Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

FUT8 (fucosyltransferase 8 (alpha (1,6) fucosyltransferase))

Hideyuki Ihara, Cong-xiao Gao, Yoshitaka Ikeda, Naoyuki Taniguchi

Division of Molecular Cell Biology, Department of Biomolecular Sciences, Saga University Faculty of Medicine, Saga, Japan (HI, YI); Department of Disease Glycomics, Institute of Scientific and Industrial Research, Osaka University, Osaka, Japan (CXG, NT); Disease Glycomics Team, Systems Glycobiology Research Group, Chemical Biology Department, Japan (NT)

Published in Atlas Database: August 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/FUT8ID40649ch14q23.html
DOI: 10.4267/2042/45014

Identity

Other names: MGC26465

HGNC (Hugo): FUT8

Location: 14q23.3

DNA/RNA

Description

Human FUT8 gene is located on chromosome 14q23.3 (Yamaguchi et al., 1999). This gene encompasses approximately 333 kb and contains nine exons with coding regions and three 5'-untranslated exons (Yamaguchi et al., 2000; Martinez-Duncker et al., 2004).

Transcription

Some splicing variants of the 5'-untranslated region arise in a developmental stage-specific and tissue-specific manner (Martinez-Duncker et al., 2004). At least three different promoters appear to be functional in regulating the expression of the FUT8 gene. Three transcripts with different 5'-untranslated regions have been identified. With respect to coding region, four variants were reported to encode polypeptides containing 575, 446, 308 and 169 amino acid residues. The 575 residue protein is a fully active alpha1,6-fucosyltransferase, which was first of the variants to be identified.

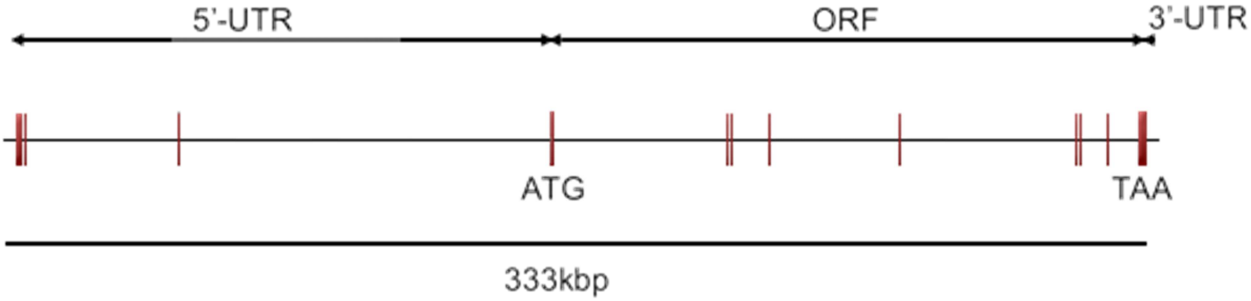

Figure 1. Genomic organization of human FUT8 gene. Exons are represented by vertical bars. Exons denoted by ATG or TAA contain start and stop codons, respectively. These exons also have a part of the noncoding region.

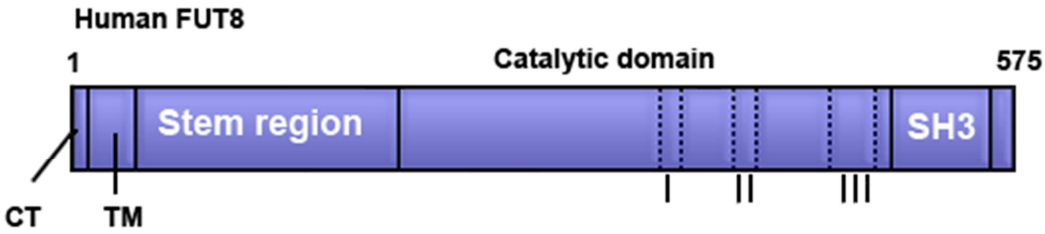

Figure 2. Protein structure of FUT8. CT and TM denote the cytoplasmic tail and the transmembrane domain, respectively. I, II and III represent the conserved motifs in alpha1,2-, alpha1,6- and protein O-fucosyltransferases.

The other variants have not yet been examined for enzymatic activity and biological function. The 308 amino acid variant is known to be expressed in the retina (Yamaguchi et al., 2000).

