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Fucosyltransferase 2: A Genetic Risk Factor for Primary Sclerosing Cholangitis and Crohn's Disease—A Comprehensive Review

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Abstract Fucosyltransferase 2 (FUT2) mediates the inclusion of fucose in sugar moieties of glycoproteins and glycolipids. ABO blood group antigens and host-microbe interactions are influenced by FUT2 activity. About 20 % of the population has a "non-secretor" status caused by inactivating variants of *FUT2* on both alleles. The non-sense mutation G428A and the missense mutation A385T are responsible for the vast majority of the non-secretor status in Caucasians, Africans, and Asians, respectively. Non-secretor individuals do not secrete fucose-positive antigens and lack fucosylation in epithelia. They also appear to be protected against a number of infectious diseases, such as Norovirus and Rotavirus infections. In recent years, genome-wide association studies (GWAS) identified inactivating variants at the *FUT2* locus to be associated with primary sclerosing cholangitis (PSC), Crohn's disease (CD), and biochemical markers of biliary damage. These associations are intriguing given the important roles of fucosylated glycans in host-microbe interactions and membrane stability. Non-secretors have a reduced fecal content of *Bifidobacteria*. The intestinal bacterial composition of CD patients resembles the one of non-secretors, with an increase in *Firmicutes* and decreases in *Proteobacteria* and *Actinobacteria*. Non-secretor individuals lack fucosylated glycans at the surface of biliary epithelium and display a different bacterial composition of bile compared to secretors. Notably, an intact biliary epithelial glycocalix is relevant for a stable 'biliary HCO_3^- umbrella' to protect against toxic effects of hydrophobic bile salt monomers. Here, the biology of FUT2 will be discussed as well as hypotheses to explain the role of FUT2 in the pathophysiology of PSC and Crohn's disease.

Keywords Fucosyltransferase 2 · FUT2 · PSC · Crohn's disease · Genetic risk factor

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Introduction

Fucosyltransferases are a group of enzymes that catalyse the transfer of the sugar fucose to acceptor substrates present on oligosaccharides, glycoproteins and glycolipids [1]. The expression of fucosyltransferases is found in a variety of eukaryotic and prokaryotic cells [1, 2], and fucosylated glycans have been shown to participate in numerous biological and pathological processes, including signal transduction, host-microbe interactions, tissue development, cancer progression and metastasis [2, 3]. In humans, the *FUT2* locus encodes a specific fucosyltransferase enzyme, which has been extensively studied for its role in the synthesis of ABO blood group antigens [4, 5]. In recent years, new interest in the biology of FUT2 has been raised by genome-wide association studies (GWAS), which consistently identified inactivating polymorphisms of the gene to be associated with the development of primary sclerosing cholangitis (PSC) and Crohn's disease (CD) among other pathophysiological conditions. These studies have thus unveiled a novel risk locus and prompted new hypotheses aiming to connect the genetic discoveries to their biological relevance, hence fostering novel research lines. With this

current review, we aim to present a concise overview on FUT2 biology and on the emerging putative roles of *FUT2* polymorphisms in the pathophysiology of PSC and CD. As an outlook, additional associations between FUT2 dysfunction and other human diseases will be briefly discussed.

Fucose Biosynthesis and Fucosyltransferases

Fucose, also know as 6-deoxy-L-galactose, is a deoxy hexose monosaccharide, with the chemical formula $C_6H_{12}O_5$, and is found as a common component of many N- and O-linked glycans. It has two peculiar characteristics compared to other six-carbon monosaccharides normally present in mammals, namely the L-configuration and the absence of a hydroxyl group on the carbon at position 6 of the molecule [3].

