Nutrigenomics is the science of the effect of nutrients and bioactive components on gene expression within the entire genome. It is the study and identification of genes that are involved in physiological responses to diet, and genes in which SNP's or polymorphisms have significant nutritional consequences. Functional genomics tools probe a biological system following a nutritional stimulus to allow for increased understanding of how nutritional molecules affect metabolic

pathways and homeostatic controls.

The goal of nutrigenomic research is to find the interaction between diet and a network of genes, on a global scale. Goal is to see how the whole body responds to food.

Nutrigenomics regulation of gene expression often occurs through common transcription-factor pathways that are regulated by macronutrients, micronutrients, and other food components.

An example of a polymorphism in the Pro12Ala gene up regulates gene expression, and when acted on by polyunsaturated fatty acids it leads to increased storage of TG's, decreasing free plasma triglyceride levels, increasing insulin sensitivity, and decreasing the risk for type 2 diabetes.

Nutrigenomics – Leptin hormone mutation that causes obesity.

Nutrigenetics is the further study of these specific polymorphisms in genes within individuals, and its sim is to understand individuals, and its aim is to understant of the genetic makeup of an individual/similar group of individuals coordinates the response to diet. Functionally relevant SNP's and their mutiple variants are identified and filtered, integrated with writent intake and Gater back to the individual and their resultant sk and susceptibilite to e iseases. The aim is to obtain a better understanding of nutrient-gene interactions depending on the genotype, and to ultimately develop personalized nutrition strategies for optimal health and disease prevention.

An important application of nutrigenetics can be related to the Inuit population, in which 35 SNP's from 20 genes related to lipid metabolism have been identified. These common genetic polymorphisms render the population especially susceptible to dietary fat intake, and these genetic variants play an important role in the modulation of cardiovascular health in the Inuit people. Increased knowledge about the interplay between the multiple gene variants can allow for tailoring of a personalized diet, that is low in saturated and trans fats, in order to prevent and cure chronic disease in the Inuit population. Other nutrigenetic examples:

-A condition that is the study of nutrigenetics is the lipid metabolic disorder sitosterolemia, that is characterized by the hyperabsorption and decreased excretion of plant sterols which leads to hypercholesterolemia, xanthomas and premature development of atherosclerosis. It is due to a mutation in either the ABCG5 or ABCG8 gene, which code for ATP-binding cassette transporter proteins, impairing the ability of the liver to excrete plant sterols into the bile. This -<u>miRNA activity</u>: a small <u>non-coding RNA</u> molecule which functions in <u>RNA silencing</u> and post-transcriptional <u>regulation of gene expression</u>. They can elicit their effects on protein expression by: cleaving mRNA, destabilizing mRNA, or by decreasing mRNA translation rates.

-Epigenetics:

<u>Methylation of genes</u> (imprinting mech) - this is an epigenetic mechanism of gene silencing, which turns genes "off". Complete lack of expression in the methylated gene on various individuals of a population, would lead to an alteration of disease **penetrance**.

- Cytosine methylation is only associated with repression/silencing of transcription. Histone modifications are associated with either repressing/silencing or increasing transcription. The similarity between the two is that neither changes the DNA nucleotide sequence.
- <u>Environmental effects</u> (temperature, light, chemicals, and nutrition) (the effect of nutritional genomics): dietary chemicals can act on the human genome directly or indirectly to alter gene expression (nutrition is the most important environmental factor modulating the action of genes and of the phenotypes being considered).
- Example: PKU (phenylketonuria) is a dispessibility to controlled by environmental choices, despite bissessing the outosomal recessive genotype. While the dier is restrictions may be bird to follow, an individual can avoid the phenotype traits of the disease (such as intellective disabilities, and non-traits) of the disease (such as intellective disabilities, and non-traits) by reducing phenylalanine consumption (present of most meat and dairy products)
- Ex. Drugs and chemicals: Environmental factors, such as supplemental oxygen administration that caused retinopathy of prematurity.
- Ex. Thalidomide: caused stunted limb development, when used during embryonic development. Lack of toxicity in adults, profoundly detrimental effect on developing fetuses.
- Ex. Temperature affecting C gene expression in Himalayan rabbits, differential phenotypic expression of coat color

In some cases, the presence of a particular SNP may increase or decrease an individual's susceptibility to the development of a phenotypic trait or a disease, as opposed to directly generating the phenotype. When 2 individuals inherit the same SNP, the presence or absence of certain concurrent (and relevant) genetic and environmental exposures may lead to the differential (or non existent) expression of the phenotype. For example, a SNP leading to lighter skin tone may be present in two individuals, thus putting them both at a heightened risk for skin cancer development. The choice of one of the individuals to limit their sun exposure (environmental alteration), could greatly decrease their chance of expressing the phenotype of interest (skin cancer). This same example could apply if one of the SNP possessors also had genetic variants that produced light hair and eyes (2 genetic factors), further enhancing their chances of developing

- Provides data on the ancestry of each subject, which assists in matching case subjects with control subjects
- Provides data on two types of structural variants--sequence and copynumber variations-- which provides more robust data.

Limitations of GWAS:

- Results need replication in independent samples in different populations.
- A large study population is required.
- GWAS studies detect association not causation.
- GWAS identifies a specific location, not complete genes. Many variants identified in GWAS are nowhere near a protein-coding gene, or are within genes that were not previously believed to associated with a trait or condition.
- Detects only variants that are common (>5%) in a population
- Typically, for any particular trait, the cumulative effects of multiple VSNPs only explains a small fraction of an individual's risk for the trait.

The issue with genome wide association is that after dere is a much smaller genetic component involved in the product@ of a disease than would probably be estimated when looking at bandpility trends octwird studies (because heritability has been overestimated in many cases, as opposed to recognizing the role of environmented). Unfortunately, these studies only focus on SNPs (although diseases are there is a user allocated by tandem repeats, OR are produced by interaction of multiple mutations). Sometimes genetic variants are difficult to detect, even in large case-control studies.

For example, phenylketonuria (PKU) can be avoided either by removing the PKU gene mutations from the population or by a low dietary phenylalanine. Thus, 100% of cases would be prevented either by removing the mutation or by adopting a low phenylalanine diet. In a population in which everyone has a high phenylalanine diet, the condition will appear to be 100% genetic; in a population in which everyone has the mutation, the condition will appear to be 100% environmental. Thus, the genetic and environmental components are inseparable. In fact, as we learn more about a particular disease, it is inevitable that the attributable proportions for different risk factors will sum to more than 100% (see examples in Table 1), whereas the proportions of population variation cannot add up to more than 100%.

19. Why might it be important to look at someone's genetic profile before prescribing a drug? Do you think that widespread genetic testing would be a useful and cost effective way to prevent adverse drug effects? Why or why not?