Protein

Description

FUT8 was purified and cloned as a cDNA from porcine brain and a human gastric cancer cell line (Uozumi et al., 1996, Yanagidani et al., 1997). Human FUT8 is comprised of 575 amino acids, with a calculated molecular weight of 66516. FUT8 contains no N-glycosylation sites. This enzyme belongs to the GT23 family of the CaZY classification. The structual analysis of a transmembrane domain-truncated form of FUT8 showed that the enzyme consists of a catalytic domain, an N-terminal coiled-coil domain and a C-terminal SH3 domain (Ihara et al., 2007). The catalytic domain was structurally classfied as a member of the GT-B group of glycosylatransferases.

Expression

FUT8 gene is widely expressed in human tissues (Martinez-Duncker et al., 2004). The FUT8 gene is expressed at relatively high levels in the brain, placenta, lung, stomach, small intestine and jejunum, while pancreas, uterus, kidney and urinary bladder exhibit moderate expression. The FUT8 gene is weakly expressed in the heart, ileum, colon and spleen. On the other hand, the expression is not detectable in the normal liver (Miyoshi et al., 1997).

Localisation

FUT8 is a typical type II membrane protein and is localized in the Golgi apparatus.

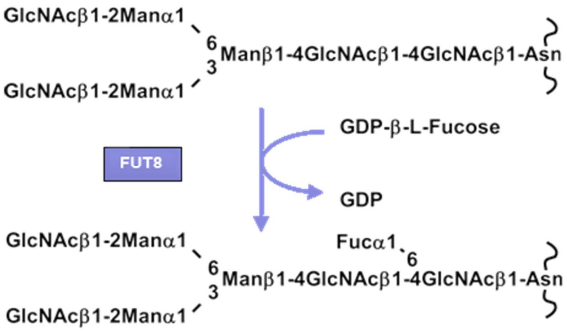

Figure 3. The reaction catalysed by FUT8.

Function

FUT8 catalyzes the transfer of a fucose residue from GDP-fucose to the reducing terminal GlcNAc of Asn-linked oligosaccharide (N-glycan) via an alpha1.6-linkage (Figure 3). The resulting fucosyl residue is often refered to as a core fucose. The reaction does not require any divalent cations or cofactors. The deletion of the FUT8 gene in mice leads to severe phenotypes that exhibit growth retardation, lung emphysema and death during postnatal development (Wang et al., 2005). As has been clearly shown in studies using knockout mice, the lack of core fucosylation resulted in the biological activities of various proteins to be perturbed (Taniguchi et al., 2006; Takahashi et al., 2009). Examples of this include the TGF-beta1 receptor (Wang et al., 2005), EGF receptor (Wang et al., 2006), VEGF receptor-2 (Wang et al., 2009), LRP-1 (Lee et al., 2006), E-cadherin (Osumi et al., 2009), alpha3beta1 integrin (Zhao et al., 2006), VCAM and alpha4beta1 integrin (Li et al., 2008). The binding affinity of the core fucose-deleted TGF-beta receptor to TGF-beta 1 is diminished in fut8-null mice, resulting in the downregulation of TGF-beta 1 signaling (Wang et al., 2005). The unusual overexpression of matrix metalloproteinases such as MMP-12 and MMP-13 is associated with the impaired receptor function, and has been proposed to cause the lung-destructive phenotypes. The EGF receptor in fut8 null mice is also affected in terms of its binding affinity to EGF and EGF-induced phoshorylation (Wang et al., 2006). These studies strongly suggest that FUT8 and core fucose structures regulate the receptor function.
In addition, core fucosylation was reported to be involved in antibodydependent cellular cytotoxicity (ADCC) (Shields et al., 2002; Shinkawa et al., 2003). The lack of core fucose of N-glycan in the Fc region of the IgG1 molecule enhances ADCC activity up to 50-100-fold. This discorvery promises to be useful in the development of antibody therapy in cancer treatment.

Homology

The sequence identities between human FUT8 and other organisms are as follows :
Chimpangee (100%), Dog (97.7%), Cow (97.5%), Pig (95.6%), Rat (96.6%), Mouse (96.5%), Chicken (93.9%), Clawed frog (90.3%), Zebrafish (79.5%), Takifugu (80.2%), Tetraodon (79.8%), Sea squirt (23.2%), Fruit fly (43.7%), C. elegans (34.8%).