Fucose can be incorporated in glycan chains by specific members of the glycosyltransferase superfamily, the fucosyltransferases. These enzymes are expressed in a variety of different organisms, including vertebrates, invertebrates, plants and bacteria, and transfer fucose using its activated monomeric form, the guanosine diphosphate (GDP)-fucose, as substrate. Two distinct pathways for the formation of GDP-fucose have been described, the so-called de novo and salvage pathways [6, 7]. In the de novo pathway, GDP-fucose is formed from GDP-mannose through the concerted action of two enzymes, the GDP-mannose 4,6-dehydratase and the FX protein, an enzyme with epimerase-reductase activity [6, 8]. In the salvage pathway, GDP-fucose is directly synthesized from the fucose derived either from the extracellular compartment [9] or released from the metabolism of fucosylated glycans in the lysosomes [10]. The salvage pathway accounts for a minor fraction (around 10 %) of GDP-fucose biosynthesis [11]. Independently of the specific biosynthetic pathway followed, GDP-fucose eventually reaches the Golgi apparatus where fucosyltransferases catalyse the transfer of GDP-fucose to acceptor sugar substrates present on glycoproteins and glycolipids [1]. Schematically, fucosyltransferases are divided in α-1,2-, α-1,3/4-, α-1,6-, and O-fucosyltransferases according to the specific site of fucose addition on substrates. The α-1,3/4-, α-1,6-, and O-fucosylation linkages are mediated by a variety of different enzymes recently reviewed by Ma et al. [2].

FUT1 and FUT2 Mediate α-1,2-Fucosylation

Only two gene products account for the α-1,2-fucosylation of the terminal galactose of glycan chains in humans: the enzymes encoded by *FUT1* and *FUT2* [12, 13]. The acceptor specificity of FUT1 and FUT2 is slightly different. FUT1 prefers type II (Galβ1,4GlcNAc) chains, and FUT2 is more active on type III (Galβ1,3GalNAc) chains. Type I (Galβ1,3GlcNAc) chains are, however, used with equal efficiency by both enzymes [14, 15]. FUT1 and FUT2 play a pivotal role in the formation of ABO blood group antigens. The ABO system consists of complex carbohydrate molecules that are present not only on the surface of erythrocytes but also on the membranes of epithelial cells and in their mucoid secretions [16]. Red blood cell precursors express FUT1, which is also known as H transferase and is responsible for the formation of the H antigen by the addition of fucose to the terminal galactose of acceptor substrates [17]. The basic H antigen remains unchanged on the cell surface of individuals of blood group O, while it is subsequently modified by different glycosyltransferases via the addition of *N*-acetylgalactosamine and/or D-galactose in individuals of blood group A and/or B, respectively [18]. Epithelial tissues predominantly express FUT2, also known as secretor (Se) transferase. This enzyme mediates the formation of the basic H antigen in epithelial cells. The epithelial H antigen may also be further modified according to the ABO blood group status [4, 5].

"Non-secretors" and Natural Selection

Notably, it has been long known that the capacity to secrete A, B, or H antigens in body fluids is absent in about 20 % of the population [16]. These individuals, who have been named "non-secretors," are homozygous for non-functional *FUT2* alleles, and ABO antigens are undetectable in their epithelial tissues and body secretions. Normal levels of these antigens are present on the membranes of erythrocytes, in line with the tissue distribution of FUT1 and FUT2 [13]. The molecular defects responsible for the non-secretor status have been extensively studied after the cloning of the *FUT2* gene [4]. *FUT2* is encoded on chromosome 19 and consists of two exons (of which the first one is a non-coding exon). Two single nucleotide polymorphisms (SNPs) occurring at the second exon are responsible for the majority of the non-secretor status. The non-sense mutation G428A, giving rise to a premature stop codon at position 143 (p.W143X), is predominant in Caucasians (Europeans and Iranians) and Africans [13, 19, 20]. In Asian populations, the most common non-secretor variant is the missense mutation A385T, causing the substitution of isoleucine by phenylalanine at position 129 (p.I120P), resulting in a deficient FUT2 activity [21–23]. In the past two decades, many other *FUT2* gene variants such as SNPs, deletions of the coding region, and a fusion gene, have been described (reviewed by Koda et al. [24]). Apart from the various specific SNPs occurring in the *FUT2* gene and giving rise to a dysfunctional protein, it is interesting to note that *FUT2*-inactivating variants are actively maintained in the genome by natural selection processes [25–27]. Beneficial effects of the non-secretor status are a possible explanation for this phenomenon [24]. Indeed, as discussed later, the inactivation of *FUT2* has been shown to protect against a

number of infectious diseases and to result in higher vitamin B12 levels in plasma [28, 29].

FUT2 and Crohn's Disease

The pathogenesis of idiopathic inflammatory bowel disease (IBD), clinically presenting as Crohn's disease (CD) or ulcerative colitis (UC), remains largely elusive to date [30, 31]. In the past two decades, however, genome-wide association studies (GWAS) have provided an important insight in the genetic factors underlying IBD development [32]. Several SNPs are associated with significantly different risks for IBD, implying contributions of a total of 163 loci to disease etiology [33].

