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THE EFFECT OF HOST GENETICS ON THE SECOND GENOME: THE GUT MICROBIOTA

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ABSTRACT

The various associations of microorganisms and their combined genome found on and within the body comprises the microbiome which makes vital contributions to the human metabolic and immune functions thereby having a significant impact on the host health. Genetic variations in the host can lead to alterations in pathogen sensitivity and gut microbiome composition (dysbiosis) which are being unraveled by genome- wide association studies (GWAS). The resulting dysbiosis of the gut microbiome can lead to an imbalance of the microbe-host homeostasis and cause gastrointestinal disorders such as Crohn's disease, ulcerative colitis as well as extra-intestinal disorders such as asthma, obesity, Type II diabetes mellitus, neurological disturbances and rheumatoid arthritis. From various articles it can be concluded that the existence of a particular taxa is mainly controlled by the host genetics whereas the environmental and dietary factors are responsible for the abundance of each taxon. On comparing the studies analysing the faecal microbial communities as obtained from the human subjects we can arrive at the fact that more similar the genome, more similar will be the membership of the gut microbial community. However, despite the progress there are challenges which are encountered during the analysis such as the effect of environment which masks the effect of genetic variants or the increased microbiome structure complexity. Linking the host genetics and individual microbial composition may help us pave a way for the potential therapies aimed at modulation of the gut microbiota and personalized medicine.

Keywords: Host genetics, gut microbiota, GWAS, heritability

INTRODUCTION

The various colonies of microorganisms including the fungi, viruses & protozoans **[1]** and their combined genome found on and within the body comprises the microbiome which makes vital contributions to the human metabolic and immune functions. The microbiome present in the gastrointestinal tract called the gut microbiota can be considered as the second genome **[2]** of our body. Itis a vigorous community that varies from person to person as well as undergoes variations in its architecture over time due to the different environmental conditions persisting in the gut **[3]**. It seems that the "forgotten organ", that is the microbiome exists in a mutualistic relationship with the host and the dysbiosis affects the host-microbe homeostasis and increases the susceptibility to various diseases.

Over the past decade, studies conducted have shed light on the importance of gut microbiota and its association with various diseases. Abnormalities in composition of gut microbiomehas been associated with the pathogenesis of gastrointestinal disorders such as Crohn's disease, ulcerative colitis as well as extra-intestinal disorders such as type 2 diabetes mellitus, asthma, obesity, neuropsychiatric disturbances and rheumatoid arthritis **[4]**. Therefore, linking the host genetics and individual microbial composition may help us pave a way for the potential therapies aimed at modulation of the gut microbiota and personalized medicine **[5]**.

MATERIALS AND METHODS

The literature review for the following article was performed by searching the databases of PubMed, ScienceDirect, Elsevier, Google Scholar and other research paper-based journals using the keywords: host genetics, gut microbiota, GWAS, heritability. Suitable information was gathered from these sources and was collated for the devising of this article.

DISCUSSION

The Gut Microbiome: Composition & Function

Microbiome occupy various sites of the body including the skin, nose, throat, as well as the urogenital and gastrointestinal tracts. The gut microbiome is dominated by bacterial species belonging to the phyla Bacteroidetes and Firmicutes, whereas phyla such as Proteobacteria, Actinobacteria, Verrucomicrobia and Fusobacteria are present in lesser proportions **[3, 4]**.

The gut microbiota has coevolved with the host and resides in different sections of the gastrointestinal tract which differ in physiochemical conditions as well as availability of substrates. Majority of the intestinal microbiota are strictly anaerobic and obtain energy by fermentation of the

dietary fibres and other substrates into short chain fatty acids (SCFA), methane, carbon dioxide and hydrogen **[3]**. These metabolites produced make the individual susceptible or immune to various disorders. The gut microbiota is also involved in the nutrient and mineral absorption, synthesis of vitamins & proteins as well as fermentation by products such as acetate, butyrate and propionate which are essential for maintaining gut health and immunomodulation **[6]**.

