (nucleotide swap) comes from each parent, the resulting enzyme works even slower and is referred to as a homozygous SNP.

Expanding our MTHFR example…, at location rs1801133 (rung) of the DNA genome, or position 677 of the MTHFR-encoding portion of DNA, one expects to find two cytosine (C) nucleotides. However, if one of the cytosine nucleotides has been replaced by a thymine (T), the SNP ("swap") is referred to a MTHFR C677T heterozygous SNP, and will reduce associated MTHFR enzymatic activity by 20-30%. If however, both of the cytosine nucleotides have been replaced by thymine, the SNP is referred to as MTHFR C677T homozygous SNP, and will reduce associated MTHFR activity by as much as 60%. As a result, a person with an MTHFR C677T hetero- or homozygous SNP, will have a decreased ability to convert 5,10-methylenetetrahydrofolate (substrate A) to 5-methyltetrahydrofolate (product B).

In layman’s terms, a MTHFR SNP means that there is poor conversion of dietary folic acid to its usable form, 5-methyltetrahydrofolate. (In that case, supplements that contain synthetic folic acid are not your friend.) 5-methyltetrahydrofolate is one of the enzymes in methylation pathways required for serotonin and dopamine generation, and conversion of homocysteine to methionine and subsequent SAMe generation, to name a few.

A bit more about SNPs as they relate to our DNA…

(1) A SNP or Single Nucleotide Polymorphism occurs when a single nucleotide differs from the majority (wild type is considered the “normal” expected nucleotide)
(2) SNPs occur in coding regions, non-coding regions or between genes (intergenic). We look at the coding regions.
(3) SNPs vary in terms of severity and benefit due to location and redundancy. Our bodies typically have back-up pathways for redundancy, but they are not as good as the primary pathways. So for example, estrogen breakdown via the Phase II liver sulfation pathway is backed-up by the Phase II
liver glucuronidation pathway. The sulfation (SULT SNPs can affect) pathway can accept a larger variety of intermediate metabolites, but will defer to the glucuronidation pathway when it gets overwhelmed, so both need to be working optimally.

(4) Most SNPs do NOT govern genetic function and expression. Diet and lifestyle do.

(5) SNPs may cause gene instability due to decreased cofactor affinity. A cofactor can be a vitamin, mineral or other byproduct of biochemical pathway processing (e.g., NAPD).

(6) SNPs may be bypassed by increasing cofactor concentration and providing end products directly. So for example, if you have an MTHFR C677T down-regulation, you can "bypass" the down-regulation via delivery of 5 MTHF (folate) as a supplement. Having said that though, its much more complicated, as the biochemical pathways interconnect. If you simply address one SNP in isolation, you run the risk of mucking up other pathways. I’ve seen this many times where a person takes a high dose of 5-MTHF (e.g., Deplin) without considering neighboring enzymes (affected by SNPs). The improper supplementation can result in feeling great for a few days, then tired, to experiencing increased anxiety.

**Why the interest in Methylation SNPs?**

There are many functions that require Methylation:

1. Turn on and off genes (gene regulation via CH3)
2. Process chemicals, endogenous and xenobiotic compounds (biotransformation via Phase II liver clearing, especially estrogen and heavy metals)
   If one has neurotransmitter issues, then looking at methylation pathway genetics and lifestyle are key.
4. Metabolize/breakdown neurotransmitters (dopamine, epinephrine)
5. Build immune cells (T cells, NK cells)
6. Build DNA "bits and pieces" and Histone Synthesis (Thymine aka 5-methyluracil)
7. Produce energy (CoQ10, carnitine, creatine, ATP via Krebs cycle)
8. Produce protective coating on nerves (myelination)
9. Build and maintain cell membranes (via utilization of phosphatidylcholine derived from phosphatidylethanolamine in the presence of estrogen and functioning PEMT enzyme)
A Few More Details:
When we talk about “methylation defects” we are actually talking about an inability of an enzyme(s) to stick a methyl group onto another “thing” which is a chemical in a pathway that results in a product. A methyl group is simply 1 carbon atom with 3 hydrogen atoms attached to the 1 carbon atom. Methylation defects however, create folks that are often more productive, hard charging, creative and emotionally sensitive. The downside is that those same folks are less capable of breaking down fight/flight neurotransmitters and they may have a difficult time relaxing and sleeping as they get older.