A number of SNPs suggestive for a *FUT2* involvement in the genetic susceptibility to IBD have been recently identified (Table 1). A previous meta-analysis of 10 genome scans of IBD patients recognized a suggestive peak of linkage for CD on chromosome 19, where the *FUT2* gene is encoded [34]. McGovern et al. subsequently performed a GWAS in 896 CD cases and 3,204 healthy controls of Caucasian origin and pinpointed a clear association with a total of four SNPs in the *FUT2* locus. Of the SNPs discovered, two are in the 3' untranslated region (UTR) of the gene (rs504963 and rs676388), one represents a synonymous polymorphism (rs485186), and one (rs602662) is a missense SNP (G739) that results in the substitution of glycine with serine (p.G247S) and gives rise to an inactive FUT2 enzyme [35, 36]. Moreover, in an independent replication cohort of 1,174 CD patients and 357 controls, the authors could confirm the association between CD and the previous four SNPs and identified two additional risk SNPs in the *FUT2* gene (rs601338 and rs492602) [35]. Notably, the SNP rs601338 is responsible for the non-sense G428A substitution that accounts for the non-secretor status in the majority of Caucasians as previously discussed [13, 19, 20]. These results are supported by a genome-wide meta-analysis that identified the association between CD and the SNP rs281379 at 19q13 [37]. All the SNPs in the *FUT2* gene discovered in the previous studies are strongly associated with the presence of the more common rs601338, thus suggesting a possible functional role of the non-secretor status in the context of CD [37]. It is important to note, however, that the FUT2 secretor status has also been associated specifically with the colonic localization of CD in a small Japanese cohort [38]. The discrepancy between this study and the GWAS previously discussed, conducted predominantly in Caucasian individuals, might be due to specific ethnic differences in the genetic susceptibility to CD, in a similar fashion to what is reported for NOD2 [39]. Moreover, the low frequency of the colonic localization of the disease might have overshadowed the importance of the secretor status in randomly recruited cohorts of CD patients, such as those used in the GWAS [38].

Table 1 Single nucleotide polymorphisms (SNPs) associated with Crohn's disease. All the SNPs are in strong linkage disequilibrium with the rs601338, the major responsible for the non-secretor status in Caucasians

SNP	SNP effect	Reference
rs601338	G428A, non-sense	[35]
rs492602	Synonymous	[35]
rs602662	G739A, missense	[35]
rs485186	Synonymous	[35]
rs504963	3′ UTR	[35]
rs676388	3′ UTR	[35]
rs281379		[37]

An improper immune response against commensal gut bacteria has been proposed as a possible pathogenetic mechanism of CD [30, 40]. The identification of *FUT2* as a risk gene appears particularly interesting considering the well-known importance of fucosylated glycans in host-microbe interactions. For example, the adhesion of *Helicobacter pylori* to the gastric epithelium has been shown to depend on the expression by the host of the Lewis^b antigen, a structure synthesized by the action of FUT2 and FUT3 [41, 42]. Similarly, fucosylated structures are important in the adhesion of *Escherichia coli* F18 to the epithelium of the small intestine [43]. Conversely, the expression of FUT2 is modulated by the intestinal microbiota, indicating a bidirectional relationship. The expression of Fut2 mRNA in the small intestine of mice is driven by the presence of a normal gut flora, while it is absent before weaning and in germ-free mice. Fut2 expression is rescued by the colonization of either an adult fecal microbiota or of a single component of it, namely *Bacteroides thetaiotaomicron* [44, 45], an organism that can use fucose as a carbon source for its metabolism. In microbiota-deficient mice, the restoration of Fut2 expression in the intestine can be achieved also by colonization by *Bacteroides fragilis*. In these mice, the re-colonization with *B. fragilis* ensures better recovery rates after DSS-induced mucosal injury compared to mice re-colonized with a mutant *B. fragilis* unable to induce Fut2 expression [46].