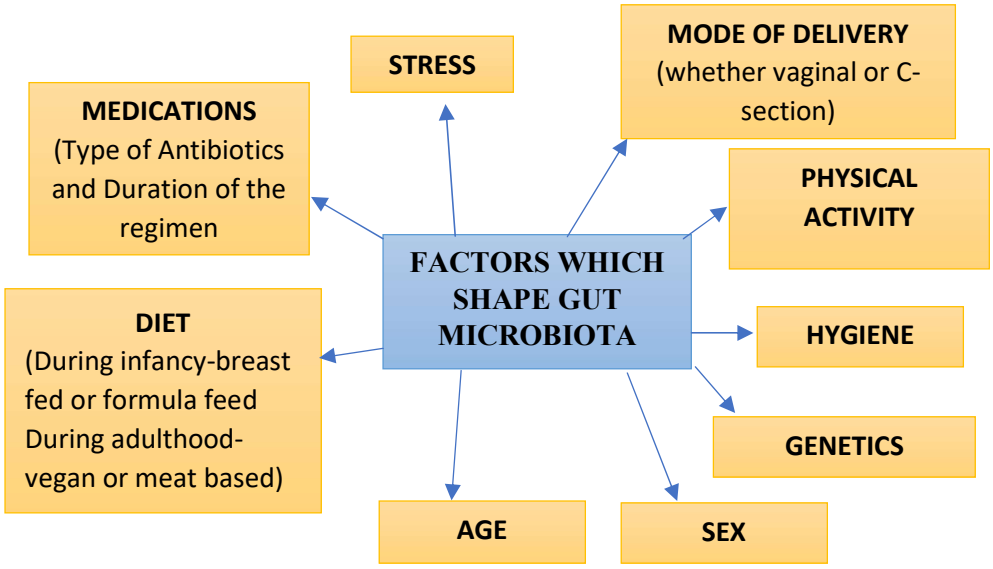

Figure 1: Factors which shape the Gut Microbiota [7]

Studies conducted on the animals raised with and without the microbiome indicate that the mutualistic relationship existing between the host and microbiome is essential for the functioning of the immune and metabolic system. Germfree animals, which are born, raisedand maintained aseptically, are devoid of microbial cells and subsequently undergo impaired postnatal development and functioning **[8]**. Thus, we can say that the microbiome is essential for the maturation of the immunity system in infants and maintenance of immune functions in adults.

Dysbiosis and diversity in the microbiota composition have been observed in numerous disease models which are attributed to factors such as age, geography, lifestyle, diet as well as host genetics **[9]**. The non-twin studies conducted in the recent decade give rise to increasing evidence that the non- genetic factors, predominantly diet, play a significant role in the composition. It is supported by the fact that the microbiota was found to be similar among the individuals sharing a household whereas no such similarity was

found to exist among individuals without a household sharing **[10]**.

A current re-evaluation of the largest twin study (2252 twins) conducted so far found that the average heritability of gut bacterial taxa likely lies between 1.9% and 8.1% **[10]** indicating that a part of the microbiota is heritable, though relatively small **[11, 12, 13]**. Early studies which attempted to find how host genetics influence the gut microbiota were based on comparing monozygotic (MZ) and dizygotic (DZ) twins in order to distinguish the effects of shared genetics from those of shared environment and found that the former had a slightly significant similarity as compared to the latter **[11]**.

Further progress in the field of technology lead to the advent of the Human Microbiome Project in 2008 using next generation sequencing methods (16SrRNA gene sequencing) and metagenomics sequencing which allowed analysis at a remarkable power.

GWAS- Genome -Wide Association Studies

The impact of host genetics on microbiota is being studied through genome- wide association studies (GWAS) which reveal tissues, pathways, and genes associated with microbiome attributes. It involves identification of genetic loci that influences a specifictaxa or a pathway using quantitative trait mapping. The microbial genes can be grouped into functional categories or pathways, and the abundances or presence/absence of those groups could be targets of modulation through host genetics **[8]**. Any and every one of these attributes may be characterized and modelled as a quantitative trait, for which heritability can be estimated and quantitative trait loci (QTLs) identified **[8, 11]**.

