Introduction:

Last few decades has witnessed revolutionary changes in clinical diagnostics. This owed to the completion of the Human Genome Project and Next Generation Sequencing (NGS). As our knowledge of the human genome has expanded post Human genome project (2001), so has our understanding regarding involvement of genes in human disease.

Several basic studies show that several nutrients and bioactive chemicals like signalling molecules, bind to the cellular sensors to directly promote and influence the expression of gene and protein and later subsequently metabolite production. For instance a person suffering from phenylketonuria, a disorder caused by mutation in phenylalanine hydroxylase coding gene should have food containing phenylalanine. In addition polymorphisms in genes coding for enzymes like methylenetetrahydrofolate tetrahydrofolate reductase (MTHFR) are seen to affect catalytic activity, which ultimately influences a person's diet and metabolism (Müller M, Kersten S. Nutrigenomics: Goals and strategies. *Nat Rev Genet* 2003; *4* : 315-22.)

Nutrigenomics addresses several diet or nutrient induced changes in metabolome, proteome and transcriptome, while nutrigenetics explains the effect of the genetic anomalies like mutations and single nucleotide polymorphisms (Müller M, Kersten S. Nutrigenomics: Goals and strategies. *Nat Rev Genet* 2003; *4* : 315-22.)

India has been encountering rapid socio economic challenges for past 2-3 decades. Imbalanced nutrition particularly undernutrition complications continue to influence major sections of the population especially the children. On the other hand, overnutrition is also causing its fair share of damage like obesity and chronic illness like type 2 diabetes (Vaz M, Yusuf S, Bharathi AV, Kurpad AV, Swaminathan S. The nutrition transition in India. *South Afr J Clin Nutr* 2005; *18* : 198-201).

In Spite of the global burden of undernutrition progressing slowly to vernutrion, undernutrition still causes everlasting damage widely in South Asia especially in India, mainly due to micronutrient deficiency. About 40% of the indian children's pediatric population are underweight or stunted. Though these deficiencies are popularly seen among rural kids, around 60% of affluent kids in cities suffer from Vitamin B2, B6, B12 and Vitamin D deficiencies (National Nutrition Monitoring Bureau. *Diet and nutritional status of rural population, prevalence of hypertension & diabetes among adults and infants & young child feeding practices-Report of third repeat survey*. Hyderabad: National Institute of Nutrition; 2012. Available from: *http://nnmbindia.org/1_NNMB_Third_Repeat_Rural_Survey___Technicl_Report_26.pdf*, accessed on February 24, 2017.)

Nutrigenomics being a subside of genomics, actively addresses the genetics involved with diet and in parallel to various dietary responses in children. Much like pharmacogenomics, nutrigenomics aims to provide a logical and more personalised approach to diet and health. Diet plays a major role in an individual from preventing disease to performance and overall quality of life (German, J. B., Zivkovic, A. M., Dallas, D. C., & Smilowitz, J. T. (2011). Nutrigenomics and personalized diets: What will they mean for food?. *Annual review of food science and technology*, *2*, 97–123. https://doi.org/10.1146/annurev.food.102308.124147).

1. **MTHFR- Methylenetetrahydrofolate Reductase- C677T/ Methylenetetrahydrofolate Reductase 1**

Methylenetetrahydrofolate reductase-1 (MTHFR 1) is a gene usually responsible for multiple functions in the human body. The gene is important for chemical reactions involving Vitamin folate (B9) *(Methylenetetrahydrofolate Reductase Gene Polymorphisms in Children with Attention Deficit Hyperactivity Disorder- Gocken. Et al 2011)*

The human MTHFR gene mapped to the chromosome 1p36.3 helps in catalyzing the conversion of 5,1q0 methylenetetrahydrofolate (5, 10-CH2-THF) to 5-methyltetrahydrofolate (5-CH3-THF), the principal form of vitamin B9. MTHFR 1 alters the amino acid sequences, replacing Alanine (Ala) with valine (Val). Individuals with the Val amino acid exhibit significantly reduced MTHFR enzyme activity, whereas baselines exhibit a mean enzyme activity of 30% in the Val/Val homozygous state and 65% in the Ala/Val heterozygote. The Ala/Val heterozygote can lead to a mild increase in homocysteine levels particularly if the folate dietary intake is low. *(Methylenetetrahydrofolate reductase polymorphism (MTHFR C677T) and headache in children: a retrospective study from a tertiary level outpatient service- Orsini et al. 2018)*.