Given these observations, it comes as no surprise that the intestinal bacterial community in non-secretor individuals (homozygous for G428A) is different from the one of secretors [47]. Diversity and abundance of *Bifidobacteria* are significantly reduced in fecal samples from non-secretor individuals. Moreover, the secretor status determined by *FUT2* genotype has been recently shown to influence the intestinal bacterial composition, diversity, and structure of CD patients [48, 49]. Rausch et al. demonstrated an increase in *Firmicutes* and a corresponding decrease in *Proteobacteria* and *Actinobacteria* in CD patients compared to controls. Notably,

these differences could only be identified among secretor control individuals, indicating that the bacterial composition of non-secretors resembles more closely the one of the CD patients [48]. In addition, by analyzing the inter-individual differences (beta diversity) of the bacterial communities, the authors could assess that both disease status and disease-by-genotype interactions contribute to the variation of the bacterial community composition between individuals [48]. Taken together, the importance of fucosylated glycans in shaping the bacterial community of the gut appears to sustain the genetic association between FUT2 dysfunction and CD.

FUT2 and Ulcerative Colitis

The contribution of FUT2 to the pathogenesis of UC remains, to date, less clear. While McGovern et al. reported no association between *FUT2* and UC [35], one study identified a total of three different inactivating SNPs in the *FUT2* gene (rs281377, rs1047781, and rs601338) to be associated with UC in a small sample population of the Han and Uyghur ethnical groups in China [50]. Conversely, an additional report based on a Finnish population showed that the homozygous G428A SNP, responsible for the non-secretor status, did not correlate with UC. On the other hand, the secretor status was associated with an increased risk of UC, suggesting a protective role for the mutated allele [51]. Although both diseases cause a chronic inflammation of the intestine, UC and CD display profound differences in tissue damage and progression [52]. A dissimilar genetic susceptibility might underline a separate etiopathogenesis of the two diseases. Moreover, the contribution of *FUT2* inactivation might differ between UC and CD and have complex interactions with the additional genetic and environmental factors that contribute to disease development.

FUT2 and Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease frequently associated with IBD. Chronic inflammation of the biliary tree in PSC leads to the development of strictures and biliary cirrhosis over time, with patients often suffering from recurrent cholangitis and ultimately needing liver transplantation [53]. The pathogenesis of PSC is still debated, but it is likely to be multifactorial. The importance of a genetic predisposition is underlined by the fact that first-degree relatives of PSC patients have an about 100-fold increased risk of developing PSC compared to the general population [54]. The most important genetic risk factors for PSC have been located in the major histocompatibility complex (MHC), suggesting the involvement of the immune system in disease development [55]. In genetically susceptible individuals, environmental factors could trigger an aberrant or inadequate immune response eventually leading to liver damage and fibrosis [56]. Given the strong association between PSC and inflammatory bowel disease (IBD), some groups have started to investigate the role of intestinal microbiota and/or of increased intestinal permeability as pathogenetic determinants of PSC development and progression in the context of an inflamed leaky gut [57]. PSC patients do not appear to have bacterial overgrowth or increased intestinal permeability measured by differential urinary excretion of lactulose/L-rhamnose [58]. It is interesting to note, however, that enteric bacteria have been detected in the bile of PSC patients [59, 60]. Also, microbial products known as pathogen-associated molecular patterns (PAMPs) are present in portal blood and in bile. PAMPS are capable to establish complex interactions with cholangiocytes and immune cells and have been implied in the pathogenesis of PSC [57, 61, 62]. In this complex scenario, a recent GWAS identified, among others, three different SNPs in the *FUT2* gene as novel risk loci for PSC, analyzing a population composed of 715 PSC cases and 2,962 healthy controls [63]. Of the three SNPs in the *FUT2* gene discovered, rs281377 is a synonymous polymorphism; rs602662 is a missense SNP (G739A) giving rise to an inactive FUT2 enzyme [36]; and rs601338 introduces the non-sense "non-secretor" point mutation G428A [13, 19, 20]. All three SNPs described are in strong linkage disequilibrium with each other. In staining liver biopsies with the α-1,2-fucose-specific lectin *Ulex europaeus* agglutinin-I (UEA-I), it was demonstrated that α-1,2-fucosylated glycans are present on the apical membrane of the cholangiocytes of individuals carrying the GG variant of the rs601338 SNP (being secretors), while they are absent in the apical side of the bile ducts of patients with the AA variant (carrying a homozygous G428A mutation and being non-secretors) [63]. Moreover, the bacterial composition of bile appears to be profoundly influenced by the secretor status of the individual. Given the effect of *FUT2* polymorphisms on the bacterial community structure in the context of Crohn's disease [48], Folseraas et al. analyzed bile samples from a total of 39 PSC patients, of which 8 were homozygous for the functional GG variant, 10 were homozygous for the dysfunctional AA variant, and 21 were heterozygous. The authors found that *Firmicutes* are significantly more abundant in non-secretor bile, while *Proteobacteria* are decreased, in a similar fashion of what is described for the colon [63]. In addition, heterozygous individuals display significantly lower diversity in the bacterial species composition (alpha diversity) and also lower inter-individual variability (beta diversity), as compared to both GG and AA homozygous genotypes [63].

