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Gene Section
Review

NKX2-3 (NK2 homeobox 3)

Zhenwu Lin, John P Hegarty, Joanna Floros, Andre Franke

Pennsylvania State University College of Medicine PA USA (ZL); Division of Colon, Rectal Surgery Department of Surgery Pennsylvania State University College of Medicine PA USA (JPH); Departments of Pediatrics, Obstetrics, Gynecology, CHILD Research Center, Pennsylvania State University College of Medicine PA USA (JF); Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel, Germany (AF)

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Abstract

NKX2-3 gene is a member of the homeobox, NKX family.

The gene encodes a homeodomain-containing transcription factor. GO (gene ontology) annotations related to this gene include sequence-specific DNA binding and gene-specific transcription factor activity. NKX2-3 is essential for normal development and functions of the small intestine and spleen of embryonic and adult mice. Disruption of Nkx2-3 in mice results in postnatal lethality and abnormal development of the small intestine and the spleen.

Villus formation in the small intestine appears considerably delayed in Nkx2-3(null) fetuses due to reduced proliferation of the epithelium, while massively increased growth of crypt cells follows in surviving adults.

A complex intestinal malabsorption phenotype and striking abnormalities of gut-associated lymphoid tissue and spleen suggest deranged leukocyte homing. RT-PCR and immunohistochemistry revealed that NKX2-3 controls regional expression of leukocyte homing coreceptor mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in specialized endothelial cells of the viscera. This indicates a potential role for NXK2-3 in establishing the developmental and positional cues in endothelia that regulate leukocyte homing through local control of cellular adhesion. Studies of disease association indicated that NKX2-3 is associated with IBD (both Crohn's disease and ulcerative colitis), intestinal fibrosis, colon rectal cancer, and dental caries.

Keywords

NKX2-3, inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative disease (UC), homeodomain-containing transcription factor

Identity

Other names: CSX3, NK2.3, NKX2.3, NKX2C, NKX4-3

HGNC (Hugo): NKX2-3

Location: 10q24.2

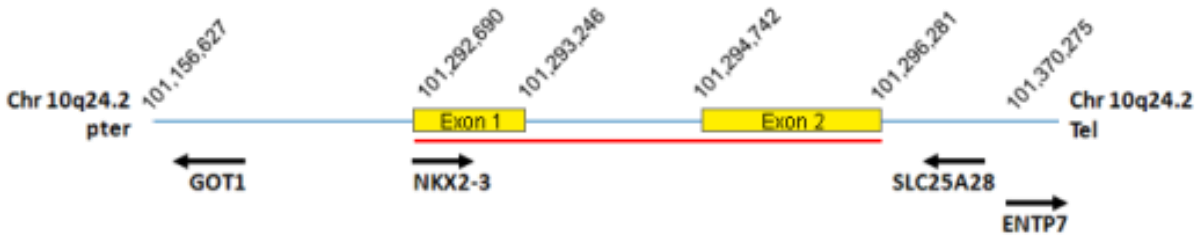
DNA/RNA

Note

The human NKX2-3 gene has two transcripts. NKX2-3-001, ENST00000344586, 2097 nt mRNA encoding a protein of 364 amino acids; NKX2-3-201, ENST00000622383, 1986 nt mRNA encoding a protein of 296 amino acids.

Description

The gene has two exons and one intron.



Chromosomal location of human NKX2-3 gene. NKX2-3 gene is located on chr 10q24.2, size 3592 bp, starting at 101292690 bp and ending at 101296281 bp from the pter (the end of short arm) of the chromosome 10. The gene orientation is on the plus strand. The NKX2-3 gene consists of 2 exons 527 bp (101292690-101293248 nt) and 1540 bp (101294742-101298281 nt) respectively, an intron 1496 bp (101293248-101294742 nt). GOT1: glutamic-oxaloacetric transaminase 1 soluble; SLC25A28: solute carrier family 25 (mitochondrial iron transporter) member 28; ENTP7: ectonucleoside triphosphate diphophohydrolase 7.

Transcription

The transcription takes place in a centromere --> telomere orientation. The length of the processed mRNA is about 2094 nucleotides.