Eight cysteine residues in the catalytic domain are conserved among these species, except for ciona (Ihara et al., 2007).
FUT8 contains three short regions that are highly conserved in FUT8, alpha1,2-, bacterial alpha1,6-, and protein O-fucosyltransferases (Oriol et al., 1999; Takahashi et al., 2000a; Chazalet et al., 2001; Martinez-Duncker et al., 2003). The structual analysis has shown that these regions are located adjacent to one another in the Rossmann fold of FUT8 (Ihara et al., 2007). In addition, the C-terminal SH3 domain of FUT8 is structually similar to the typical SH3 domain that is found in many proteins.

Mutations

Note
One frame-shit mutation and 4 substitution mutants have been identified to date in various SNPs of the FUT8 gene. The frame shift mutant is due to the insertion of a T at position 2 of the codon for Val-85, resulting in 85-VLEEQLVK-92 being change to 85-VFRRAACter-92. The four substitution mutants are K101Q, L153V, E181G and T267K. These mutants are due to A being substituted by C at position 1 of codon 101, C to G at position 1 of codon 153, A to G at position 2 of codon 181, and C to A at posision 2 of codon 267, respectively. Effects of these substitutions on enzymatic activity are not currently known.

Implicated in

Hepatocellular carcinoma (HCC)

Note
It is well known that the core fucosylation of alpha-fetoprotein (AFP) is implicated in the development of HCC. AFP is a major fetal plasma protein, and its expression is elevated in hepatic diseases such as HCC, hepatitis and liver cirrhosis (Alpert et al., 1968; Ruoslahti et al., 1974). The AFP-L3 fraction was identified as the core-fucosylated isoform of AFP. The elevation in serum and liver tissue was found to be specific to HCC, but was not observed in other liver diseases (Taketa, 1990; Aoyagi, 1995; Miyoshi et al., 1999).
Thus, it appears that AFP-L3 could be used as a marker for HCC. The FUT8 gene is not expressed in the normal adult liver, but is highly expressed in HCC tissue. Surprisingly, however, such an elevation was also observed in liver cirrhosis in spite of the absence of a concomitant increase in AFP-L3 levels (Noda et al., 1998). This discrepancy can be attributed to the difference in the synthesis of GDP-fucose, a glycosyl donor substrate for fucosyltransferases, including FUT8, and by the altered intracellular sorting of fucosylated glycoproteins in hepatic cells. Because the intracellular concentration of GDP-fucose is higher in HCC, as compared to a normal liver, chronic hepatitis and liver cirrhosis, this increase would be expected to facilitate core fucosyltion of AFP (Noda et al., 2003). Core fucosylation appears to serve as a sorting signal for a glycoprotein to be directed to the bile, as revealed by the predominant distribution of fucosylated glycoproteins in bile rather than serum (Nakagawa et al., 2006). In fact, the levels of alpha-antitrypsin and alpha1-acid glycoprotein, both of which are fucosylated glycoproteins, are quite low in the bile of Fut8-null mice. The loss of polarity in cancer cells is likely to impair the regulated sorting, thus allowing abnormal secretion into the serum.

Prognosis
AFP-L3-positive HCC patients were reported to show a poor prognosis (Yamashita et al., 1996).

Ovarian cancer

Note
FUT8 activity and mRNA levels are highly and specifically elavated in cases of ovarian serous adenocarcinoma, as compared to nomal ovary and other types of epithelial ovarian carcinoma (Takahashi et al., 2000b). In addition, core fucosylation levels in glycoproteins is also significantlly increased in cases of serous adenocarcinoma tissues.

Thyroid cancer

Note
The overexpression of FUT8 occurs in 33.3% of cases of papillary carcinoma of the thyroid (Ito et al., 2003), although FUT8 was not expressed in normal follicular cells. This overexpression was also shown to be correlated with tumor size and lymph node metastasis. These phenomena were not observed in cases of follicular carcinoma and anaplastic carcinoma.

Pancreatic cancer

Note
Haptoglobin was identified as a highly fucosylated glycoprotein in the serum of patients with pancreatic cancer (Okuyama et al., 2006). The increment of fucosylated haptoglobin was observed in pancreatic cancer rather than other diseases such as HCC, liver cirrhosis, gastric cancer and colon cancer, and also appeared to be correlated with the clinical stage. Structural analyses using lectin blotting and mass spectrometry showed that core fucosylation as well as alpha1,3/4-fucosylation is increased in haptoglobin from the serum of such patients. In addition, it was shown that interleukin 6 expressed in pancreatic cancer is a possible inducing factor for increasing the production of fucosylated haptoglobin in the liver (Narisada et al., 2008).

