

Predictive Genomics

Most disease occurs from a misadaptation or disharmony between the environment and the genetic capacity of the individual.

Predictive Genomics is that branch of medicine, which identifies polymorphisms in individuals in order to predict the likelihood of that individual developing a particular chronic disease or functional imbalance given a particular “environment”.

New scientific genetic testing has permitted testing for genetic polymorphisms, which can be looked at as mutations but which are found in more than 1% of the population. Single amino acid variations from the norm in a gene are called SNIPS. Over 100,000 SNIPS have thus far been found since we have had an explosion of research following the discovery of the sequencing of the human genome in 2000. There will be many more.

Up to 50% of the human population has some degree of SNIPS in their system. As we learn more, perhaps everyone will. Polymorphisms can be good, bad or neutral. Some mutations, just as some genetic traits, are unchangeable such as the color of your hair or eyes. About 50% of SNIPS, according to Jeffery Bland PhD, can be influenced by our diet, lifestyle and environmental conditions. A SNIP causes the production of a product such as a protein but depending on the environment can produce a different protein or less of the first protein. In other words depending upon what we do once we identify them, SNIPS can often be modified to our advantage.

Great Smoky Diagnostic Laboratory is one of the first labs in the world to create panels of SNIPS that apply to human disease. They chose to measure only those that can be changed by what you do. SNIPS or genetic mutations that they chose don't make disease. They only predispose one to a disease. They carefully chose only those SNIPS that are relevant, prevalent, modifiable and measurable. The importance of this testing is that they have taken the first steps to remove the guesswork from wondering what disease we will get. In the future more panels will be added and the costs will go lower. Using third wave Invader testing which is even more reliable and sensitive than polymerase chain reaction testing (PCR), a linear amplification of the flap is created from two oligonucleotide probes, which then bind to a target sequence.

Panels available thus far study genetic mutations in the immunity, detoxification pathways, cardiovascular disease and osteoporosis.

The osteoporosis genomic polymorphism panel identifies those individuals with increased risk of developing osteoporosis. Osteoporosis can occur if there is a flaw genetically in processing VitD3, Calcium,

impaired collagen, high parathyroid hormone or low calcitonin activity, increased osteoclast activity and chronic inflammation. Remember osteoclasts are cells in the bone that break down the bone and osteoblasts are cells in the bone that create new bone. They are normally both active.

The first three markers in the GSDL panel are bone formation markers. A genetic flaw or SNIP will interfere with bone formation to a variable extent. Note whether the SNIP is heterozygous or both genes as they are paired (allele). The next deals with the resorption or destruction of bone. The last two deal with inflammatory markers.

Beside a popular bone densitometry test for osteoporosis, measuring the rate of bone turnover is relevant. Are the treatments working? Measuring the Pyridinium collagen crosslinks and the Deoxypyridinoline helps look at the concept of an abnormally fast bone turnover rate. It can find a problem before the densitometry can.

Osteoporosis

Marker	Meaning	Consequence of polymorphism	Therapy
COL1A	Collagen 1 alpha is the main protein matrix used to create bone	Mildly wrong collagen formation	Higher calcium intake than usual Estrogen especially valuable here Cohosh, soy isoflavones?
CALCR P463L	Calcitonin receptor mediates that hormone. Calcitonin decreases calcium and osteoclast activity	Can lead to decreased bone density	Vitamin D, Calcium, Weight bearing exercises.
VDR BsmI RFLP	Vitamin D3 receptors increase calcium intake from the gut and increase osteoblasts	Inhibit calcium absorption and decrease bone mineralization	Diet, Vit D rich foods: sardines, salmon, sunflower seeds, cod liver oil Calcium rich foods, greens, dairy. Weight bearing exercises.
PTHR D3S1289	Parathyroid receptors mediate the actions of the hormone, which increases the loss of bone and raises the calcium. The opposite of	Flaws her increase the PTH activity and increase bone resorption.	Vit D3 –inhibits parathyroid activity. 400iu from cod liver oil or more is required. Insulin resistance makes bone loss worse. Treat central obesity.

	calcitonin.		
IL-1RN*2	Interleukin –1 receptor antagonist Shuts down inflammation	Polymorphisms predispose one to chronic inflammation	Fish oil Silmyran Soy isoflavones, black Cohosh Monitor d-pyd
TNF – α	Tumor necrosis factor creates inflammation and is important in asthma, arthritis and osteoporosis.	Mutations increase production of TNF and make more inflammation	Fight inflammation, TNF inhibitors? Food that can help osteoporosis: Onions, garlic, parsley, dill, lettuce, tomato, arugula and cucumber.