Pseudogene

Not known.

Protein

Note

The NKX2-3 protein is a 364-amino acid (molecular weight 38405.63g/mol) protein.

Description

The NKX2-3 protein (364 amino acids) translated from the long transcript contains a TN domain (residues 10-19), HD domain (residues 148-207), SD domain (residues 222-238) and TAD domain (residues 239-364).

Expression

Expression is mainly observed in pharynx, small intestine, liver, spleen, heart, lymph node, thyroid, adrenal gland, breast, skin, ovary, prostate, testis, and retina.

Localisation

Nucleus, but also observed outside the nucleus.

Function

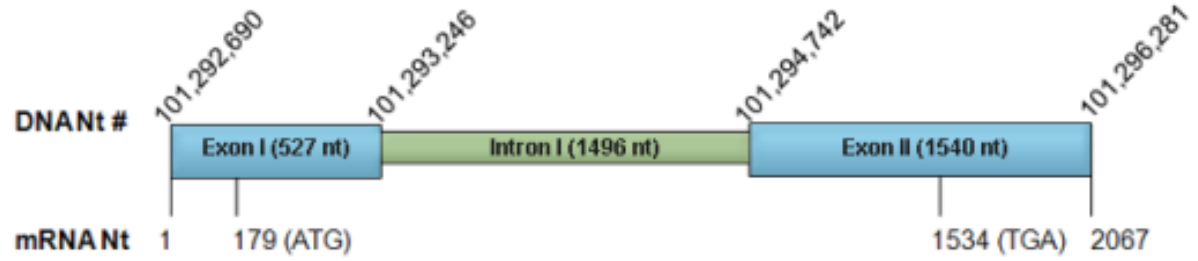
NKX2-3 is a nuclear transcription factor that plays an important role in the regulation of gene transcription. Studies from siRNA knockdown followed by cDNA profiling indicate that many genes are regulated by NKX2-3.

This indicates involvement of NKX2-3 in the regulation of transcription, of immune and inflammatory response, cell growth and proliferation, cell adhesion, metabolic processes, angiogenesis, lymph-angiogenesis, and others (Yu et al., 2011).

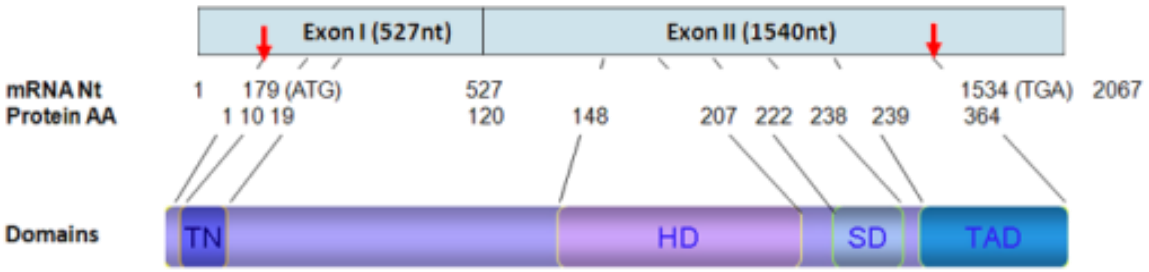
Results from NKX2-3 deficient mice and other studies demonstrate that NKX2-3 is essential for intestine and spleen development (Pabst et al., 1999; Pabst et al., 2000).

NKX2-3 is required for heart formation (Fu et al., 1998) and salivary gland and tooth morphogenesis and plays a role during pharyngeal organogenesis (Biben et al., 2002).

NKX2-3 is essential for B cell maturation and T cell dependent immune response (Shaffer et al., 2013), and regulates leukocyte homing through local control of cellular adhesion molecules including MADCAM-1 and VCAM in mice (Wang et al., 2000) and IBD patients (our unpublished data).



Human NKX2-3 mRNA. The gene for NKX2-3 consists of two exons of 527 and 1540 bp, respectively. The intron is 1496 bp. Positions of start (cDNA 179 nt) and stop (cDNA 1534 nt) codons are indicated. These data refer to ENSEMBL transcript.



