Int J Mol Epidemiol Genet 2022;13(1):1-14
www.ijmeg.org /ISSN:1948-1756/IJMEG0141661

Review Article

FUT2 gene as a genetic susceptible marker of infectious diseases: A Review

Paramvir Kaur, Madhu Gupta, Vivek Sagar

Department of Community Medicine and Public Health, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Received January 10, 2022; Accepted June 13, 2022; Epub June 15, 2022; Published June 30, 2022

Abstract: Some blood group antigens are reported as a susceptibility marker for some diseases. For instance, HBGA (Histo-blood group antigen) which is controlled by gene FUT2 also considered as a susceptible marker. The FUT2 gene which exhibits the expression of alpha-1, 2-L-fucosyltransferase enzyme also leads to HBGA expression for the gut, and it provides a composition of the phenotypical profile that exists in some populations with unique histories of evolution and it can be considered as a marker of the genetic population. It is found to have an association with many diseases which is discussed in this review. Polymorphic mutations are known to inhibit and reduce its function which are population specific. Detailed understanding and deeper knowledge of its role in the pathogenesis and prevention of many diseases is required. FUT2 may also have a potential role in the case of COVID-19 as a susceptible marker due to its association with respiratory diseases and the ABO blood group. There is an utmost need for this kind of review knowing its importance and owing to limited collective information.

Keywords: FUT2, HBGA, susceptibility marker, α2FucT1, genetics

Introduction

Biological markers of susceptibility are closely associated with the estimation of populations at risk. Individuals in a population may differ widely in their susceptibility. In the absence of susceptibility information, a population classified at risk may consist mainly of individuals who aren't susceptible and thus considered at lower risk [1]. Since the discovery of FUT2 as a genetic susceptible marker, the possible function of blood groups in infectious diseases has always been a constant interest. In epidemiological studies, the FUT2 gene is one of the frequent targets since it is a genetically determined trait between individuals and populations with defined polymorphic expressions. Toxins, parasites, and bacteria have receptors that help them colonize, invade, or avoid being cleared by the host with the help of blood group antigens managed by FUT2 [2]. As pathogens are selective agents, they use host-cell surface molecules as the signature for identifying signals. These are mostly oligosaccharides and produced by glycosyltransferases, for example, A and B antigens are recognized by certain pathogens as receptors. If fucosyltransferase, which is accountable for ABO biosynthesis in other body fluids other than blood, is active then these antigens can also be present in other tissues [2]. This type of association (pathogen with blood group antigen) is discussed in this paper.

In human, FUT2 gene encodes an enzyme known as Galactoside 2-alpha-L-fucosyltransferase 2 which is responsible for secretor status of ABO antigens [3]. Other names for FUT2 are B12QTL1, SE, Se2, SEC2, and sej [4]. The size of FUT2 gene is 9,980 bases with Plus strand orientation and, present on chromosome 19q13.33. It consists of 2 exons (118 and 2995 bp) which are separated by an intron of 6865 bp. The former exon is a non-translated coding region and another exon codes for 343 protein amino acids [5]. Around 20 percent of people worldwide are unable to release ABO in other body fluid. There are several polymorphisms in FUT2 which inactivates its function, although these polymorphisms are population specific and important to understand.

This paper hypothesized that the FUT2 is a determinant for the infectious disease which arises various questions like literature availability, its role in infectious diseases, and its relationship with a new arising disease like COVID-19.

There is limited and scattered published information on the role and overview of FUT2 as a susceptible marker and how it's associated with infectious diseases. The main objectives of this paper are to outline the role of FUT2 in susceptibility, its association with other diseases, and its interaction with pathogens. We also tried to verify its importance in coming scenarios where pandemic like COVID-19 exists. Also, this review focuses on a brief overview of the importance of FUT2 in human health, its relationship with the blood group system, global distribution, and its polymorphic allele.

Methodology

Search strategy

We formulated the search strategy using the MeSH terminology, which was then adapted for the databases being searched mainly Pubmed, Embase, Web of Science and Ovid. The terms used for Medical Topic Headings (MeSH) were 'FUT2 gene', 'prevalence', 'susceptibility marker', 'genetics', 'FUT2 disease association', 'FUT2 role in COVID19'. Cross-references were checked for associated studies when related papers were found.

Criteria of inclusion for a searched article are as follow:

(i) A peer-reviewed article published in a scientific journal in English.

(ii) Studies on FUT2 gene prevalence.

(iii) Cohort, case control studies or reviews assessing association between FUT2 and disease, also its relation with blood group.

(iv) Studies including the SNPs of FUT2.

(v) Studies including the importance of FUT2.

(vi) Studies including the methodologies of detecting FUT2 gene.

The titles and abstracts of potentially important papers were used for screening. The entire article was retrieved when the abstract was not available.

FUT2 mechanism and polymorphism

Terminology and their role linked with FUT2

FUT2 gene is a part of ABO serology. It plays an integrated and important role in the mechanism of blood group structure and disease association. The International Blood Transfusion Society (ISBT) officially recognizes 34 blood group systems. Some mechanisms, for instance, ABO, have several associations with infective diseases. Similarly, several pathogens may use many different blood group antigens to interact with them. This is especially true in the case of malaria which shows interaction with different blood group systems [2].

ABO, Lewis and secretor

The ABO histo-blood group comprises 4 types of groups (AB, O, A, and B) and two antigens (A & B). These two antigens are autosomal co-dominant and are formed by the ABO gene. Owing to the homozygous inheritance of two null ABO alleles, the group O phenotype is autosomal-recessive. The H antigen, which is the biosynthetic precursor to the A and B antigens, is expressed by people with blood group O. The blood type ABO has antigens A, B, and H. Different ethnic groups have different relative distributions of ABO forms, but group O appears to be the most common [2]. ABH antigens can be found in a range of tissues and secretions, as well as in the mucosa of the intestine, endothelium, kidney, heart, and other organs in addition to red blood cells. Blood group typing or ABO is also associated with many diseases as described in the detailed study done by L. cooling [2]. The implication of ABO typing for epidemiological research may be influenced by many developmental, clinical, and genetic factors. ABO expression is strongly dependent on Secretor/FUT2 gene inheritance in many epithelial tissues [6].

Secretor gene (FUT2)

In the autosomal dominant pattern, Fucosyltransferase 2, is also known as the Secretor gene. The inherited dominant form is 'Se',

whereas 'se' is indicated as the recessive form. Therefore, 'SeSe' or 'Se' is secretors and 'se' is non-secretor [7]. For individuals who secrete antigens that are present in the blood than other body fluids like mucus, saliva, etc., the words secretor are specified. On the other hand, though, a non-secretor status pointed to those that were not or very little interested in these body fluids [4]. Secretor status refers to the presence of ABH, Lewis antigen, and HBGA (histo blood group antigen) in mucous of the intestine and other bodily fluids or in secretions [8].

FUT2 in ABO biosynthesis

H, A, and B blood type antigens are alpha 1, 2-linked glycan-containing fucose existing on red blood cell glycoproteins and glycolipids (erythrocytes) in individuals representing the blood group A, B and H, respectively [8]. Fucosyltransferase enzymes H (FUT1) add fucose to the alpha (1, 2) binding of type 2 glycoproteins on RBCs to form H antigen, whereas FUT2 adds fucose to the alpha (1, 2) binding of type 1 glycoprotein chains to make ABH antigens in other body fluids (secretor phenotype). Almost 20 percent of the population lacks ABH antigens in secretions because of the presence of non-functional (mutated) fucosyltransferase Se (FUT2) (non-secretor phenotype) [9].

There is a single functional H gene (FUT1) for individuals with a non-secretor phenotype and do not have a functional secretor gene i.e. FUT2. Therefore, people with this expression have H antigen on the surface of RBCs but no H antigen in their secretions. H antigen is located on the surface of RBCs as well as in secretions of individuals belonging to the secretor phenotype. The rare Bombay (group O) and Para-Bombay phenotypes resulting from homozygosity of inactive H (FUT1) and Se (FUT2) and homozygosity of null allele H (FUT1) are induced by this process but have at least one functional allele of Se (FUT2) respectively [9].