In the context of liver injury, it is worth mentioning that *FUT2* polymorphisms have been linked with the plasma levels of alkaline phosphatase (ALP) and γ-glutamyl transferase (GGT) [64], common markers of biliary damage [65].

Taken together, the expression of fucosylated glycans along the biliary tree, according to the secretor status of the patients, might determine the adhesion of specific bacterial species to the biliary epithelium and consequently influence the development and/or severity of recurrent cholangitis, a well-known complication in the natural history of PSC [66]. In addition, the lack of fucosylated glycans in the mucus layer of non-secretor individuals may alter the permeability of the intestinal epithelium and favor an enhanced translocation of PAMPs reaching the liver through the portal circulation.

In the pathogenesis of PSC and other cholangiopathies, an important role has been attributed to the intrinsic toxicity of bile acids towards biliary epithelial cells [56]. Our group has recently proposed the "biliary HCO_3^- umbrella hypothesis" indicating that cholangiocytes protect their integrity against hydrophobic bile acids by secreting high amounts of HCO_3^- close to the apical membrane; the biliary HCO_3^- umbrella would then lead to the deprotonation of toxic hydrophobic bile acids to bile salts, rendering them unable to diffuse across cellular membranes and cause apoptosis [67] or cholangiocyte senescence. Functional impairment of the biliary HCO_3^- umbrella, or of its regulation, may therefore predispose to cholangiocyte damage and contribute to the development of chronic cholangiopathies [68]. Polymorphisms in the *FUT2* gene might affect the stability of the biliary HCO_3^- umbrella (Fig. 1). We have recently shown that cholangiocytes express a 20–30 nm thick glycocalyx layer on the outer leaf of the apical membrane [68]. Notably, the modification of the glycocalyx by the removal of sialic acid residues (derivatives of neuraminic acid, a monosaccharide commonly found in the glycocalyx [69, 70]) has profound effects on pH-dependent cholangiocyte toxicity induced by chenodeoxycholic and glycochenodeoxycholic acid in vitro [68]. These results support the idea that the specific composition of the glycocalyx in terms of sugar residues may stabilize the pH nanoenvironment close to the apical membrane as earlier described for melanoma cells [71, 72] and might thus contribute to the stabilization of the biliary HCO_3^- umbrella. In this context, it is attractive to speculate that non-secretor individuals, lacking α-1,2-fucosylated glycans on the apical glycocalyx of cholangiocytes [63], may have an impaired capacity to effectively maintain an alkaline pH microclimate close to the apical surface of cholangiocytes and may, therefore, be more susceptible to the toxic effect of bile acids. Of note, preliminary experiments of our group indicate that *Fut2*$^{-/-}$ mice might have an increased susceptibility to hepatobiliary damage (Maroni et al., manuscript in preparation). Further studies aiming to dissect in detail the role of FUT2 in the biology of the biliary epithelium and its possible role in the pathophysiology of PSC are warranted.

FUT2 Involvement in Other Human Diseases and Conditions

The status (non-secretor versus secretor) of the *FUT2* gene has been associated with a variety of pathophysiological processes other than IBD and PSC (Table 2). In particular, bacterial adhesion and plasma levels of vitamin B12 appear to be strongly influenced by the secretor status of the individual. An altered bacterial adhesion and consequently a different susceptibility to infections are possible reasons why the non secretor-status is actively maintained in about 20 % of the population [16, 24]. For example, different studies have identified that non-secretor individuals are effectively protected