Human NKX2-3 protein. The NKX2-3 protein is a 364-amino acid (molecular weight 38405.63g/mol) protein including a TN domain (tinman domain; transcription repressor domain), HD domain (homeodomain, 60 aa), SD domain (NK2 specific domain), and TAD domain (transcriptional activation domain).

Nkx2-3 and regulation of the arteriovenous endothelial profile

Individual transcription factors interact in a complex network to regulate the arteriovenous profile. Aranguren et al. 2013 examined the expression of 64 known arterial and 12 known venous genes from freshly isolated arterial and venous endothelial cells from human umbilical cord. The expression of approximately 36% of the examined arterial genes was found to be regulated by NKX2-3 (Aranguren et al., 2013).

Nkx2-3 and lymphoid tissue development

It remains to be determined whether the formation of enteric lymphatic capillaries is affected by the absence of Nkx2-3, similar to the observed reduction of Peyer's patches. In contrast to the leukocyte homing in pLNs and Peyer's patches, the spleen lacks high endothelial venules (HEVs) and requires no L-selectin binding for subsequent leukocyte extravasation. Evidence indicated that the integrity of the marginal sinus and the proper vascular segregation of the red pulp was controlled by NKX2-3 (Balogh et al., 2007).

Czömpöly et al. 2011 found that the disruption of Nkx2-3 expression in mice, the spleen develops a peripheral lymph node (pLN)-like mRNA expression signature, coupled with the appearance of HEVs. These HEV-like vessels undergo postnatal maturation and progressively replace MAdCAM-1 by pLN addressin together with the display of CCL21 arrest chemokine, reminiscent of HEV formation in pLNs (Czömpöly et al., 2011). This transformation of splenic vasculature into pLN-like vessels emphasizes the importance of Nkx2-3 in correct vessel formation for spleen ontogeny in mammals.

Kellermayer et al. 2011 reported that Nkx2.3-deficient mice develop splenic and gut-associated vascular and lymphoid tissue abnormalities with disordered segregation of T- and B- cells. Splenic defects include absence of the marginal sinus vasculature and an atrophic red pulp sinus network with an extensive network of lymphocyte-filled endothelial sacs lined by cells expressing LYVE-1, a marker associated with lymphatic endothelium cells (Kellermayer et al., 2011).

This raises the possibility that endothelial differentiation and maturation may be affected by altered expression of Nkx2-3.

Homology

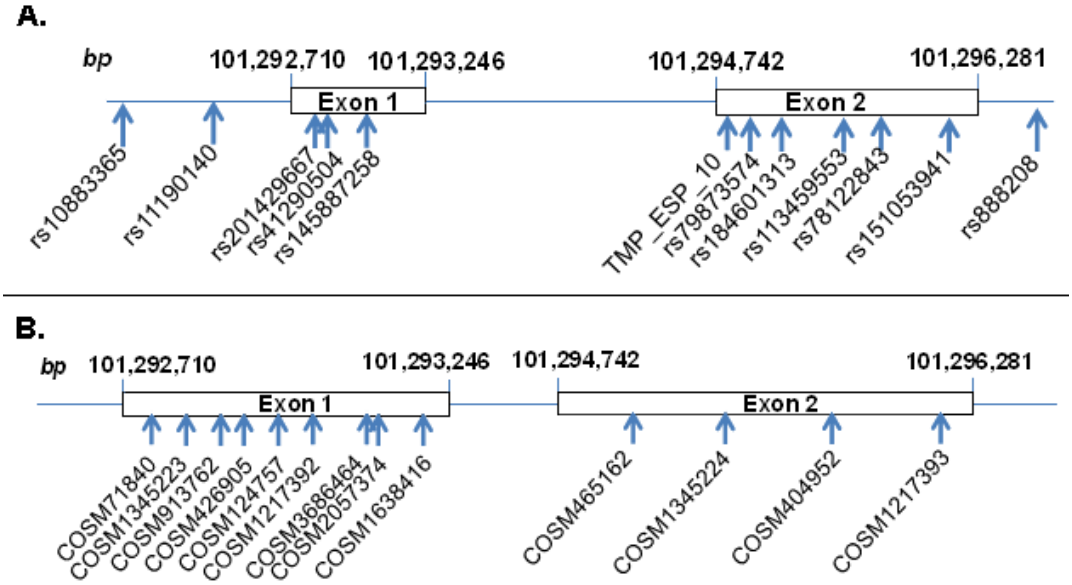
NKX2-3 is a homeodomain protein belonging to the NK2 family.