The FUT1 and FUT2 gene fucosyltransferase product encodes a protein which is present on Golgi stack membrane and have at least one functional Se (FUT2) and glycoproteins on the RBC membrane and in body fluids (**Figure 1**) [3, 10].

Lewis (FUT3) and HBGA

The FUT2 gene, along with the FUT3 gene encodes an enzyme named fucosyltransferase-3 (Lewis type alpha 1, 3/4-fucosyltransferase), which is necessary for the presence of Lewis b antigen (Le a-b+) in secretions. In this case, FUT3 encodes Lewis as a histo-blood group (Le a+b-) antigen in individuals with nonsense FUT2 mutations (non-functional fucosyltransferase 2). Although, Lewis-ve (Le a-b-) has a Lewis null phenotype mutation in the FUT3 gene, irrespective of the FUT2 gene or secretor status, as shown in **Figure 2**. In the case of several microbes, these mucosal ABH and Lewis HBGAs are proven to act as energy sources and adhesion receptors [8].

HBGAs are complex carbohydrates present as soluble oligosaccharides on the exterior of RBC (red blood cell) surfaces, mucosal epithelia, and body fluids like intestinal secretions, milk, and saliva [11]. HBGA contains an antigen of type H 1. HBGA synthesis relies on the alpha 1, 2-fucosyltransferase enzyme produced by the FUT2 gene, which define the secretors. In order to promote cell attachment, microbes may recognise HBGA from hosts (**Figure 2**) [12].

Global prevalence of FUT2 (Secretors)

The presence of secretor and Non-secretor genotypes is greatly varies in different ethnic groups. For example, according to a study, only a few non-secretors are reported in East and Southeast Asians [12]. According to Le Pendu and co-workers, 80% of the population of Europe and North America has Secretor antigen [13]. While other research studies in Latin America, Africa, and several Asian countries have indicated a dominance of secretor plus Lewis Negative individuals, as opposed to Europe and North America, where people with secretor Lewis-positive prevail [14]. Another studies showed Lewis-positive secretor phenotype in North America and other parts of Europe especially in Spanish population [11, 15-17]. In Burkino Faso, Lewis antigen is negative for the majority of the population [17, 18]. The delay in Lewis antigen expression in the initial months of life, regardless of the FUT3 gene activity, has also been documented by some studies [2, 11].

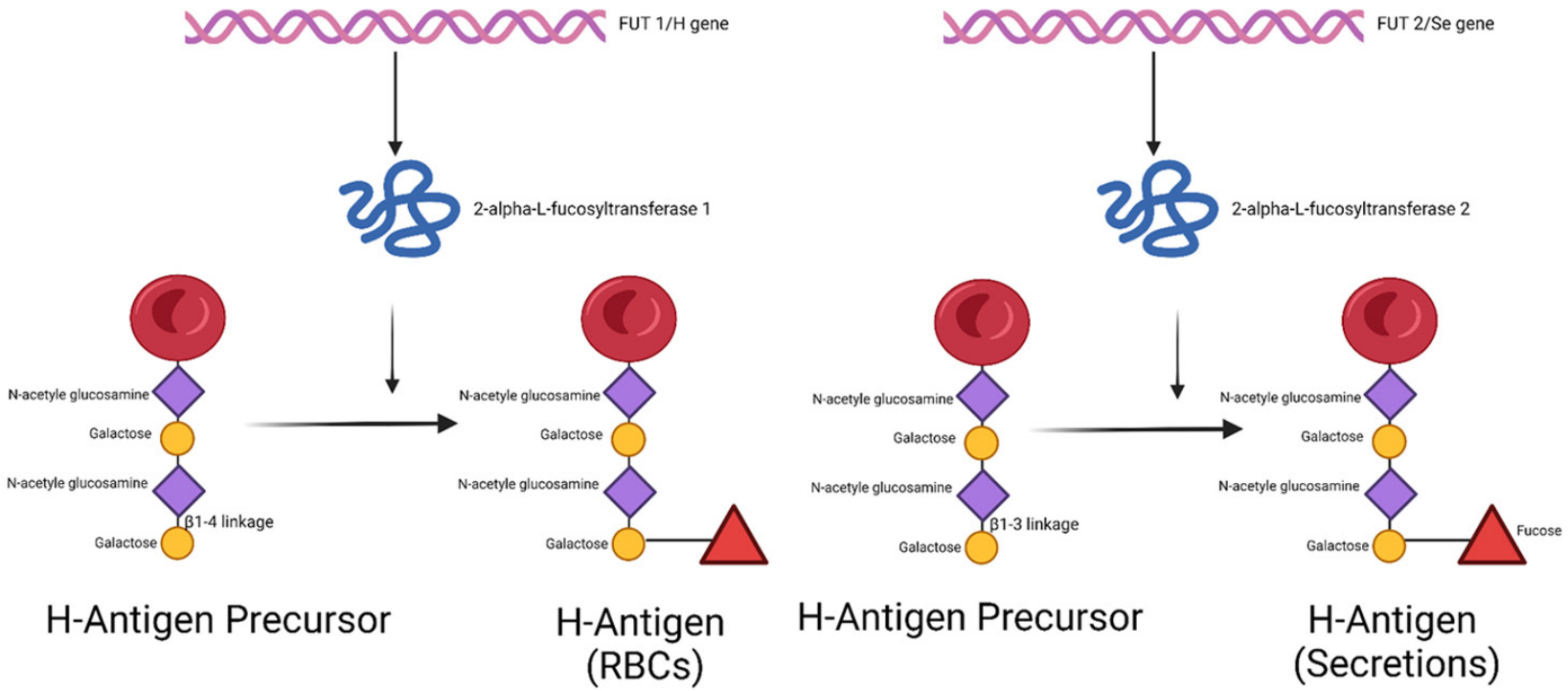

Figure 1. Role of FUT1 and FUT2. Fucosyltransferase enzymes H (FUT1) add fucose to the alpha (1, 2) binding of type 2 glycoproteins on RBCs to form H antigen, whereas FUT2 adds fucose to the alpha (1, 2) binding of type 1 glycoprotein chains to make ABH antigens in other body fluids (secretor phenotype).