Colorectal cancer

Note
The enzymatic activity and protein expression of FUT8 were increased in tumor tissues of human colorectal carcinoma, but not in healthy tissues (Muinelo-Romay et al., 2008). This increment was well observed in cases

of male, polypoid growth, no regional lymph node metastasis and early clinical stage. In addition, immunohistochemical examination has demonstrated that FUT8 is expressed at higher levels in tumor tissues of colorectal carcinoma than in healthy and transitional tissues.

Cystic fibrosis

Note

Fucosylation is known to be increased in cystic fibrosis. The alpha1,6-fucosylation of a membrane glycoprotein is elevated in cystic fibrosis fibroblast (Wang et al., 1990).

References

Alpert ME, Uriel J, de Nechaud B. Alpha-1 fetoglobulin in the diagnosis of human hepatoma. N Engl J Med. 1968 May 2;278(18):984-6

Ruoslahti E, Salaspuro M, Pihko H, Andersson L, Seppälä M. Serum alpha-fetoprotein: diagnostic significance in liver disease. Br Med J. 1974 Jun 8;2(5918):527-9

Taketa K. Alpha-fetoprotein: reevaluation in hepatology. Hepatology. 1990 Dec;12(6):1420-32

Wang YM, Hare TR, Won B, Stowell CP, Scanlin TF, Glick MC, Hård K, van Kuik JA, Vliegenthart JF. Additional fucosyl residues on membrane glycoproteins but not a secreted glycoprotein from cystic fibrosis fibroblasts. Clin Chim Acta. 1990 May;188(3):193-210

Aoyagi Y. Carbohydrate-based measurements on alpha-fetoprotein in the early diagnosis of hepatocellular carcinoma. Glycoconj J. 1995 Jun;12(3):194-9

Uozumi N, Yanagidani S, Miyoshi E, Ihara Y, Sakuma T, Gao CX, Teshima T, Fujii S, Shiba T, Taniguchi N. Purification and cDNA cloning of porcine brain GDP-L-Fuc:N-acetyl-beta-D-glucosaminide alpha1-->6fucosyltransferase. J Biol Chem. 1996 Nov 1;271(44):27810-7

Yamashita F, Tanaka M, Satomura S, Tanikawa K. Prognostic significance of Lens culinaris agglutinin A-reactive alpha-fetoprotein in small hepatocellular carcinomas. Gastroenterology. 1996 Oct;111(4):996-1001

Miyoshi E, Uozumi N, Noda K, Hayashi N, Hori M, Taniguchi N. Expression of alpha1-6 fucosyltransferase in rat tissues and human cancer cell lines. Int J Cancer. 1997 Sep 17;72(6):1117-21

Yanagidani S, Uozumi N, Ihara Y, Miyoshi E, Yamaguchi N, Taniguchi N. Purification and cDNA cloning of GDP-L-Fuc:N-acetyl-beta-D-glucosaminide:alpha1-6 fucosyltransferase (alpha1-6 FucT) from human gastric cancer MKN45 cells. J Biochem. 1997 Mar;121(3):626-32

Noda K, Miyoshi E, Uozumi N, Yanagidani S, Ikeda Y, Gao C, Suzuki K, Yoshihara H, Yoshikawa K, Kawano K, Hayashi N, Hori M, Taniguchi N. Gene expression of alpha1-6 fucosyltransferase in human hepatoma tissues: a possible implication for increased fucosylation of alpha-fetoprotein. Hepatology. 1998 Oct;28(4):944-52

Miyoshi E, Noda K, Yamaguchi Y, Inoue S, Ikeda Y, Wang W, Ko JH, Uozumi N, Li W, Taniguchi N. The alpha1-6-fucosyltransferase gene and its biological significance. Biochim Biophys Acta. 1999 Dec 6;1473(1):9-20

Oriol R, Mollicone R, Cailleau A, Balanzino L, Breton C. Divergent evolution of fucosyltransferase genes from vertebrates, invertebrates, and bacteria. Glycobiology. 1999 Apr;9(4):323-34