Microbiome attributes which are generally used as traits embody individual level measurements such as alpha diversity, and cross sample traits such as beta diversity **[8]**. Alpha diversity refers to the mean species diversity within a particular site whereas beta diversity allows us to compare the diversity between two particular areas.

In humans, the first genetic studies were based on the association of host genetic variants with the microbiome composition or function **[11]**. For example, genetic variants in FUT2 genes were associated with microbial energy metabolism and mucosal inflammation **[11, 14]** and MEFV polymorphisms were associated with major shifts in bacterial phyla **[11, 15]**.

The most consistent finding from all studies indicates that the host's genetic variation in the immunity related genes and pathways is correlated with the microbiome composition **[8, 16]**.

From the population studies it is noted that a bidirectional interaction take place between the microbiome and the immune system mainly with the help of pattern recognition receptors (PRRs): the proteins or group of innate molecules which are capable of recognizing molecules found in the pathogens. It comprises of various receptors such as TLRs, RIG-I-like receptors and C-type Lectin receptors (CLECs) **[11]**. Studies involving modulation of these molecules in mice point to gut dysbiosis. For example, mice lacking the TLR-5 expressed alterations in the gut microbiota as well as an increased susceptibility to metabolic syndrome **[17]**.

Microbiome GWAS, developed by Hua *et al*, is used for associating beta diversity with each genetic variant. It's supported the intuition that if a variant is related to the microbiome, then any two people with additional alleles in common at a given locus can have additional similar microbiotas and so smaller beta diversity distances **[10]**. From the genome- wide mbQTL studies, the strongest association of microbiota function clusters with three CLECs- CLEC4F–CD207 at2p13.3, CLEC4A– FAM90A1 at12p13 and CLEC16A at16p13 **[2, 11, 18]**. CLECs are receptors which have the ability to acknowledge carbohydrate molecules. The role of C-type lectins within host–microbiome balance is supported by recent studies in shrimp, mosquitos and mice **[11]**. These studies further prove that multiple CLECs are involved in regulation of host-microbiota interaction.

Candidate gene approach studies is based on correlating genetic variation observed in pre- specified genes with certain disease states whereas GWAS involves examining the whole genome for a common genetic variation. Using this approach, several genetic studies conducted have found association for variation in specific gene to a disease state. Studies conducted on humans **[19]** revealed that,

- Variations in NOD2, ATG16L1, CARD9, FUT2, NLRP12, SLC39A8, TNFSF15 affect gut microbiota composition and diversity and leads to IBD.
- Variation in IFN-I affect the microbes associated with tryptophan metabolism leading to multiple sclerosis.
- Variation in A2ML1 & DEFB-CN affect the middle ear microbiome and the colonization patterns of nasopharyngeal bacteria respectively, leading to otitis media.
- Variation in C4B affect the gut microbiome composition and leads to paediatric IBD.
- Variation in ELANE and CARD15 affect the subgingival and

periodontal microbiome respectively, and lead to periodontitis.

Studies conducted on mice using knockout models **[19]** have revealed that,

- Variations in TNF causes dysbiosis and leads to colitis.
- Variation in Can and LCN2 affects E-coli and Alistipes respectively, and leads to colorectal cancer.
- Variation in NOD2 affects the gut microbiome under high fat diet and leads to obesity.
- Variation in TREM1 leads to dysbiosis and causes inflammation.

Bleckman *et al*., **[16]** used pathway-based analysis wherein they aggregated the SNPs into pathways in order to determine the biological functions and processes involving the host genome and the microbiome. The identified overlapping or nearby genes were used to perform a functional enrichment analysis **[16]**.

The most significant enrichment with genes was involved in Leptin Signalling in Obesity. Using the InnateDB database, additional pathways were identified including enrichment of genes in the REACTOME pathways Sulfide Oxidation to Sulphate indicating that variation in host genome may influence the sulfate abundance in the microbiota as well as enrichment in the KEGG pathway Primary Bile Acid Biosynthesis indicating the role of microbiome in bile acid metabolism **[16]**.