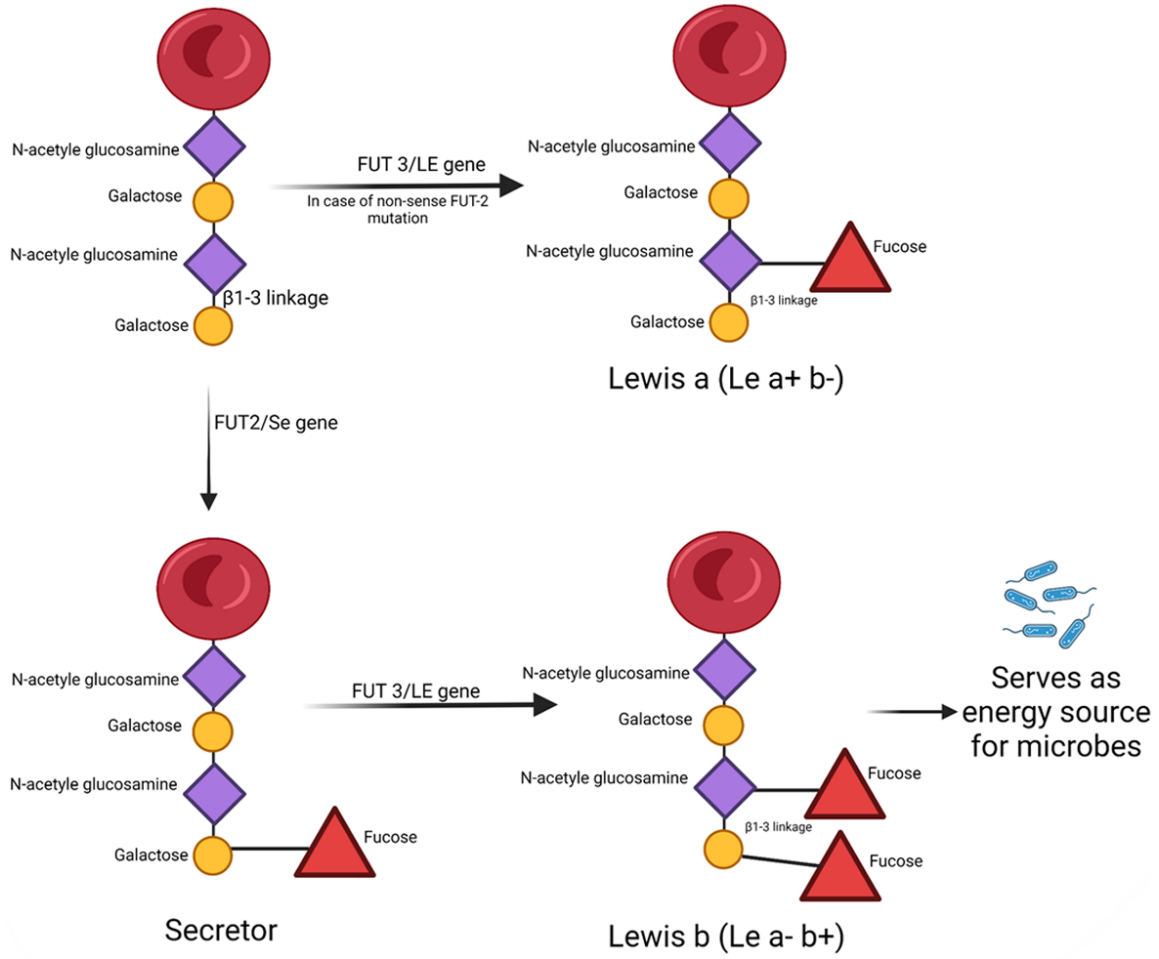

Figure 2. Representation of FUT2 plays a role in the attachment of microbes.

FUT2 polymorphism

FUT2 is predominantly expressed in the salivary glands, trachea, parotid, stomach, and mucosa of the intestine, epithelium of kidney, and tract of the human reproductive system especially in females (ovary, cervical canal, and cervix); however, there is not any FUT2 messenger RNA in the placenta, bone marrow, or spleen, which almost exclusively uses FUT1 [19]. Natural selection is evident in polymorphism in the FUT2 promoter [20]. Mutations in α2FucT1 or α2FucT2 enzymes activity (encoded by *FUT1* and FUT2, respectively) that affect negatively reduce or stop the production of antigen H. Mostly, Non-secretors are non-sense mutations in FUT2 gene [8].

There are currently 29 null and weaker alleles of the FUT2 gene (http:/www.isbtweb.org/) listed in the ISBT [10]. Se^{428} (Trp143stop) is the very prevalent non-secretor allele in Caucasians and is used in genome research (G428A; rs601338). Studies from Turks, Africans, and Iranians found the presence of se^{428} allele [21, 22]. In Asia, FUT2 variants with low activity (Se^{W}) are usual. Se^{385} (Ile129Phe) is the predominant Se^{W} allele in China and neighbouring Asian countries [23-25]. Se^{W}/Se^{W} and Se^{W}/se people can also be presented as Le (a+b^{W}), Le (a+b-), or Le (a-b-) respectively. Individuals who are mainly at consequences of having a non-secretor phenotype are Se^{W}/se genotype [24].

Several other studies also reported polymorphism in FUT2 gene. Ting-An Yang et al., reported a mis-sense mutation (A385T), two nonsense mutation (C571T and G849A), and a silent mutation (C357T) in FUT2 alleles in Taiwanese population [12]. FUT2 gene polymorphism has been noted to regulate the

innate immune response and also play a role in evolution for the survival of humans during pathogen outbreaks [26]. According to Pirjo wacklin et al., in 2011 and Goke Gunaydin et al., in 2015 when the FUT2 428G>A SNP was AA, the person's secretor status was specified as non-secretor, and if the FUT2 428G>A (Se^{428}, W143X, rs601338) SNP was GA or GG, the individual status was stated as secretor [8, 27]. In south Africa Se^{375}, Se^{481}, and Se^{40} are the most common polymorphisms and in Europeans, Xhosas, and Ghanaians se^{375} and Se^{480} is most common [28-30].

While several FUT2 polymorphisms are unique to individuals, in most populations there is dominance of non-secretor phenotypes [30]. Non-secretor phenotypes occur due to mutations in the second exon of the FUT2 gene, the most common explanation for the non-secretor status among all two alleles is the non-functional allele se^{428}, which codes for a stop codon at position 143 (Trp-Ter) [28, 29]. The most common reason of non-secretor phenotype in South East and East Asians is Se^{385}, which is triggered by a decrease in alpha-(1, 2) fucosyltransferase activity due to mis-sense mutation on codon 129 (Ile-Phe) [30-33]. There tends to be a more limited geographical distribution of two other non-secretor alleles: se^{302} and se^{571} which are reported to found in Thai, Bangladeshi and samoans population, respectively [30, 34].

According to Lara M. Silva and co-workers, the time duration of global genetic diversity in FUT2 may be as old as three million years, according to the hypothesis that FUT2 is under long-term balancing selection. The 428G>A mutation happened at least 1.87 million years earlier, and the 739G>A substitution occurred approximately 816,000 years ago, according to specific variant age estimates. In East Asians, the non-secretor phenotype is caused by the 385A>T missense mutation and possibly occurred around 256,000 years ago [35]. Studies also showed that Lewis HBGAs and H type 1 expression in the FUT2 and FUT3 genes is genetically determined on the basis of polymorphisms. The frequency of these polymorphisms varies greatly among ethnicities; for example, around 4-6% of white populations do not exhibit Lewis antigens, while in certain African and Latin American populations, the frequency of this Lewis-negative trait are more than 30% [18]. One recent study explained that polymorphism are population specific. Three alleles, Se^{357}, Se and se^{428} were common, and the frequency of non-secretors was relatively low in Latin American populations and concluded that the high number of non-secretors may affect the expansion or effect of diseases in particular population [36].

Host-parasite interactions

Secretors and non-secretors have different carbohydrate phenotypes, which influences their sensitivity to various pathogens. According to Raul Perez-Ortin et al., human rotaviruses have been reported to recognise individuals' various host histo-blood group antigens (HBGAs) in a type-specific manner [37]. Anna Ferrer-Admetlla et al., reported that pathogens are effective selective agents and the signature of selection can be revealed by pathogen's host-cell surface molecules as identification signals [5].

As per another study the frequency of FUT2 alleles is related to pathogen richness, implying that secretor and non-secretor status can play a function in susceptibility and resistance to various pathogens. As a result, to fully comprehend the role of FUT2 alleles in the evolution of host pathogens, a detailed understanding of their function is needed [5].

Linkage of FUT2 with other diseases

Mourant and co-workers explained that there is epidemiological reason to link ABO blood types, secretor status, and exposure to pathogens, as well as other conditions like carcinoma and ulcers [38]. Non-secretors are often more commonly related to low-level infections including yeast (Candida) and Streptococcus. Peter and co-workers also indicated that it is also recognized that non-secretors suffer from several types of autoimmune disorders, especially Crohn's disease. Non-secretors of blood type A in some cases experience bacterial overgrowth in the stomach, which may lead to severe complications including Barrett's Esophagus, esophagus and upper stomach chronic inflammation [39]. Many such associations of non-secretor and secretors are mentioned in **Table 1**. Although it seems that being a non-secretor does not have an advantage,