Heart disease is still our number one killer. It even occurs with healthy individuals who follow the right diet and exercise at times though less likely than if you break all the rules. About half of the cases of heart disease occur in individuals with normal cholesterol levels. Though we don't have all of the answers, there are some changeable genetic polymorphisms that can help us find these folks ahead of time.

Heart Disease and hypertension

Cholesterol metabolism			
APO E 2,3,4	Apolipoprotein E is involved with lipid transportation	Higher LDL cholesterol and triglycerides. E4 involved with Alzheimers disease risk.	Eat a low fat, high fiber diet. Eat salmon 3x/week, alcohol 1 day, avoid simple sugars Niacin, red rice, policosanol, 800 iu Vit E. ASA & probucol for Double E4
Alzheimers E4	Nothing proven	Radical scavengers such as ginkgo, acetyl l carnitine, C, E, estrogen, selegiline	Phosphotidylserine chronic and drugs such as reserdipine
CETP	Cholesteryl ester transfer protein.	Results in more removal of insoluble cholesteryl esters from HDL and	Drinking alcohol daily helped the B1 CETP variant. Statins or Policosanol and

		drops the HDL down.	hexaniacinate, red rice yeast
Methylation			
MTHFR	Methylenetetrahydrofolate reductase. 80% of American Caucasians are heterozygous for a defect with some impaired methylation. 12% of homozygous or severely impaired. 28% don't respond to natural therapy. 6TTC -T SNP defect. Use Betaine with this group and 5-methyl tetrahydrofolate with resistant cases.	Elevated homocysteine levels with defective methylation. Low methylation causes problems with heavy metal removal, neurotransmitter production, nerve demyelination, CQ10 and carnitine reduced production, DNA damage	Can have normal blood B12 and folate test but cognitive decline. Measure homocysteine And urinary methylmalonic acid. Treat with B12, Folate and B6. Also B2 is important. If no response look at column 1.
Hypertension			
GNB3	Guanine Nucleotide-binding protein B3 - Signal transduction including angiotensin II effects.	Increases tendency for essential hypertension and obesity.	Thiazide better with 825T than 825C polymorphism. May try herbal diuretics. ACE receptor blockers?
AGT M235T	Elevates angiotensin production and doubles MI risk.	Polymorphism of the M235T causes hypertension with retained sodium and water.	Thiazides, natural diuretics. ACE inhibitors
AGTR1	Angiotensin II receptor 1	Another important genetic variant that will lead to hypertension.	ACE inhibitors, variable effect.
Coagulation			
Factor 2	Chromosome 11. Prothrombin	Elevated Prothrombin with increased risk of venous thrombosis, MI and stroke.	Avoid oral contraceptives and don't smoke. EPA/DHA, Fish oils, ASA, Licorice inhibits thrombin activation, E
Factor 5	Chromosome 1 Leiden	Combines with factor X to form	

		prothombin activator. Increased risk of venous thromboembolism. Worse with concurrent Factor2 or oral contraceptives.	
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Immunology

Cytokines are a family of polypeptide that are concerned with inflammation, cell division, cell differentiation and cell death (apoptosis).

TH-1 subset of cytokines are IL2, IL 18, INF- γ , TNF- β , TNF- α and is involved in the chronic inflammatory process that is cell mediated. Delayed hypersensitivity.

TH-2 cytokines are IL-4, IL-5, IL6, IL 10, and IL 13. It is suppressed by IFN (interferon) γ . TH-2 is involved in the acute inflammatory process that involves antibody response. IL-1 initiates both types.