In women, some of the same methylation defects may affect their liver’s ability to process estrogens, so they may have more extreme PMS symptoms, not do well on BCPs and tend to be a bit emotionally destabilized when estrogen and fight/flight hormones (epinephrine) compete for the same down-regulated enzyme (COMT) to break them down. In men, these downregulated enzymes may translate into early prostate issues.

Folks with methylation defects do well in their youth, as they are the hard-charging types and often over-achievers. Over time however, the adrenal glands get tapped-out as the sympathetic nervous system is in a high alert state. Its an intersection of cortisol and nor-epinepherine and SAMe that creates epinephrine (adrenaline…stress hormone). Thyroid function is affected as a result, and almost every cell in our body has a thyroid hormone receptor.

Lack of ability to break down (methylate) stress hormones, takes its toll, especially as we move into our 50’s, in the form of higher cancer and heart disease rates.

Bottom line; first support downstream methylation enzymes via a full spectrum of minerals, Krebs cycle support and all B vitamins, except for methylfolate and B12 initially. Clean up the gut as those 3 lbs of gut bacteria that we carry around do lots to signal immune system and modulate neurotransmitter status. When the foundational mineral and B vitamins and Krebs cycle output is in place, then layer in the B12 and methylfolate for methylation support. This is the tricky part and requires support from a Practitioner to navigate.
The Epigenome

OK, so let’s shift gears and talk about what’s going on with our children and grand-children wrt to methylation and resulting metabolic issues that were once limited to older folks, but are now expressing in children.

For those of us over 50, we would be hard-pressed to ID a childhood friend who was on the Spectrum or who had an eating disorder. Now, we have children and grandchildren who have been diagnosed with some sort of neuro issue (e.g., Autism spectrum, Aspergers, PANDAS, anorexia/bulimia and more). Why is this happening when our genetics don’t change?

The short answer is, our environment and exposures have changed. There is a layer between the outside world and our fixed nuclear DNA called the epi-genome. The epi-genome interface is capable of toggling segments of our fixed DNA, on and off. The toggling is the result of outside influences.

How? Our body’s enzyme activity reacts to food, high frequency electromagnetic waves (think WiFi), plastic byproducts, genetically modified grains that have been saturated by an organo-phosphate herbicide (I can’t type the trade name, but its found in spray bottles in local big box store garden section and is now delivered by tons on our grains and soy prior to harvest starting in 1991). Its worth mentioning that protein bio-mass in cows, chickens and farm raised fish come from genetically modified corn. Think about it; we eat meat that comes from cows, who eat the corn, which is genetically modified. We eat chicken, which eats the corn, that is genetically modified. We eat fish from a fish farm, which has been fed meal from chicken parts where the chicken ate genetically modified corn. Corn is sprayed with organo-phosphates. How much of our bio-mass can be traced back to the same corn. Answer: lots, unless we eat organic and grass fed and wild caught fish.

So the question is, what is toggling our DNA segments on and off so that parts that contribute to compromised neuro issues are expressing through our epi-genome interface? Its difficult to tell but we have much data. Our fixed DNA expression is toggled on/off via an attaching methyl group
at a particular location on our DNA due to outside influences, and/or histone winding or unwinding (think garden hose wrapped tightly around its histone base so that segment can’t be copied and therefore doesn’t express, and then it unwinds due to outside influences).

These epigenetic changes can travel with our DNA as we pass them along, generation after generation via sperm and egg to our off-spring. It’s therefore imperative to eat clean and address methylation enzymatic pathway deficits.

Stepping off my soap box… If you would like more info, please go to PubMed and type in key words to research topics.

Cynthia