Table 1. Representing association of Secretor and Non-Secretor with diseases

S. No	Status	Linked Disease	Reference
1	Non-Secretors	Imbalance in their bacteria flora, a condition known as dysbiosis	[40]
2	Non-Secretors	Autoimmune diseases like Rheumatoid arthritis, Psoriasis, Diabetes mellitus	[41]
3	Non-Secretors	Peptic ulcers	[42]
4	Non-Secretors	Vaginal candidiasis	[43]
5	Non-Secretors	Oral changes like oral submucous fibrosis	[44]
6	Non-Secretors	Dental caries	[45, 46]
7	Non-Secretors	Periodontal disease	[47]
8	Non-Secretors	Precancerous oral lesions and oral cancer	[48, 49]
9.	Secretors genotype and lewis positive genotype (independently)	Higher risk of moderate to serious rotavirus AGE	[12]
10	Lewis negative children	Susceptible for Rotavirus P [6] infection and responsible for resistance to P [8] strains that it's likely that in Sub-Saharan Africa, rotavirus vaccine potency is limitedis due to this factor	[11]
11	Non-Secretors	Lower incident of rotavirus symptomatic infections	[37]
12	Secretor status	Strong association with intestine micro-biota particularly with bifidobacterial diversity	[8]
13	Non-Secretor phenotype	Strongly associated with Crohn's disease and necrotizing enterocolitis	[50-52]
14	Non-Secretor	Urinary tract infection and vaginal candidiasis are more likely to occur	[50]
15	Secretor	Certain Norovirus genotypes increase the chance of diarrhea	[53]
16	Non-Secretor (women)	Recurrent urinary tract infection due to E. coli	[54]
17	Secretor	In both humans and Rhesus monkeys, positive BabA Secretors are necessary for Helicobacter pylori adhesion and infection	[33, 55]
18	Non-Secretor	Cholera infection	[56]
19	Secretor	HIV progression and infection	[41]
20	Secretor	Respiratory Viral illness in patients of Influenza	[57]

some preliminary research indicates that non-secretors can have a less chance of some digestive tract tumours [40].

There has been a significant correlation between phenotypic expression of HBGA and NoV infection in many previous studies, which is thought to be a significant factor in GII NoV prevalence. The GII.4 NoVs recognize HBGAs which represent more than 80 percent of the common population. Few strains may also recognise non-secretors, explaining their dominance in triggering NoV epidemics worldwide [58].

Secretor has been recognised as a biomarker of necrotizing enterocolitis, which is predominantly a premature infant disease [59]. In 2020, A new study in Korea, concluded that O type blood and secretors are one of the protective factors against Cohrn's Disease in Asian population [60]. Another research supported the hypothesis that FUT2 loss-of-function mutation participates in the IBD pathogenesis by decreasing binding sites for adherent bacteria and thus altering the gut microbiota. Decreased abundances of adherent bacteria may allow the overgrowth of bacteria that induce inflammatory T cells, leading to intestinal inflammation [61]. One study reported the responsibility for a range of gastrointestinal disorders, such as salivary tumors, gastric cancer, pernicious anaemia, and duodenal ulcer, was found to be related to the blood groups of ABO. The causes of these connections are unclear, specifically linked to the basic defensive behaviour of substances in the blood group in the secretions [62]. One study also reported association of non-secretor with C. Jejuni [2]. There was no correlation found in Se/FUT2 genotype with severity of cystic fibrosis in some studies [63].

The presence of a secretor determines why a particular disease is prevalent in that area. The type 1 chain precursor (Gal3GlcNAc) as well as all HBGAs on glycolipids carrying the end products of the ABH, secretor, and Lewis genes, are typically abundant in the neonatal gut. The type 1 chain predecessor is normally undetectable

in the adult small bowel, and has only been observed in one Lewis- and secretor-negative person and a proximal resection of jejunum taken from a gastric cancer sufferer. While fucosylated glycosphingolipids undergo minor structural changes across the villus axis of the adult intestine less information is available about the cell-specific, temporal, and longitudinal changes of HBGAs in early childhood intestinal tissues, especially concerning changes in intestine microflora [18]. In one recent research, it is proved that low Fut2 expression and α-1, 2-fucosylation in the colon were seen in patients with Ulcerative colitis and Crohn's disease. It also found in this study that Fut2 deficiency in intestinal epithelium exacerbated colitis, including promoting the release of proinflammatory cytokines and aggravating epithelial barrier damage [52]. Like others, intussusceptions are another condition whose cause is unknown and predicted to be related to many of these viruses which are associated with Secretors and Non-secretors. It may have been hypothesized that intussusceptions can be directly or indirectly associated with the status of host genetic susceptibility. There is a need for more studies to infer the hypothesis. One study also suggested that although a lot of research studies exist for direct interactions between host and pathogen, determining the more complex and variable mechanisms underlying three-way interactions involving the intestinal microbiota will be the subject of much-needed future research [64]. One possibility is that the higher frequency of negative Lewis people leads to viral evolution, but this is just a speculation [38].

Some recent studies also hypothesised that ABO antibodies, group O people are highly immune to SARS CoV, reducing the level of infection in the people. However, The ABO antibody titre, secretor status, and the presence of group O in the population can all influence the degree of protection [65]. It would also nullify viral neutralisation by a non-secretor phenotype, because viruses transmitted from a non-secretor lack ABH expression [2]. The effect of host genetics on COVID-19 susceptibility and severity has been studied less. In people with Covid-19 and respiratory failure, a 3p21.31 gene cluster was discovered to be a genetic susceptibility locus. A recent study in 2020 reported that the ABO blood group system may be involved in new or emerging infections suggesting the involvement of host genetics with COVID-19, which is a significant indicator of the significance of the FUT2 gene and directs the need for further studies in this direction [66]. According to a mini-review done in 2020, FUT2 polymorphisms may profoundly influence gut microbiota composition and host susceptibility to viral infections and chronic inflammatory disease and indicated that it might play a very essential role in type 1 diabetes (T1D) etiology and unveil novel targets of intervention to contrast T1D development and progression which has steadily increased over the last decades [67].

Methods for ascertaining FUT2 genes

Different studies used different methods to ascertain the presence of secretor. Some of relevant studies are discussed in this paper. A group genotyped FUT2 and FUT3 using PCR-RFLP following genomic DNA extraction using Qiagen QIAamp DNA Mini Pack kit [12]. Two other studies determined the Histo-blood group antigen in saliva using enzyme-linked immunosorbent assay (ELISA) [18, 37]. PCR was also used for FUT2 (secretor status) genotypic characterization in a study [18]. Lewis a and b typing in monoclonal anti-sera tubes was performed by Pirjo wacklin et al., in 2011. The secretor status determination was dependent on Lewis antigens. Phenotyping of lewis negative people did not determine secretor status and the genotyping of the FUT2 gene was used to assess their status of secretors [8]. In 2018 a study determined the HBGA phenotype by testing saliva for Lewis a, Lewis b, and H antigen with enzyme immunoassays, lectin, and anti-HBGA antibodies.

Further Nordgren et al. described a detailed method using saliva for phenotyping. In summary, Histo blood group antigens (A, B, Lewis a, and Lewis b) in saliva were determined using an ELISA method, as mentioned earlier. An ELISA assay was used to test a subset of saliva samples for Ulex europaeus agglutinin (UEA-I), which detect Fuc1-2Gal-R present in the secretor's saliva [18].

Role and importance of FUT2 genes

The role of the secretor/FUT2 gene has been thoroughly discussed in this review. To achieve

a greater understanding of the pathogenesis of illness and to better foresee and avoid negative outcomes for premature infants, children, and adults, novel biomarkers are required. For instance, Secretor fucosyltransferase 2 (FUT2) gene variation and varying H antigen expression, a carbohydrate formed by secretor gene enzymes, biomarkers that are promising for predicting early outcomes in infants which may be due to an infection/inflammation, such as death, NEC, and sepsis. Secretors, who have an active FUT2 allele, have a lot of H antigen in their saliva and other secretions, including fetal tissues and secretions, on mucosal surfaces [59]. Marrow et al. also mentioned in their research that in mouse pups with regular postnatal maturation and microbial colonization of the intestine, secretor gene expression increases. Immature and irregular microbial colonization lead to adverse effects in premature infants, thus, it is a lack of early postnatal secretor gene expression was hypothesized to be the cause may indicate a poor prognosis, and it was being investigated as a predictive biomarker of premature infant risk of NEC, sepsis, and death [59].