Diagnostic genomic testing looks at some representatives that are affiliated with chronic inflammation IL 1 β , IL 1RN ; TH1 response such as chronic viral infection and cancer TNF α ; TH 2 response as seen in acute infections, allergies, asthma. IL -4, IL-6, IL-10, IL 13. This area cannot be reviewed at this time. It is subject to expansion by the laboratory and is a complex subject. Genetic polymorphism can lead to a tendency for chronic inflammation and may play a role in chronic fatigue syndrome and Fibromyalgia.

Detoxification

Lastly a detoxification panel has been created. We are all exposed to a virtual sea of toxins and the body constantly tries to get rid of these. Some bioaccumulation can occur. This is especially clear with chlorinated pesticides such as DDT and its metabolite, DDE. Heavy metals such as arsenic, lead, mercury can accumulate as can certain fat-soluble chemicals.

The process of detoxification is complex and many organs are involved including skin, lungs, kidney and especially liver. To convert a fat-soluble toxin into a water soluble toxin the body uses two different enzyme systems. These are termed Phase I and Phase 2 systems. Phase I are

hydroxylation and Cytochrome P450 reactions, Phase 2 are conjugation reactions. Sometimes both are needed. Some the by products or partially converted products such as epoxides are worse than the original toxin.

Agent	Result	Further clinical facts	Treatment	Goals
Detox reaction Phase 1 and II	Result of polymorphism	Note Phase 1 reactions are inducible and Phase II are not.	Phase I byproducts can outstrip the Phase II ability to process them	
CYP 1A1 Phase I	Hyperinduction can lead to mutagenic metabolites and theoretically predispose to cancer	Can present with a pattern of CFS or fibromyalgia	Support with Sulfates, Glycine, Taurine, Glutathione, Hypoglycemic diet Brassica, High antioxidants	Identify toxic agents and eradicate them
CYP 2D6	Polymorphisms can result in rapid, moderate or slow metabolizers	Involved with 20% of all pharmaceuticals, opiates, tricyclics, beta blockers, SSRIs	Modify dose as slow reactors cause drug toxicity. Fast are non-responsive	Have higher risk of smoking addiction
CYP 2E1	Detoxifies alcohol, benzene, styrene, alkanes, freon. nitrosamines	Can be associated with lung cancer, MCS, Ethanol hepatitis or cirrhosis.	Associated with higher risk of lymphoma	Higher risk of alcoholism
CYP 3A4	Decreased detoxification capacity. Four different snips.	Involved with more than 50% of all drug metabolism	Associated with higher amounts of prostate and breast cancer.	Support with Sulfates, Glycine, Taurine, Glutathione, Hypoglycemic diet Brassica, High antioxidants
Glutathione S transferase -3 isomers	More than 60% of the population has one or more polymorphism to these enzymes.	Used to detoxify solvents, herbicides, fungicides, PAH, heavy metals, lipid peroxidases	GST M1 -deletion; GST T1-deletion; GST P-1	In general GST polymorphisms increase risk of numerous cancers and a poorer prognosis with

				asthma, cystic fibrosis, and MS.
NAT 1 –	Slow Acetylators	Increased risk of lung, colon and bladder cancer	N-acetyltransferases used in the Phase II acetylation . Caffeine, Heterocyclic aromatic amine.	Avoid PAH, charcoaled meat, Increase Brassica vegetables. Flavinoids in onion, red wine, lettuce, apples.
NAT 2 -	Slow acetylators	Increased risk of lung, colon and bladder cancer, head neck and oropharyngeal cancer.	Toxins eliminated more slowly	Watch your occupation. Avoid petroleum byproducts if possible.
NAT 2	Fast acetylators	Increase DNA adducts, adenomas, colorectal cancers	Moderate smokers with this polymorphism have a higher risk of lung cancer.	More activation or O-acetylation and less N-acetylation are present.
SOD -1	Less capacity to transform nascent oxygen into less reactive peroxide.	Higher risk of cardiovascular disease, RA, neurodegenerative diseases, pre mature aging.		Add more antioxidants than usual. Watch for adequate cofactors.
SOD -2	Same	Higher risk of cardiovascular disease, RA, neurodegenerative diseases, pre mature aging, breast cancer and diabetes		Reduce oxidant load. Be careful of ozone, peroxides, Excess O2, pollutants, Fog. Haze