The other NK2 family members are Nkx2-1 (at 14q13), Nkx2-2 (at 20p11), Nkx2-3 (at 10q24.2), Nkx2-4 (at 20p11), Nkx2-5, Nkx2-6, Nkx2-8, Nkx2-9 (at 14q13), and Nkx2-10.

Orthologs of NKX2-3 show a high similarity with the homologues in other species, such as 88.46% (nt) and 90.86% (aa) with mouse, 60% (aa) with chicken, 79% (nt) with Xenopus laevis, 76.29% (nt) with zebrafish, 20% (aa) with fruit fly, and 33% (aa) with worm.

Mutations

A total of 304 genetic variants are documented, including 128 upstream and 87 downstream of the gene, 5 variants in the 5' prime and 15 in the 3' primer untranslated regions, 26 missense and 17 synonymous variants in exons, 23 variants in introns, and 2 in-frame deletions.



Mutations in human NKX2-3 gene. A. The base number at the beginning and the end of each exon is shown. Genetic variations rs10883365 and rs11190140 in 5'-prime upstream are the most used for genetic association study, and rs888208 in 3'UTR is used for allele specific expression. TMP_ESP_10_101294794-101294796 GAA/- in Exon 2 is an in-frame deletion. Of the 26 missense genetic variants only three, rs201429667 (p.A49T), rs79873574 (p.P145T, and rs15105391 (p.L358W) have been observed in multiple studies. Of the 17 synonymous variants five have been observed in multiple studies with high MAF (minor allele frequency): rs41290504 (MAF: 0.483), rs145887258 (MAF: 0.001), rs184601313 (MAF: 0.001), rs113459553 (MAF: 0.039), and rs78122843 (MAF: 0.006) in amino acid residue 49, 80, 156, 185, and 194 respectively. **B.**The base number at the beginning and the end of each exon is shown. The somatic mutations are shown from left to right: COSM71840 p.T10I, COSM1345223 p.D35G, COSM913762 p.A43V, COSM426905 p.A49A, COSM124757 p.G52E, COSM1217392 p.L70S, COSM3686464 p.S102R, COSM2057374 p.S102S, COSM1638416 p.E109Q, COSM465162 p.R165H, COSM1345224 pA216T, COSM404952 C817_837del21 in-frame, and COSM1217393 p.R362L.

Somatic

A total of 13 somatic mutations have been reported: one is a 21 bp deletion, two are synonymous variants, and 10 missense variants.
Histological examination showed all the mutations are observed in carcinoma.

Implicated in

Colorectal cancer (CRC)

Loss of heterozygosity on chromosome 10 where IL10 is located was observed in sporadic CRC. RT-PCR results indicated that the NKX2-3 gene is down regulated (Wang et al., 2008).
A high expression of NKX2-3 was found in the CRC experimental group compared to the control group (Li et al., 2012).

CRC with synchronous liver metastasis

NKX2-3 with other 6 genes was incorporated into a genetic model for estimating chemotherapy sensitivity.
The result from 30 ACC (advanced colorectal cancer) patients (13 were assigned to experimental group and 17 to the control group) showed an overall accurate prediction rate of 99.3% (Lu et al., 2013).

Liver metastases

NKX2-3 is expressed to a low level in liver metastases than in primary tumors and normal enterochromaffin cells (Leja et al., 2009).