The microbiota in the intestine plays an important role in human health, according to a study in 2013, many factors affect the structure of microbiota, including the host's diet and genotype. More recent research has shown that on the cell membrane, certain bacteria bind to particular sugars. Helicobacter pylori, which infects most people's stomach lining, survive in the stomachs of secretors because of proper binding with the extra fucosyl residues to the glycan branches. H. pylori does the most damage to the gastric lining in secretors, where it is most likely to interfere with the release of the intrinsic vitamin B12 absorption factor. Secretors with a lower intrinsic factor have a harder time absorbing vitamin B12 from food and biliary recirculation. They are having a difficult time maintaining adequate vitamin B12 supplies. undoubtedly, then many Europeans with H. pylori infections have lower vitamin B12 levels than those of their pathogen-free individuals and most of the affected individuals are FUT2 461G variant secretors. This highlights the value of other lifestyle and genetic factors [68].

The proof that the FUT2 gene has developed in a non-neutral manner contributes to the functional value of the Se/se variant, indicating a significant role in the arms race of the host/pathogens. Therefore, it is important to properly characterize the efficacy of allelic variation at the FUT2 locus [35].

The secretor gene in early ontogeny appears to be important. It is known that the secretor gene is expressed in the epithelial tissues of the fetus and saliva. Low levels of H antigen are found in the uncolonized gut. The intestinal epithelium displays a marked rise in fut2-mRNA and fucosyltransferase activity during the first weeks after birth, there is bacterial colonization, which can be treated with antibiotic treatment. In this study, they found that in the saliva and tracheal aspirates of newborns alive, the secretor (H) antigen expresses highly postnatal. Although the mechanisms underlying the absence or low levels of H antigen as a biomarker for adverse premature outcomes are unclear, potential explanations include a connection to mucosal immaturity or irregular colonization [59].

Discussion

Recently, the role of histo-blood group antigens (HBGAs) as receptors/ligands for RV cell attachment has been investigated. These studies demonstrated that the binding of RV to glycans is dependent on P genotype specificity. One of the early studies investigating the binding of synthetic oligosaccharides to the VP8* domain of VP4 protein of P [4] and P [8] genotypes found strong binding to the Lewis b and H type 1 glycan, while P [6] strains are bound to H type 1 only. Besides H type 1 and Lewis b, H type 2 precursor glycans and A-type HBGA binds to RV in P genotype specific manner. Recently, several studies have established the function of HBGAs as RV cell attachment receptors/ligands. The specificity of the P genotype influences RV binding to glycans, according to these population-specific studies. One of the first studies of synthetic oligosaccharide binding to the VP8 domain of the VP4 protein genotypes P [4] and P [8] find strong binding to type 1 glycans of Lewis b and H, while P [6] only binds to type H 1. H type 2 precursor glycans and A-type HBGA specifically bind to RV in the P-genotype, in addition to type 1 H antigen and Lewis b [69].

In addition, in the present research, there is insufficient geographical representation. Most

of the studies were performed in the United States and European countries. On the other hand, Asian populations, including Middle Eastern and South Asian populations, have little to no data. Participants from American countries were also underrepresented, even though these countries have significant indigenous populations [14]. According to another paper, to date, epidemiological studies have not fully described the role of enteric viruses in inflammatory flare-ups, especially that of human noroviruses and rotaviruses, which are the main causative agents of viral gastroenteritis. Genome-wide association studies have demonstrated the association between IBD, polymorphisms of the *FUT2* and *FUT3* genes (which drive the synthesis of histo-blood group antigens), and ligands for norovirus and rotavirus in the intestine [70].

In the view of FUT2 and FUT3 prevalence, polymorphisms, and most significantly, susceptibility patterns, which differ between different populations and due to the lack of diverse topographical representation, as a result, there may be differences in infection risk among those populations. The dominance of the missense mutation at nucleotide 385 (A>T) in East Asian populations and the Lewis negative expression in African populations are two examples [14]. Because people from certain regions are not yet represented, future research should focus on these ethnicities to see how susceptibility based on secretory status differs between ethnic groups.

Studies linked to FUT2 as susceptibility may have implications for the production of vaccines and the design of studies. Some people may be resistant to infection and therefore will not respond to the vaccine. The findings of vaccine efficacy research should be interpreted by taking into account the proportion of individuals with FUT2 or FUT3 polymorphisms in the sample population.

In conclusion, FUT2 gene is closely linked to the risk of norovirus and rotavirus infection as studied. Further observational studies in Asia, South and Central America and among multiple ethnic groups are needed to better understand differences in innate susceptibility to enteric viruses. For the advancement of vaccines and therapeutics as well as the administration of vaccines to communities at risk of infection, understanding trends of susceptibility will be useful [3, 10, 14]. Collaborative data from all ethnicity will enhance the understanding of full functioning and role of FUT2 as a susceptible marker. This may further help in studying the mechanism involved in the spread of infection of many other diseases like COVID19 and in their prevention [14].

Disclosure of conflict of interest

None.

Address correspondence to: Madhu Gupta, Department of Community Medicine and Public Health, Postgraduate Institute of Medical Education and Research, Chandigarh, India. E-mail: madhugupta21@gmail.com

References

[1] National Research Council (US) Subcommittee on Biologic Markers in Urinary Toxicology. Biologic Markers in Urinary Toxicology. In: editors. Washington (DC): National Academies Press (US) Copyright 1995 by the National Academy of Sciences. All rights reserved; 1995. pp. 1.

[2] Cooling L. Blood groups in infection and host susceptibility. Clin Microbiol Rev 2015; 28: 801-870.

[3] Campi C, Escovich L, Moreno A, Racca L, Racca A, Cotorruelo C and Biondi C. Expression of the gene encoding secretor type galactoside 2 α fucosyltransferase (FUT2) and ABH antigens in patients with oral lesions. Med Oral Patol Oral Cir Bucal 2012; 17: e63-68.

[4] Mohn JF, Owens NA and Plunkett RW. The inhibitory properties of group A and B non-secretor saliva. Immunol Commun 1981; 10: 101-126.

[5] Ferrer-Admetlla A, Sikora M, Laayouni H, Esteve A, Roubinet F, Blancher A, Calafell F, Bertranpetit J and Casals F. A natural history of FUT2 polymorphism in humans. Mol Biol Evol 2009; 26: 1993-2003.

[6] Mankelow TJ, Singleton BK, Moura PL, Stevens-Hernandez CJ, Cogan NM, Gyorffy G, Kupzig S, Nichols L, Asby C, Pooley J, Ruffino G, Hosseini F, Moghaddas F, Attwood M, Noel A, Cooper A, Arnold DT, Hamilton F, Hyams C, Finn A, Toye AM and Anstee DJ. Blood group type A secretors are associated with a higher risk of COVID-19 cardiovascular disease complications. EJHaem 2021; 2: 175-187.

[7] Bakhtiari S, Far SM, Alibakhshi Z, Shirkhoda M and Anbari F. Salivary secretor status of blood group antigens in patients with head and neck