MTHFR 1 has been associated with a wide range of disorders, particularly migraine in the pediatric population. According to a study by *Orsini et al. 2018,* the wild type MHFTR-1 T/T genotype was associated with an increased risk of migraines- headaches in children. Additionally, the homocysteine levels were higher in the MTHFR T/T homozygosity pediatric population increasing the susceptibility to migraine.

Another study by *Pasca et al. 2009* indicates that the MTHFR 1 gene analysis revealed that a normal distribution of C677T polymorphism was noticed to be higher in children with Autistic disorder when compared to the normal children- control group. *(One carbon metabolism disturbances and the C677T MTHFR gene polymorphism in children with autism spectrum disorders- Pasca et al).*

2. MTHFR- Methylenetetrahydrofolate Reductase- A1298C/ Methylenetetrahydrofolate Reductase 2

Methylenetetrahydrofolate Reductase is vital for folate chemical reactions. The gene is usually located at the end of the short arm of the chromosome 1p 36.3. (Goyette P, Sumner JS, Milos R, et al. Human methylenetetrahydrofolate reductase: Isolation of cDNA, mapping, and mutation identification. Nat Genet. 1994;7:195-200).

MTHFR 2 in particular affects the nucleotide synthesis and DNA methylation. Several studies prove that homocysteine/ folate levels affect the cognitive functions leading to defects like Attention Deficit Hyperactivity Disorder (ADHD) in children (Moretti P, Peters SU, Del Gaudio

D, et al. Brief report: Autistic symptoms, developmental regression, mental retardation, epilepsy, and dyskinesias in CNS folate deficiency. (J Autism Dev Disord. 2008;38:1170-7.). Deficiency in mothers during gestation can also lead to a child's hyperactivity. (Schlotz W, Jones A, Phillips DI, et al. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. J Child Psychol Psychiatr. 2010;51:594-602).

ADHD is a complex disorder and there are a number of factors involved in its symptoms. In particular, MTHFR 2 genetic abnormality is found commonly in children with ADHD and its presence could offer a lot of explanation and solution (Gilbody S, Lewis S, Lightfoot T. MethyleneTetrahydrofolate Reductase (MTHFR) genetic polymorphisms and psychiatric disorders: A huge review. Am J Epidemiol. 2007;165:1-13)

Parents with ADHD kids are more likely to have kids with ADHD. The MTHFR gene controls the process in the body that affects the neurological functions. The gene instructs the body to make the enzyme methylenetetrahydrofolate reductase which in turn is important to turn folate into its bioavailable alternative methyl folate (Mattson MP, Shea TB. Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci. 2003;26:137-46).

3. Methionine Synthase (MTR):

The Methionine synthase (MTR) gene is usually crucial for making the enzyme methionine synthase. This particular enzyme plays a crucial role in processing several amino acids- the building blocks of protein. In specific, the gene carries out the chemical reaction helping in converting homocysteine amino acid into another methionine. To function properly the MTR gene requires a form of vitamin B12- methylcobalamin (https://ghr.nlm.nih.gov/gene/MTR#conditions).

According to *Haghiri et al. 2016,* genes involved in the homocysteine pathway may be a risk factor for autistic children. Autism is usually characterized by impairment in speech and communication. One of the genes that poses a risk for autism is MTR since it is responsible for the regeneration of methionine from homocysteine *Haghiri, Rosa & Mashayekhi, Farhad & Bidabadi, Elham & Salehi, Zivar. (2016). Analysis of methionine synthase (rs1805087) gene polymorphism in autism patients in Northern Iran. Acta Neurobiologiae Experimentalis. 76. 318-323. 10.21307/ane-2017-030.*

4. MTRR- Methionine Synthase Reductase

The MTRR gene is responsible for the change in methionine from homocysteine. The enzyme encoded by the gene forms part of the S- adenosylmethionine biosynthesis and regeneration cycle. In humans, the enzyme is driven by folate type Vitamin B12 (cobalamin).

Low dietary folate and maternal polymorphisms in genes encoding Vitamin B12 metabolizing enzymes like MTRR and MTHFR are potential risk factors of down syndrome in

the pediatric population. A polymorphism in MTRR present in 25% homozygous state in many people, may lead to neural defects (MTRR and MTHFR polymorphism: link to Down syndrome?- Leary et al 2002).

5. Cystathionine Beta Synthase (CBS):

Cystathionine Beta Synthase (CBS) is an enzyme produced in humans encoded by the CBS gene. With the aid of Vitamin B6, the enzyme converts amino acid homocysteine (Hcy) to a molecular called cystathionine. It is later converted to cysteine to build proteins.

At times children inherit a rare inherited disorder- a Cystathionine Beta Synthase deficiency, also known as homocystinuria. In the pathway of converting Hcy to cystathionine, CBS deficiency impairs the conversion, leading to the accumulation of Hcy.