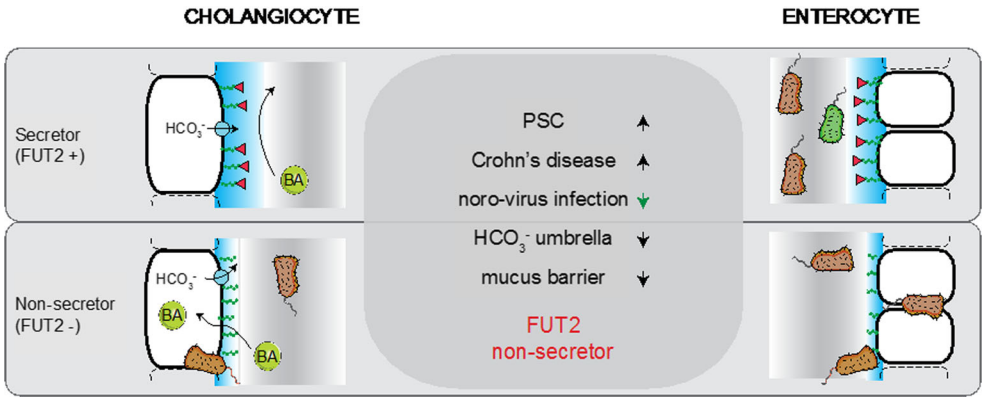

Fig. 1 FUT2 in cholangiocytes and enterocytes (schematic overview). FUT2-positive individuals (FUT2+; secretors; *top part* of the figure) have fucose moieties at the cell surface of cholangiocytes (*left*) and enterocytes (*right*), whereas non-secretor (FUT2-) individuals lack this fucosylation. This results in differences in the mucus layer in epithelia and possibly alteration in barrier function and pathogen adhesion. In the liver, the constitution and thickness of the mucus layer will affect the diffusion rate of HCO_3^-, secreted by cholangiocytes, and thus the local pH. Increased pH in close proximity of the cell surface (biliary HCO_3^- umbrella) results in more deprotonated, charged bile salts which do not enter the cell in a carrier-independent fashion. FUT2-negative individuals might have an altered (thinner) mucus layer, rendering the cholangiocytes more susceptible to bile acid-induced cell damage

Table 2 Effects of the FUT2 "non-secretor" status on different pathophysiological conditions

Condition	Effect	Reference(s)
Helicobacter pylori infection	Lower susceptibility	[73–75]
Symptomatic Norovirus infection	Resistance/protection	[28, 78, 79]
Rotavirus A infection	Resistance	[85]
Urinary tract infections	Increased (in B and AB blood group women)	[86]
Acute uncomplicated pyelonephritis	Increased (in women)	[88]
Oral or vaginal Candida infections	Increased	[89–91]
H. influenzae infection	Increased susceptibility	[92]
N. meningitidis and *S. pneumoniae* infections	Increased susceptibility	[93]
Axillary lymph node metastasis	Increased risk (in breast cancer patients)	[109]

against the susceptibility to *H. pylori* (HP) infection and the severity of the gastric lesions caused by it [73–75]. Indeed, the presence of fucosylated glycans in the gastric epithelium promotes the attachment of HP to the gastric mucosa [41, 42]. Its adhesion is mediated by the bacterial expression of the BabA adhesin, which recognizes Le^b and H type 1 structures expressed on gastric mucins [76]. Notably, it has long been known that the non-secretor status plays a role in the risk of bleeding and perforation of duodenal ulcer [77]. Inactivation of the *FUT2* gene has been also shown to confer protection against nosocomial and sporadic outbreaks of Norovirus infection [28, 78, 79], one of the major causes of acute gastroenteritis worldwide [80]. In a similar fashion to what is described for HP, Norovirus is thought to bind to H type 1 antigens expressed along the gastrointestinal tract [81]. Consistently, FUT2 non-secretor individuals have a lower prevalence and titer of immunoglobulin G antibody to Norovirus [82]. Of note, despite the lack of evidence for a specific pattern of antibodies in CD patients [83], some authors have hypothesized that asymptomatic Norovirus infections in non-secretors may alter the homeostasis of the gut microbiota, and therefore contribute to CD development [84]. Recently, non-secretor individuals have been also described to be resistant to Rotavirus of the P8 genotype [85]. Along the same line, the susceptibility to different other infectious diseases, such as recurrent urinary tract infection in women [86, 87], acute pyelonephritis [88], development of oral and vaginal candidiasis [89–91], and infections with *Haemophilus influenzae* [92], *Neisseria meningitidis*, and *Streptococcus pneumoniae* [93], have been linked to the secretor status of affected individuals, confirming a pivotal role of FUT2 in host-microbe interactions.