cancer. Open Access Maced J Med Sci 2019; 7: 373-377.
[8] Wacklin P, Mäkivuokko H, Alakulppi N, Nikkilä J, Tenkanen H, Räbinä J, Partanen J, Aranko K and Mättö J. Secretor genotype (FUT2 gene) is strongly associated with the composition of Bifidobacteria in the human intestine. PLoS One 2011; 6: e20113.
[9] Rahorst L and Westhoff CM. Chapter 25 - ABO and H Blood Group System. In: Shaz BH, Hillyer CD, Reyes Gil M, editors. Transfusion Medicine and Hemostasis (Third Edition). Elsevier; 2019. pp. 139-147.
[10] ISBT. Names for H (ISBT 018) Blood Group Alleles. 2019; 1-5.
[11] Pérez-Ortín R, Santiso-Bellón C, Vila-Vicent S, Carmona-Vicente N, Rodríguez-Díaz J and Buesa J. Rotavirus symptomatic infection among unvaccinated and vaccinated children in Valencia, Spain. BMC Infect Dis 2019; 19: 998.
[12] Yang TA, Hou JY, Huang YC and Chen CJ. Genetic susceptibility to rotavirus gastroenteritis and vaccine effectiveness in Taiwanese children. Sci Rep 2017; 7: 6412.
[13] Le Pendu J. Histo-blood group antigen and human milk oligosaccharides: genetic polymorphism and risk of infectious diseases. Adv Exp Med Biol 2004; 554: 135-143.
[14] Kambhampati A, Payne DC, Costantini V and Lopman BA. Host genetic susceptibility to enteric viruses: a systematic review and meta-analysis. Clin Infect Dis 2016; 62: 11-18.
[15] Marionneau S, Ruvoën N, Le Moullac-Vaidye B, Clement M, Cailleau-Thomas A, Ruiz-Palacois G, Huang PW, Jiang X and Le Pendu J. Norwalk virus binds to histo-blood group antigens present on gastroduodenal epithelial cells of secretor individuals. Gastroenterology 2002; 122: 1967-1977.
[16] Van Trang N, Vu HT, Le NT, Huang PW, Jiang X and Anh DD. Association between norovirus and rotavirus infection and histo-blood group antigen types in Vietnamese children. J Clin Microbiol 2014; 52: 1366-1374.
[17] Nordgren J, Nitiema LW, Ouermi D, Simpore J and Svensson L. Host genetic factors affect susceptibility to norovirus infections in Burkina Faso. PLoS One 2013; 8: e69557.
[18] Nordgren J, Sharma S, Bucardo F, Nasir W, Günaydın G, Ouermi D, Nitiema LW, Becker-Dreps S, Simpore J, Hammarström L, Larson G and Svensson L. Both Lewis and secretor status mediate susceptibility to rotavirus infections in a rotavirus genotype-dependent manner. Clin Infect Dis 2014; 59: 1567-1573.
[19] Yamamoto M, Yamamoto F, Luong TT, Williams T, Kominato Y and Yamamoto F. Expression profiling of 68 glycosyltransferase genes in 27 different human tissues by the systematic multiplex reverse transcription-polymerase chain reaction method revealed clustering of sexually related tissues in hierarchical clustering algorithm analysis. Electrophoresis 2003; 24: 2295-2307.
[20] Fumagalli M, Cagliani R, Pozzoli U, Riva S, Comi GP, Menozzi G, Bresolin N and Sironi M. Widespread balancing selection and pathogen-driven selection at blood group antigen genes. Genome Res 2009; 19: 199-212.
[21] Reid ME, Lomas-Francis C and Olsson ML. RH - Rh Blood Group System. In: Reid ME, Lomas-Francis C, Olsson ML, editors. The Blood Group Antigen FactsBook (Third Edition). Boston: Academic Press; 2012. pp. 147-262.
[22] Soejima M, Nakajima T, Fujihara J, Takeshita H and Koda Y. Genetic variation of FUT2 in Ovambos, Turks, and Mongolians. Transfusion 2008; 48: 1423-1431.
[23] Yip SP, Lai SK and Wong ML. Systematic sequence analysis of the human fucosyltransferase 2 (FUT2) gene identifies novel sequence variations and alleles. Transfusion 2007; 47: 1369-1380.
[24] Kudo T, Iwasaki H, Nishihara S, Shinya N, Ando T, Narimatsu I and Narimatsu H. Molecular genetic analysis of the human Lewis histo-blood group system. II. Secretor gene inactivation by a novel single missense mutation A385T in Japanese nonsecretor individuals. J Biol Chem 1996; 271: 9830-9837.
[25] Hong YJ, Hwang SM, Kim TS, Song EY, Park KU, Song JH and Han KS. Significance of Lewis phenotyping using saliva and gastric tissue: comparison with the Lewis phenotype inferred from Lewis and secretor genotypes. Biomed Res Int 2014; 2014: 573652.
[26] Lindén S, Mahdavi J, Semino-Mora C, Olsen C, Carlstedt I, Borén T and Dubois A. Role of ABO secretor status in mucosal innate immunity and H. pylori infection. PLoS Pathog 2008; 4: e2.
[27] Günaydın G, Nordgren J, Sharma S and Hammarström L. Association of elevated rotavirus-specific antibody titers with HBGA secretor status in Swedish individuals: the FUT2 gene as a putative susceptibility determinant for infection. Virus Res 2016; 211: 64-68.
[28] Liu Y, Koda Y, Soejima M, Pang H, Schlaphoff T, du Toit ED and Kimura H. Extensive polymorphism of the FUT2 gene in an African (Xhosa) population of South Africa. Hum Genet 1998; 103: 204-210.
[29] Kelly RJ, Rouquier S, Giorgi D, Lennon GG and Lowe JB. Sequence and expression of a candidate for the human Secretor blood group alpha (1, 2) fucosyltransferase gene (FUT2). Homozygosity for an enzyme-inactivating nonsense mutation commonly correlates with the non-