In order to correlate host genetic variation with a specific bacterial taxa, abundance data from the HMP 16S rRNA gene sequences were taken and revealed that several immunity related genes such as HLA-DRA and TLR-1 were concerned with the abundance of *Selenomonas* in the throat and *Lautropia* in the tongue dorsum, respectively **[16]**.

Genetic variants can also act indirectly by influencing diet or behaviour leading to dysbiosis. For example, variation in OR6A2, an odorant receptor implicated in the aversion to cilantro due to a soapy taste **[4, 20]**. Variation in this gene led to varied composition of gut microbiota.

The twin pair studies as conducted by Turnbaugh *et al* **[13]** has addressed the query of how genotype and environmental exposure influence the gut microbiota. In this study, 154 adult individuals comprising female MZ or DZ twins and their mothers, if available were selected and the fecal gut microbiota was analyzed **[11, 13]**. It was observed that the gut microbiota was similar among the family members although individual variations were also observed, i.e., specific bacterial lineages were present in each person's gut.

Goodrich *et al* **[12]** analyzed the fecal microbiota from the Twins UK group comprising of 416 twin pairs. Here, the microbes were found to be more similar for MZ than the DZ twins. The analysis of distance metrics in the most dominant bacterial families- *Lachnospiraceae, Ruminococcacea* (*Firmicutes*) and *Bacteroidaceae* shed light on its diversity. It was observed that there were greater similarities within the *Ruminococcaceae* and *Lachnospiraceae* in the MZ twins as compared to the DZ twins. Similar pair wise diversity was confined to the *Bacteroidaceae* family which lead to the conclusion that it was more sensitive to environmental responses.

Moreover, due to the greater number of subjects, the detection of taxa with significant heritabilities was possible. A module of co-occuring heritable families was observed in which the hub was the *Christensenellaceae* (Phylum *Firmicutes*) thereby indicating that it was the most heritable family **[12]**. The heritable module also comprises the families *Methanobacteriaceae* (*Archaea*) and *Dehalobacteriaceae* (*Firmicutes*) and the orders SHA-98 (*Firmicutes*), RF39 (*Tenericutes*), and ML615J-28 (*Tenericutes*). Further it was reported that *Christensenellaceae* was found be enriched in subjects with lean BMI (< 25) thus having an inverse relation with susceptibility to obesity. It was found that when *Christensenellaceae* was introduced into a mouse model it led to reduction in weight in treated mice when compared with controls **[12]**.

The study conducted by Zhou *et al* **[21]** comprises of analysing 5000 stool samples and obtaining the 16S rRNA sequencing data from individuals aged between 3 days to 87 years, living on five continents and demonstrates that the presence or absence of a particular taxa is controlled by host genetics whereas the abundance of each taxon is determined by non- genetic factors, predominantly diet. It further states that more similar the genome, more similar is the gut community membership. Therefore, genes influence health through their ability to promote a stable microbial community in the gut **[21]**.

Challenges encountered in GWAS:

Several hurdles are encountered while analysing the association of microbiome with host genetics, despite obtaining data from large cohorts. Major challenges are:

a. **Effect of the environmental factors on the gut microbiota [8, 11]**:

From various population studies it has been noted that due to the inter individual differences such as age, sex, diet, medication use as well as exogenous factors, the effect of host genetics on the microbiota is often masked thereby

reducing the resolution of the GWAS analysis.

Another challenge is dealing with confounders as it reflects the cumulative effect of various factors over an individual's lifetime beginning from early colonization in childhood. Therefore, it is essential to create prospective microbiome cohorts of new-borns followed until late adulthood as it will help in analysing both the effect of genetics on shaping the gut ecosystem and the role of the microbiome in health and disease traits later in life **[11]**.

b. Complexity in the structure of the microbiome data [8, 11]:

Since the individual microbial features which comprise the microbiome are over dispersed, zero inflated and have many outliers (challenges) various statistical models have been proposed. However due to the absence of a standard model, the population studies use different models to determine the mbQTLs which leads to varied results.

c. Cohort sizes:

The cohort design can influence the results of GWAS. In order to improve the resolution we must increase the cohort size as well as focus on replicating results from previous studies based on independent cohorts **[10, 11]**. Processing microbiome datasets into traits to be modeled and reducing the burden of multiple testing are just some of the technical hurdles in microbiome GWAS **[8]**.