Yamaguchi Y, Fujii J, Inoue S, Uozumi N, Yanagidani S, Ikeda Y, Egashira M, Miyoshi O, Niikawa N, Taniguchi N. Mapping of the alpha-1,6-fucosyltransferase gene, FUT8, to human chromosome 14q24.3. Cytogenet Cell Genet. 1999;84(1-2):58-60

Takahashi T, Ikeda Y, Miyoshi E, Yaginuma Y, Ishikawa M, Taniguchi N. alpha1,6fucosyltransferase is highly and specifically expressed in human ovarian serous adenocarcinomas. Int J Cancer. 2000 Dec 15;88(6):914-9

Takahashi T, Ikeda Y, Tateishi A, Yamaguchi Y, Ishikawa M, Taniguchi N. A sequence motif involved in the donor substrate binding by alpha1,6-fucosyltransferase: the role of the conserved arginine residues. Glycobiology. 2000 May;10(5):503-10

Yamaguchi Y, Ikeda Y, Takahashi T, Ihara H, Tanaka T, Sasho C, Uozumi N, Yanagidani S, Inoue S, Fujii J, Taniguchi N. Genomic structure and promoter analysis of the human alpha1, 6-fucosyltransferase gene (FUT8). Glycobiology. 2000 Jun;10(6):637-43

Shields RL, Lai J, Keck R, O'Connell LY, Hong K, Meng YG, Weikert SH, Presta LG. Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. J Biol Chem. 2002 Jul 26;277(30):26733-40

Ito Y, Miyauchi A, Yoshida H, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, Yokozawa T, Matsuzuka F, Taniguchi N, Matsuura N, Kuma K, Miyoshi E. Expression of alpha1,6-fucosyltransferase (FUT8) in papillary carcinoma of the thyroid: its linkage to biological aggressiveness and anaplastic transformation. Cancer Lett. 2003 Oct 28;200(2):167-72

Noda K, Miyoshi E, Gu J, Gao CX, Nakahara S, Kitada T, Honke K, Suzuki K, Yoshihara H, Yoshikawa K, Kawano K, Tonetti M, Kasahara A, Hori M, Hayashi N, Taniguchi N. Relationship between elevated FX expression and increased production of GDP-L-fucose, a common donor substrate for fucosylation in human hepatocellular carcinoma and hepatoma cell lines. Cancer Res. 2003 Oct 1;63(19):6282-9

Shinkawa T, Nakamura K, Yamane N, Shoji-Hosaka E, Kanda Y, Sakurada M, Uchida K, Anazawa H, Satoh M, Yamasaki M, Hanai N, Shitara K. The absence of fucose but not the presence of galactose or bisecting N-acetylglucosamine of human IgG1 complex-type oligosaccharides shows the critical role of enhancing antibody-dependent cellular cytotoxicity. J Biol Chem. 2003 Jan 31;278(5):3466-73

Martinez-Duncker I, Michalski JC, Bauvy C, Candelier JJ, Mennesson B, Codogno P, Oriol R, Mollicone R. Activity and tissue distribution of splice variants of alpha6-fucosyltransferase in human embryogenesis. Glycobiology. 2004 Jan;14(1):13-25

Wang X, Inoue S, Gu J, Miyoshi E, Noda K, Li W, Mizuno-Horikawa Y, Nakano M, Asahi M, Takahashi M, Uozumi N, Ihara S, Lee SH, Ikeda Y, Yamaguchi Y, Aze Y, Tomiyama Y, Fujii J, Suzuki K, Kondo A, Shapiro SD, Lopez-Otin C, Kuwaki T, Okabe M, Honke K, Taniguchi N. Dysregulation of TGF-beta1 receptor activation leads to abnormal lung development and emphysema-like phenotype in core fucose-deficient mice. Proc Natl Acad Sci U S A. 2005 Nov 1;102(44):15791-6

Lee SH, Takahashi M, Honke K, Miyoshi E, Osumi D, Sakiyama H, Ekuni A, Wang X, Inoue S, Gu J, Kadomatsu K, Taniguchi N. Loss of core fucosylation of low-density lipoprotein receptor-related protein-1 impairs its function, leading to the upregulation of serum levels of insulin-like growth factor-binding protein 3 in Fut8-/- mice. J Biochem. 2006 Mar;139(3):391-8