secretor phenotype. J Biol Chem 1995; 270: 4640-4649.
[30] Soejima M, Pang H and Koda Y. Genetic variation of FUT2 in a Ghanaian population: identification of four novel mutations and inference of balancing selection. Ann Hematol 2007; 86: 199-204.
[31] Yu LC, Yang YH, Broadberry RE, Chen YH, Chan YS and Lin M. Correlation of a missense mutation in the human Secretor alpha 1,2-fucosyltransferase gene with the Lewis(a+b+) phenotype: a potential molecular basis for the weak Secretor allele (Sew). Biochem J 1995; 312: 329-332.
[32] Henry S, Mollicone R, Fernandez P, Samuelsson B, Oriol R and Larson G. Molecular basis for erythrocyte Le(a+ b+) and salivary ABH partial-secretor phenotypes: expression of a FUT2 secretor allele with an A–>T mutation at nucleotide 385 correlates with reduced alpha(1,2) fucosyltransferase activity. Glycoconj J 1996; 13: 985-993.
[33] Koda Y, Tachida H, Pang H, Liu Y, Soejima M, Ghaderi AA, Takenaka O and Kimura H. Contrasting patterns of polymorphisms at the ABO-secretor gene (FUT2) and plasma alpha(1,3) fucosyltransferase gene (FUT6) in human populations. Genetics 2001; 158: 747-756.
[34] ENCODE Project Consortium, Birney E, Stamatoyannopoulos JA, Dutta A, Guigó R, Gingeras TR, Margulies EH, Weng Z, Snyder M, Dermitzakis ET, Thurman RE, Kuehn MS, Taylor CM, Neph S, Koch CM, Asthana S, Malhotra A, Adzhubei I, Greenbaum JA, Andrews RM, Flicek P, Boyle PJ, Cao H, Carter NP, Clelland GK, Davis S, Day N, Dhami P, Dillon SC, Dorschner MO, Fiegler H, Giresi PG, Goldy J, Hawrylycz M, Haydock A, Humbert R, James KD, Johnson BE, Johnson EM, Frum TT, Rosenzweig ER, Karnani N, Lee K, Lefebvre GC, Navas PA, Neri F, Parker SC, Sabo PJ, Sandstrom R, Shafer A, Vetrie D, Weaver M, Wilcox S, Yu M, Collins FS, Dekker J, Lieb JD, Tullius TD, Crawford GE, Sunyaev S, Noble WS, Dunham I, Denoeud F, Reymond A, Kapranov P, Rozowsky J, Zheng D, Castelo R, Frankish A, Harrow J, Ghosh S, Sandelin A, Hofacker IL, Baertsch R, Keefe D, Dike S, Cheng J, Hirsch HA, Sekinger EA, Lagarde J, Abril JF, Shahab A, Flamm C, Fried C, Hackermüller J, Hertel J, Lindemeyer M, Missal K, Tanzer A, Washietl S, Korbel J, Emanuelsson O, Pedersen JS, Holroyd N, Taylor R, Swarbreck D, Matthews N, Dickson MC, Thomas DJ, Weirauch MT, Gilbert J, Drenkow J, Bell I, Zhao X, Srinivasan KG, Sung WK, Ooi HS, Chiu KP, Foissac S, Alioto T, Brent M, Pachter L, Tress ML, Valencia A, Choo SW, Choo CY, Ucla C, Manzano C, Wyss C, Cheung E, Clark TG, Brown JB, Ganesh M, Patel S, Tammana H, Chrast J, Henrichsen CN, Kai C, Kawai J, Nagalakshmi U, Wu J, Lian Z, Lian J, Newburger P, Zhang X, Bickel P, Mattick JS, Carninci P, Hayashizaki Y, Weissman S, Hubbard T, Myers RM, Rogers J, Stadler PF, Lowe TM, Wei CL, Ruan Y, Struhl K, Gerstein M, Antonarakis SE, Fu Y, Green ED, Karaöz U, Siepel A, Taylor J, Liefer LA, Wetterstrand KA, Good PJ, Feingold EA, Guyer MS, Cooper GM, Asimenos G, Dewey CN, Hou M, Nikolaev S, Montoya-Burgos JI, Löytynoja A, Whelan S, Pardi F, Massingham T, Huang H, Zhang NR, Holmes I, Mullikin JC, Ureta-Vidal A, Paten B, Seringhaus M, Church D, Rosenbloom K, Kent WJ, Stone EA, Batzoglou S, Goldman N, Hardison RC, Haussler D, Miller W, Sidow A, Trinklein ND, Zhang ZD, Barrera L, Stuart R, King DC, Ameur A, Enroth S, Bieda MC, Kim J, Bhinge AA, Jiang N, Liu J, Yao F, Vega VB, Lee CW, Ng P, Shahab A, Yang A, Moqtaderi Z, Zhu Z, Xu X, Squazzo S, Oberley MJ, Inman D, Singer MA, Richmond TA, Munn KJ, Rada-Iglesias A, Wallerman O, Komorowski J, Fowler JC, Couttet P, Bruce AW, Dovey OM, Ellis PD, Langford CF, Nix DA, Euskirchen G, Hartman S, Urban AE, Kraus P, Van Calcar S, Heintzman N, Kim TH, Wang K, Qu C, Hon G, Luna R, Glass CK, Rosenfeld MG, Aldred SF, Cooper SJ, Halees A, Lin JM, Shulha HP, Zhang X, Xu M, Haidar JN, Yu Y, Ruan Y, Iyer VR, Green RD, Wadelius C, Farnham PJ, Ren B, Harte RA, Hinrichs AS, Trumbower H, Clawson H, Hillman-Jackson J, Zweig AS, Smith K, Thakkapallayil A, Barber G, Kuhn RM, Karolchik D, Armengol L, Bird CP, de Bakker PI, Kern AD, Lopez-Bigas N, Martin JD, Stranger BE, Woodroffe A, Davydov E, Dimas A, Eyras E, Hallgrímsdóttir IB, Huppert J, Zody MC, Abecasis GR, Estivill X, Bouffard GG, Guan X, Hansen NF, Idol JR, Maduro VV, Maskeri B, McDowell JC, Park M, Thomas PJ, Young AC, Blakesley RW, Muzny DM, Sodergren E, Wheeler DA, Worley KC, Jiang H, Weinstock GM, Gibbs RA, Graves T, Fulton R, Mardis ER, Wilson RK, Clamp M, Cuff J, Gnerre S, Jaffe DB, Chang JL, Lindblad-Toh K, Lander ES, Koriabine M, Nefedov M, Osoegawa K, Yoshinaga Y, Zhu B and de Jong PJ. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 2007; 447: 799-816.
[35] Silva LM, Carvalho AS, Guillon P, Seixas S, Azevedo M, Almeida R, Ruvoën-Clouet N, Reis CA, Le Pendu J, Rocha J and David L. Infection-associated FUT2 (Fucosyltransferase 2) genetic variation and impact on functionality assessed by in vivo studies. Glycoconj J 2010; 27: 61-68.
[36] Soejima M and Koda Y. FUT2 polymorphism in Latin American populations. Clin Chim Acta 2020; 505: 1-5.
[37] Pérez-Ortín R, Vila-Vicent S, Carmona-Vicente N, Santiso-Bellón C, Rodríguez-Díaz J and Bue-

sa J. Histo-blood group antigens in children with symptomatic rotavirus infection. Viruses 2019; 11: 339.
[38] Mourant AE. Recent advances in the study of associations between infection and genetic markers. FEMS Microbiol Immunol 1989; 1: 317-319.
[39] Ewald DR and Sumner SCJ. Human microbiota, blood group antigens, and disease. Wiley Interdiscip Rev Syst Biol Med 2018; 10: e1413.
[40] D'Adamo P. Bugs and blood types. D'Adamo Personalized Nutrition 2019.
[41] Blackwell CC, James VS, Davidson S, Wyld R, Brettle RP, Robertson RJ and Weir DM. Secretor status and heterosexual transmission of HIV. BMJ 1991; 303: 825-826.
[42] Suadicani P, Hein HO and Gyntelberg F. Genetic and life-style determinants of peptic ulcer. A study of 3387 men aged 54 to 74 years: The Copenhagen Male Study. Scand J Gastroenterol 1999; 34: 12-17.
[43] Kulkarni DG and Venkatesh D. Non-secretor status; a predisposing factor for vaginal candidiasis. Indian J Physiol Pharmacol 2004; 48: 225-229.
[44] Hallikeri K, Udupa R, Guttal K and Naikmasur V. Analysis of salivary secretor status in patients with oral submucous fibrosis: a case-control study. J Investig Clin Dent 2015; 6: 261-266.
[45] Holbrook WP and Blackwell CC. Secretor status and dental caries in Iceland. FEMS Microbiol Immunol 1989; 1: 397-399.
[46] Kárpáti K, Braunitzer G, Toldi J, Turzó K, Virág K, Reiche WT, Rakonczay Z and Nagy K. Caries and ABO secretor status in a Hungarian population of children and adolescents: an exploratory study. Caries Res 2014; 48: 179-185.
[47] Tabasum ST and Nayak RP. Salivary blood group antigens and microbial flora. Int J Dent Hyg 2011; 9: 117-121.
[48] Bakhtiari S, Toosi P, Dolati F and Bakhshi M. Evaluation of salivary secretor status of blood group antigens in patients with oral lichen planus. Med Princ Pract 2016; 25: 266-269.
[49] Thom SM, Blackwell CC, MacCallum CJ, Weir DM, Brettle RP, Kinane DF and Wray D. Non-secretion of blood group antigens and susceptibility to infection by Candida species. FEMS Microbiol Immunol 1989; 1: 401-405.
[50] McGovern DP, Jones MR, Taylor KD, Marciante K, Yan X, Dubinsky M, Ippoliti A, Vasiliauskas E, Berel D, Derkowski C, Dutridge D, Fleshner P, Shih DQ, Melmed G, Mengesha E, King L, Pressman S, Haritunians T, Guo X, Targan SR and Rotter JI; International IBD Genetics Consortium. Fucosyltransferase 2 (FUT2) non-secretor status is associated with Crohn's disease. Hum Mol Genet 2010; 19: 3468-3476.
[51] Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, Anderson CA, Bis JC, Bumpstead S, Ellinghaus D, Festen EM, Georges M, Green T, Haritunians T, Jostins L, Latiano A, Mathew CG, Montgomery GW, Prescott NJ, Raychaudhuri S, Rotter JI, Schumm P, Sharma Y, Simms LA, Taylor KD, Whiteman D, Wijmenga C, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Cohen A, Colombel JF, Cottone M, Stronati L, Denson T, De Vos M, D'Inca R, Dubinsky M, Edwards C, Florin T, Franchimont D, Gearry R, Glas J, Van Gossum A, Guthery SL, Halfvarson J, Verspaget HW, Hugot JP, Karban A, Laukens D, Lawrance I, Lemann M, Levine A, Libioulle C, Louis E, Mowat C, Newman W, Panés J, Phillips A, Proctor DD, Regueiro M, Russell R, Rutgeerts P, Sanderson J, Sans M, Seibold F, Steinhart AH, Stokkers PC, Torkvist L, Kullak-Ublick G, Wilson D, Walters T, Targan SR, Brant SR, Rioux JD, D'Amato M, Weersma RK, Kugathasan S, Griffiths AM, Mansfield JC, Vermeire S, Duerr RH, Silverberg MS, Satsangi J, Schreiber S, Cho JH, Annese V, Hakonarson H, Daly MJ and Parkes M. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet 2010; 42: 1118-1125.
[52] Tang XL, Wang WJ, Hong GC, Duan CH, Zhu SR, Tian YE, Han CQ, Qian W, Lin R and Hou XH. Gut microbiota-mediated lysophosphatidylcholine generation promotes colitis in intestinal epithelium-specific Fut2 deficiency. J Biomed Sci 2021; 28: 20.
[53] Larsson MM, Rydell GE, Grahn A, Rodriguez-Diaz J, Akerlind B, Hutson AM, Estes MK, Larson G and Svensson L. Antibody prevalence and titer to norovirus (genogroup II) correlate with secretor (FUT2) but not with ABO phenotype or Lewis (FUT3) genotype. J Infect Dis 2006; 194: 1422-1427.
[54] Ahmed T, Lundgren A, Arifuzzaman M, Qadri F, Teneberg S and Svennerholm AM. Children with the Le(a+b-) blood group have increased susceptibility to diarrhea caused by enterotoxigenic Escherichia coli expressing colonization factor I group fimbriae. Infect Immun 2009; 77: 2059-2064.
[55] Azevedo M, Eriksson S, Mendes N, Serpa J, Figueiredo C, Resende LP, Ruvoën-Clouet N, Haas R, Borén T, Le Pendu J and David L. Infection by Helicobacter pylori expressing the BabA adhesin is influenced by the secretor phenotype. J Pathol 2008; 215: 308-316.
[56] Datta-Roy K, Dasgupta C and Ghose AC. Hemagglutination and intestinal adherence properties of clinical and environmental isolates of non-01 Vibrio cholerae. Appl Environ Microbiol 1989; 55: 2403-2406.