The association between *FUT2* polymorphisms and serum levels of vitamin B12 has been identified in three different GWAS and one meta-analysis [29, 94–96]. In particular, the levels of vitamin B12 appear to be higher in individuals carrying the non-functional SNPs (or other polymorphisms in strong linkage disequilibrium with the latter). Some authors have hypothesized that atrophic gastritis developing after HP infection, towards which non-secretor individuals are protected, could be a possible functional explanation for the genetic association [29]. Atrophic gastritis might indeed lead to a decrease of the intrinsic factor, a glycoprotein secreted by gastric cells and required for vitamin B12 absorption [97]. Recently, however, Oussalah et al. demonstrated that the HP serological status has no influence on the association between *FUT2* SNPs and vitamin B12 levels [98], and subsequent work confirmed that *FUT2* secretor variants lower the vitamin B12 levels through an impaired intrinsic factor secretion, independently of HP-induced gastritis [99].

Table 3 Pathophysiological conditions associated with polymorphisms in the *FUT2* gene

Condition	Effect	SNPs identified	Reference(s)
Levels of ALP and GGT	Influence on plasma concentrations	rs281377, rs516246	[64]
Vitamin B12 levels	Higher levels in plasma	rs492602, rs602662	[29]
		rs602662	[94]
		rs1047781	[95]
		rs602662, rs601338	[96]
Psoriasis	Increased risk	rs1047781, c.271C>T, c.516C>G	[100]
		rs281379	[101]
Behcet's disease	Increased risk	rs632111, rs601338	[102]

GWAS and meta-analyses of GWAS have identified important associations between *FUT2* polymorphisms and a number of other pathophysiological conditions (Table 3). Indeed, *FUT2* variants have been recently recognized to predispose to psoriasis [100, 101] and also to Behcet's disease development [102]. Plasma concentrations of total homocysteine are also influenced by *FUT2* [103]. Conversely, no link with the occurrence of venous thrombosis could be demonstrated [104], despite a previous study that identified *FUT2* to be associated with the levels of fibrinogen A-α [105].

Finally, fucosylated glycans have been shown to contribute to cancer progression and metastasis. Indeed, α-1,2-fucosyltransferase activity appears to be higher in colonic carcinoma tissues than in normal epithelium [106, 107] and to be correlated with the progression of colonic adenocarcinoma [108]. The secretor status has been shown to predict the risk of axillary lymph node metastasis in the context of breast cancer [109]. Given the altered glycosylation pattern of cancerous tissues, fucosylated glycans have also attracted interest as possible tumor markers [110]. In this context, serum levels of cancer antigen 19–9 (CA19-9) clearly correlate with the secretor status of the individuals, both in colorectal cancer patients [111] and in PSC patients diagnosed with cholangiocarcinoma [112]. Moreover, a recent GWAS identified the locus of *FUT2* to be associated with plasma concentrations of both CA19-9 and carcinoembryonic antigen (CEA) [113].

Conclusions

Growing evidence supports an involvement of FUT2 in the pathogenesis of a number of human diseases and conditions. Various inactivating polymorphisms in the *FUT2* gene, responsible for the non-secretor status occurring in about 20 % of the population, have been described in literature. Inactivating variants of the *FUT2* gene are maintained in the human genome, possibly due to beneficial effects under evolutionary pressure of infectious diseases. However, inactivating SNPs at the *FUT2* locus have also been identified as possible risk factors in a variety of human diseases, in particular CD and PSC in recent GWAS. As for many other loci identified by GWAS, the biological relevance of the genetic associations in the pathophysiological processes still remains to be completely unraveled. Nonetheless, the involvement of fucosylated glycans in host-microbe interaction and the finding that the secretor status of individuals play a crucial role in shaping the intestinal microbiota in health and disease appear particularly interesting in the study of diseases such as CD and PSC, in which a complex dysregulation of the immune system is thought to contribute to disease development. Future studies aiming to selectively investigate the role of FUT2, in the context of the genetic associations uncovered by the GWAS, will undoubtedly deepen the knowledge on the biology of different diseases and, possibly, open doors to new therapeutic strategies.

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