Modulation of Gut Microbiota with the aid of Potential Therapies-

1. Probiotics:

Dysbiosis can be targeted by correcting the altered microbiota composition by the oral administration of specific bacterial species. These beneficial bacteria, mostly *Saccharomyces cerevisiae*, *Lactobacillus*and *Bifidobacterium* species, are called probiotics. Interaction of probiotics with the host involves competitive inhibition of other microbes and functional changes in the mucosal barrier **[22]**.

2. Prebiotics:

A selectively fermented nutrient supplement which when administered, fosters the growth of beneficial bacteria that is capable of inducing changes in the microbiota composition and function are called prebiotics. These substances are usually non- digestible carbohydrates, oligosaccharides or short polysaccharides with inulin, oligofructose, galactofructose, galacto-oligosaccharides and xylo-oligosaccharides **[22]**.

3. Polyphenols:

Polyphenols are secondary plant metabolites which are associated with the physiological processes as well as defence mechanisms of the fruits & vegetables. Post administration, the gut microbes

convert the dietary polyphenols into biologically active species which modulate the composition of the gut microbe in a health promoting manner.

4. Faecal Microbiota Transplantation:

It is also known as stool transplant and involves transferring faecal microbiota from a healthy donor to a recipient, in order to restore the composition of the gut microbiota, via nasogastric tube, nasoduodenal tube, rectal enema **[22]** or by mouth in form of capsules containing freeze dried faeces from a healthy donor.

CONCLUSION

We can conclude that the gut microbiome is heritable to a certain extent, implying that host genetics determines the microbial phenotype whereas its abundance and presence/absence of specific taxa is determined by the non-genetic factors predominantly, diet. Identification of the host alleles which are responsible for the heritability of the microbes is important as it will help us to correlate dysbiosis caused due to genetic variants of the host and specific disease. More investigations should be done in order to reveal the mechanisms through which the genetic variants are affecting the composition of the microbes. Once the affected alleles as well as the mechanisms are identified, it will be easier to prevent, treat or cure the disease by modulating the gut microbiota with the help of potential therapies such as administration of probiotics, prebiotics, polyphenols etc. thereby giving rise to personalised medicines.

ABBREVIATION USED: SCFA- short chain fatty acids, DZ- dizygotic, MZ- monozygotic, GWAS- genome-wide association studies, QTL- quantitative trait loci, mbQTL- microbiome QTL, FUT2- Fucosyltransferase-2, TLR- Toll like receptors, RIG-I- Retinoic acid-inducible gene I, CLEC- C type Lectin receptors, NOD2- Nucleotide-binding oligomerization domain-containing protein 2**,** ATG16L1-Autophagy Related 16 Like 1, CARD9- Caspase Recruitment Domain Family Member 9,NLRP12- NLR Family Pyrin Domain Containing 12, SLC39A8- Solute Carrier Family 39 Member 8, TNFSF15- TNF Superfamily Member 15, IBD- Inflammatory Bowel Disease, A2ML1- Alpha-2-Macroglobulin Like 1, C4B- Complement C4B (Chido Blood Group), ELANE- Elastase, Neutrophil Expressed, TNF- Tumor Necrosis Factor, LCN2-Lipocalin 2, TREM-1-Triggering Receptor Expressed On Myeloid Cells 1, HMP- Human Microbiome Project, HLA-DRA- Major Histocompatibility Complex, Class II, DR Alpha, TLR-1 -Toll Like Receptor 1, OR6A2- Olfactory Receptor Family 6 Subfamily A Member 2.

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