[57] Raza MW, Blackwell CC, Molyneaux P, James VS, Ogilvie MM, Inglis JM and Weir DM. Association between secretor status and respiratory viral illness. BMJ 1991; 303: 815-818.
[58] Zhang XF, Huang Q, Long Y, Jiang X, Zhang T, Tan M, Zhang QL, Huang ZY, Li YH, Ding YQ, Hu GF, Tang SX and Dai YC. An outbreak caused by GII.17 norovirus with a wide spectrum of HBGA-associated susceptibility. Sci Rep 2015; 5: 17687.
[59] Morrow AL, Meinzen-Derr J, Huang PW, Schibler KR, Cahill T, Keddache M, Kallapur SG, Newburg DS, Tabangin M, Warner BB and Jiang X. Fucosyltransferase 2 non-secretor and low secretor status predicts severe outcomes in premature infants. J Pediatr 2011; 158: 745-751.
[60] Ye BD, Kim BM, Jung S, Lee HS, Hong M, Kim K, Moon JW, Baek J, Oh EH, Hwang SW, Park SH, Yang SK and Song K. Association of FUT2 and ABO with Crohn's disease in Koreans. J Gastroenterol Hepatol 2020; 35: 104-109.
[61] Cheng SJ, Hu J, Wu XR, Pan JA, Jiao N, Li YC, Huang YB, Lin XT, Zou YF, Chen Y, Zhu LX, Zhi M and Lan P. Altered gut microbiome in FUT2 loss-of-function mutants in support of personalized medicine for inflammatory bowel diseases. J Genet Genomics 2021; 48: 771-780.
[62] Waissbluth JG and Langman MJ. ABO blood groups, secretor status, salivary protein, and serum and salivary immunoglobulin concentrations. Gut 1971; 12: 646-649.
[63] Taylor-Cousar JL, Zariwala MA, Burch LH, Pace RG, Drumm ML, Calloway H, Fan H, Weston BW, Wright FA and Knowles MR; Gene Modifier Study Group. Histo-blood group gene polymorphisms as potential genetic modifiers of infection and cystic fibrosis lung disease severity. PLoS One 2009; 4: e4270.
[64] Galeev A, Suwandi A, Cepic A, Basu M, Baines JF and Grassl GA. The role of the blood group-related glycosyltransferases FUT2 and B4GALNT2 in susceptibility to infectious disease. Int J Med Microbiol 2021; 311: 151487.
[65] Guillon P, Clément M, Sébille V, Rivain JG, Chou CF, Ruvoën-Clouet N and Le Pendu J. Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology 2008; 18: 1085-1093.
[66] Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, Fernández J, Prati D, Baselli G, Asselta R, Grimsrud MM, Milani C, Aziz F, Kässens J, May S, Wendorff M, Wienbrandt L, Uellendahl-Werth F, Zheng T, Yi X, de Pablo R, Chercoles AG, Palom A, Garcia-Fernandez AE, Rodriguez-Frias F, Zanella A, Bandera A, Protti A, Aghemo A, Lleo A, Biondi A, Caballero-Garralda A, Gori A, Tanck A, Carreras Nolla A, Latiano A, Fracanzani AL, Peschuck A, Julià A, Pesenti A, Voza A, Jiménez D, Mateos B, Nafria Jimenez B, Quereda C, Paccapelo C, Gassner C, Angelini C, Cea C, Solier A, Pestaña D, Muñiz-Diaz E, Sandoval E, Paraboschi EM, Navas E, García Sánchez F, Ceriotti F, Martinelli-Boneschi F, Peyvandi F, Blasi F, Téllez L, Blanco-Grau A, Hemmrich-Stanisak G, Grasselli G, Costantino G, Cardamone G, Foti G, Aneli S, Kurihara H, ElAbd H, My I, Galván-Femenia I, Martín J, Erdmann J, Ferrusquía-Acosta J, Garcia-Etxebarria K, Izquierdo-Sanchez L, Bettini LR, Sumoy L, Terranova L, Moreira L, Santoro L, Scudeller L, Mesonero F, Roade L, Rühlemann MC, Schaefer M, Carrabba M, Riveiro-Barciela M, Figuera Basso ME, Valsecchi MG, Hernandez-Tejero M, Acosta-Herrera M, D'Angiò M, Baldini M, Cazzaniga M, Schulzky M, Cecconi M, Wittig M, Ciccarelli M, Rodríguez-Gandía M, Bocciolone M, Miozzo M, Montano N, Braun N, Sacchi N, Martínez N, Özer O, Palmieri O, Faverio P, Preatoni P, Bonfanti P, Omodei P, Tentorio P, Castro P, Rodrigues PM, Blandino Ortiz A, de Cid R, Ferrer R, Gualtierotti R, Nieto R, Goerg S, Badalamenti S, Marsal S, Matullo G, Pelusi S, Juzenas S, Aliberti S, Monzani V, Moreno V, Wesse T, Lenz TL, Pumarola T, Rimoldi V, Bosari S, Albrecht W, Peter W, Romero-Gómez M, D'Amato M, Duga S, Banales JM, Hov JR, Folseraas T, Valenti L, Franke A and Karlsen TH. Genomewide association study of severe Covid-19 with respiratory failure. N Engl J Med 2020; 383: 1522-1534.
[67] Giampaoli O, Conta G, Calvani R and Miccheli A. Can the FUT2 non-secretor phenotype associated with gut microbiota increase the children susceptibility for type 1 diabetes? A mini review. Front Nutr 2020; 7: 606171.
[68] Kohlmeier M. Chapter 4 - How Nutrients are Affected by Genetics. In: Kohlmeier M, editors. Nutrigenetics. San Diego: Academic Press; 2013. pp. 103-221.
[69] Miura T, Sano D, Suenaga A, Yoshimura T, Fuzawa M, Nakagomi T, Nakagomi O and Okabe S. Histo-blood group antigen-like substances of human enteric bacteria as specific adsorbents for human noroviruses. J Virol 2013; 87: 9441-9451.
[70] Tarris G, de Rougemont A, Charkaoui M, Michiels C, Martin L and Belliot G. Enteric viruses and inflammatory bowel disease. Viruses 2021; 13: 104.