Inflammatory bowel disease (IBD)

NKX2-3 was first identified as IBD susceptibility gene from a GWAS study in 2006 (Wellcome Trust Case Control, 2007) and then it was replicated in several cohorts in both CD and US (Parkes et al., 2007; Franke et al., 2008; Barrett et al., 2008). The association is widely studied with genetic variations rs10883365 and rs11190140, in different IBD populations, including Japanese population (484 CD and 470 controls (Yamazaki et al., 2009), Dutch-Belgian (2731IBD: 1656 CD and 1075UC) (Weersma et al., 2009), Eastern European IBD patients (810 CD and 428 UC) (Meggyesi et al., 2010), Central Pennsylvania population in US (Yu et al., 2009), Italian cohort (both CD and UC, adult and pediatric IBD) (Latiano et al., 2011), and Lithuanian-Latvian population (444 UC and 1154 controls) (Skieceviciene et al., 2013). A specific association of NKX2-3 rs1088365 with smoking CD patients has been observed (310 CD and 976 controls) (van der Heide et al., 2010). These studies have been reviewed (Cho and Brant, 2011; Van Limbergen et al., 2014).

SNP	Varian	Method	CD	UC	other	OR	95% CI	P value	Reference
rs10883365	A/G	GWAS	2000					1.4×10-8	WTCC, 2007 [5]
rs10883365	A/G	GWAS	1182			1.18	1.05-1.32	0.00373	Parkes et al, 2007 [6]
rs10883365	A/G	GWAS		1,841					Fisher et al, 2007 [7]
rs10883365	A/G	GWAS	1850			1.21	1.04-1.40	4.03×10^{-5}	Franke et al, 2008 [8]
rs10883365	A/G	GWAS		1,103		1.31	1.10-1.56	2.44×10^{-7}	Franke et al, 2008 [8]
rs11190140	T/C	GWAS	1850			1.22	1.05-1.42	8.87×10^{-6}	Franke et al, 2008 [8]
rs11190140	T/C	GWAS		1,103		1.39	1.16-1.67	1.33×10^{-8}	Franke et al, 2008 [8]
rs10883365	A/G	SNPlex	75			1.24	0.92-1.66	0.0412	Yu et al 2009 [9]
rs11190140	T/C	RFLP				0.5	0.33-0.76	<0.001	John et al (unpublished)
rs10883365	A/G	SNPlex	1621			1.48	1.23-1.77	5.91×10^{-6}	Weersma et al 2009 [10]
rs10883365	A/G	SNPlex		1442		1.24	1.02-1.51	3.95×10^{-2}	Weersma et al 2009 [10]
rs10883365	A/G	LightCycler allele descrimination	810			1.24	1.06-1.48	0.009	Meggyesi et al 2010 [11]
rs10883365	A/G	LightCycler allele descrimination		428		1.36	1.13-1.63	0.001	Meggyesi et al 2010 [11]
rs10883365	A/G	TaqMan	484					0.0065	Yamazaki et al 2009 [12]
rs10883365	A/G	TaqMan		296				0.003	Tanaka et al 2009 [13]
rs10883365	A/G	TaqMan	344			1.29	1.02-1.63	0.0366	Arai et al, 2011 [14]
rs10883365	A/G	TaqMan		253		1.54	1.20-1.99	7.79×10^{-4}	Arai et al, 2011 [14]
rs888208	G/A	TaqMan		253		1.41	1.10-1.81	7.70×10^{-3}	Arai et al, 2011 [14]
rs10883365	A/G	Prime extension MALDI-TOF	164		smoking	1.35	1.05-1.73	0.021	van der Heide 2009 [15]

Studies on genetic association of Nkx2-3 gene with IBD.

A recent comprehensive meta-analysis of 17 studies involving 17329 patients and 18029 controls showed a significantly increased CD or UC risk in persons carrying a G allele at rs10883365 polymorphism (A/G) compared with those with an A allele. (OR = 1.226, 95%CI: 1.177-1.277 and OR = 1.274, 95%CI: 1.175-1.382 respectively).

In the subgroup analysis, a significantly increased CD risk was found in both Europeans and Asians. For rs11190140 polymorphism (C/T) and CD risk, the risk estimate for the allele contrast was OR = 1.201 (1.136-1.269) (Lu et al., 2014).

Prognosis

Results from a study in 572 CD, 328 UC patients, 437 non-IBD, and 137 healthy controls using 29 biomarkers, 4 genetic markers including NKX2-3, 8 serological markers, and 17 inflammatory markers, indicated that these markers can differentiate non-IBD from CD and UC patients (Plevy et al., 2013).