Patients with CBS deficiency show a wide array of symptoms. During childhood, some patients suffer from multisystem disease and some are asymptomatic into adulthood. The main symptoms are learning disability, optical issues, and a predisposition to thromboembolism (Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency- Morris et al. 2017).

6. VDR 1 (Vitamin D receptor- Taq1)

Vitamin D Receptor (VDR) is a ligand-dependent transcription factor that, along with Vitamin D, regulates more than 900 genes for a wide array of physiological functions. VDR is a vital factor for calcium homeostasis as well as immunomodulation, cell differentiation, and division *(The vitamin D receptor and T cell function Kongsbak et al. 2013).*

Past studies have reported that Vitamin D is associated with an anti-proliferative effect on many cancer types such as glaucoma, leukemia breast, and colon cancer. In a study conducted by Ahmad et al. 2017 in the Iranian pediatric population, VDR polymorphism-Taq1 showed a significant association with Acute lymphoblastic leukemia *(Taq1 Polymorphism (rs731236) of Vitamin D Receptor Gene in Children with Acute Lymphoblastic Leukemia- Ahmad et al. 2017).*

7. VDR 2 (Vitamin D receptor- Bsm1)

Vitamin D is a steroid in structure. It usually bonds to several receptors and plays an important role in cell proliferation and inflammation. From years of research, it is known that the Vitamin D receptors (VDR) gene shows the genetic difference in structure. One such important polymorphism is Bsm 1 (Investigation of Vitamin D Receptor Gene Polymorphism in Pediatric Patients with Brain Cancer- Yilmaz et al. 2017)

Lupus is an autoimmune disease with no exact etiology. Studies speculate that Vitamin D receptor polymorphism along with oxidative stress may be major risk factors for lupus. In a study conducted in Egypt Children hospital, experts studied the difference in VDR polymorphism Bsm1 between the healthy and lupus patients. The results revealed that VDR

Bsm 1 polymorphism is associated with an increased risk of SLE among the Egyptian pediatric population (Oxidative stress and vitamin D receptor *BsmI* gene polymorphism in Egyptian children with systemic lupus erythematosus: a single-center study- Yahia et al. 2019).

Several small studies also have associated Bsm1 with osteoporosis. Osteoporosis is a health concern characterized by unhealthy bone density and the risk of bone fragility (Barr R, Macdonald H, Stewart A, McGuigan F, Rogers A, Eastell R, Felsenberg D, Glüer C, Roux C, Reid D. Association between vitamin D receptor gene polymorphisms, falls, balance and muscle power: results from two independent studies (APOSS and OPUS) Osteoporos Int. 2010;21:457–466. doi: 10.1007/s00198-009-1019-6)

8. VDR 3- Vitamin D receptor- Fok 1

Vitamin D is an immune regulator hormone that exerts its effects through its highly polymorphic Vitamin D Receptor (VDR) gene. The gene is expressed in several types including the immune cells like antigen-presenting cells and lymphocytes. For the past several years, VDR polymorphisms have been associated with autoimmune disease.

Recently it was found that single polymorphism nucleotides (SNP) in VDR genes, specifically in Fok 1 polymorphism crates alternative ATG initiation codon in exon 2 leading to autoimmune disease- Diabetes 1 in children (Association of vitamin D receptor polymorphisms and type 1 diabetes susceptibility in children: a meta-analysis- Sahin et al. 2017).

9. FADS1- Fatty acid Desaturase 1

In humans, fatty acids play multiple functions. They serve as energy sources, substrates for lipid mediators and modulators of gene transcription.

Fatty acid desaturase 1 is an enzyme encoded by FADS1 gene in humans. The protein encoded by the gene desaurates omega- and omega-3, catalysing the final step in formation of eicosapentaenoic acid (EPA) and Arachidonic acid (ARA). The enzyme regulates unsaturation of fatty acid by introducing double bonds between carbons of the fatty acyl chain (https://www.genecards.org/cgi-bin/carddisp.pl?gene=FADS1#:~:text=FADS1%20(Fatty%20Acid%20Desaturase%201,omega6)%20acid%20metabolism%20and%20Metabolism.)

Recent increase in obesity of children heightens the risk of hypertension. For a long time it is known that Blood Pressure (BP) is associated with long unsaturated fatty acids. In a study conducted by Wolters et al. 2017, it was noticed that polymorphism in FADS1 influences BP via ARA and Body Mass Index (BMI) (The role of a *FADS1* polymorphism in the association of fatty acid blood levels, BMI and blood pressure in young children—Analyses based on path models- Wolters et al. 2017).