Nakagawa T, Uozumi N, Nakano M, Mizuno-Horikawa Y, Okuyama N, Taguchi T, Gu J, Kondo A, Taniguchi N, Miyoshi E. Fucosylation of N-glycans regulates the secretion of hepatic glycoproteins into bile ducts. J Biol Chem. 2006 Oct 6;281(40):29797-806

Okuyama N, Ide Y, Nakano M, Nakagawa T, Yamanaka K, Moriwaki K, Murata K, Ohigashi H, Yokoyama S, Eguchi H, Ishikawa O, Ito T, Kato M, Kasahara A, Kawano S, Gu J, Taniguchi N, Miyoshi E. Fucosylated haptoglobin is a novel marker for pancreatic cancer: a detailed analysis of the oligosaccharide structure and a possible mechanism for fucosylation. Int J Cancer. 2006 Jun 1;118(11):2803-8

Taniguchi N, Miyoshi E, Gu J, Honke K, Matsumoto A. Decoding sugar functions by identifying target glycoproteins. Curr Opin Struct Biol. 2006 Oct;16(5):561-6

Wang X, Gu J, Ihara H, Miyoshi E, Honke K, Taniguchi N. Core fucosylation regulates epidermal growth factor receptor-mediated intracellular signaling. J Biol Chem. 2006 Feb 3;281(5):2572-7

Zhao Y, Itoh S, Wang X, Isaji T, Miyoshi E, Kariya Y, Miyazaki K, Kawasaki N, Taniguchi N, Gu J. Deletion of core fucosylation on alpha3beta1 integrin down-regulates its functions. J Biol Chem. 2006 Dec 15;281(50):38343-50

Ihara H, Ikeda Y, Toma S, Wang X, Suzuki T, Gu J, Miyoshi E, Tsukihara T, Honke K, Matsumoto A, Nakagawa A, Taniguchi N. Crystal structure of mammalian alpha1,6-fucosyltransferase, FUT8. Glycobiology. 2007 May;17(5):455-66

Li W, Ishihara K, Yokota T, Nakagawa T, Koyama N, Jin J, Mizuno-Horikawa Y, Wang X, Miyoshi E, Taniguchi N, Kondo A. Reduced alpha4beta1 integrin/VCAM-1 interactions lead to impaired pre-B cell repopulation in alpha 1,6-fucosyltransferase deficient mice. Glycobiology. 2008 Jan;18(1):114-24

Muinelo-Romay L, Vázquez-Martín C, Villar-Portela S, Cuevas E, Gil-Martín E, Fernández-Briera A. Expression and enzyme activity of alpha(1,6)fucosyltransferase in human colorectal cancer. Int J Cancer. 2008 Aug 1;123(3):641-6

Narisada M, Kawamoto S, Kuwamoto K, Moriwaki K, Nakagawa T, Matsumoto H, Asahi M, Koyama N, Miyoshi E. Identification of an inducible factor secreted by pancreatic cancer cell lines that stimulates the production of fucosylated haptoglobin in hepatoma cells. Biochem Biophys Res Commun. 2008 Dec 19;377(3):792-6

Osumi D, Takahashi M, Miyoshi E, Yokoe S, Lee SH, Noda K, Nakamori S, Gu J, Ikeda Y, Kuroki Y, Sengoku K, Ishikawa M, Taniguchi N. Core fucosylation of E-cadherin enhances cell-cell adhesion in human colon carcinoma WiDr cells. Cancer Sci. 2009 May;100(5):888-95

Takahashi M, Kuroki Y, Ohtsubo K, Taniguchi N. Core fucose and bisecting GlcNAc, the direct modifiers of the N-glycan core: their functions and target proteins. Carbohydr Res. 2009 Aug 17;344(12):1387-90

Wang X, Fukuda T, Li W, Gao CX, Kondo A, Matsumoto A, Miyoshi E, Taniguchi N, Gu J. Requirement of Fut8 for the expression of vascular endothelial growth factor receptor-2: a new mechanism for the emphysema-like changes observed in Fut8-deficient mice. J Biochem. 2009 May;145(5):643-51

This article should be referenced as such:

Ihara H, Gao CX, Ikeda Y, Taniguchi N. FUT8 (fucosyltransferase 8 (alpha (1,6) fucosyltransferase)). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(5):410-414.