Intestinal fibrosis

Intestinal fibrosis is among the most common complications of IBD, and is usually defined as an excessive accumulation of scar tissue in the intestinal wall. Severe fibrosis is seen in up to 30% of patients with CD, a high proportion of them require surgery.

In addition, endothelial-to-mesenchymal transition (EndoMT) results in the trans-differentiation of intestinal mucosal microvascular cells (HIMEC) into mesenchymal cells.

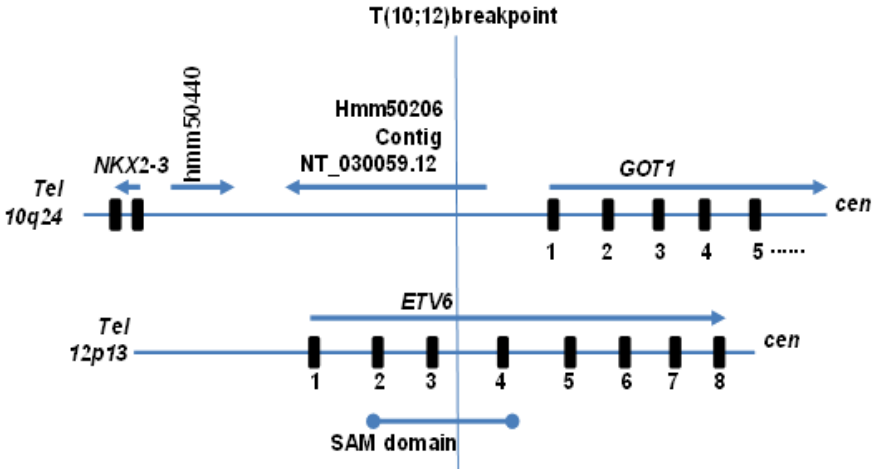
This indicates that the intestinal microvasculature may also contribute to IBD-associated fibrosis (Rieder et al., 2011).

Nkx2-3 is highly expressed in the gut mesenchyme, such as myofibroblasts and the smooth muscle cells of the muscularis mucosae. Myofibroblasts are known to play key roles in wound healing and fibrosis. Known Nkx2-3 regulation of genes mediating fibrogenesis and wound healing, such as endothelins, angiotensin converting enzyme, and angiotensin-II, and nitric oxide, may result in active deposition of ECM resulting in the characteristic fibrosis of CD (Yu et al., 2011).

Interestingly, related Nkx2.5 is a known repressor of myofibroblast α-smooth muscle actin (α-SMA) gene transcription in the lung (Hu et al., 2010). Similarly, aberrant Nkx2-3 expression in the gut may result in increased intestinal myofibroblast differentiation intestinal fibrosis. We note that the Nkx2-3-regulated transcription factor KLF-4 (gut-enriched Krüppel-like factor) represses α-SMA gene expression by interacting with Smad3 (TGF-β signaling) to prevent Smad3 binding, resulting in reduced myofibroblast differentiation (Hu et al., 2007).

Dental caries

Dental caries, also known as tooth decay or a cavity, is an infection, bacterial in origin. It causes demineralization and destruction of the hard tissues of the teeth (enamel, dentin and cementum) as a result of the production of acid by bacterial fermentation of food debris accumulated on the tooth surface. In a GWAS study with 518987 genetic variations NKX2-3 was shown to be a suggestive genetic association with dental caries pattern in the permanent dentition (Shaffer et al., 2013).



Schematic representation of 10q24 and 12p13 regions implicated in the t(10;12). Genomic representation of t(10;12) ETV6 (exon 3)-GOT1 (exon 12) fusion is in frame. The fusion transcript was identified by RT-PCR with primers located in the exon 6 of ETV6 and the exon 3 of GOT1 followed by sequence analysis. The sterile alpha motif (SAM) domain (exons 2 to 4) responsible for hetero- and homodimerization with other ETV6 protein and possibly other ETS family members, are indicated.

Breakpoints

A ETV6-GOT1 fusion contains a chimeric transcript containing ETV6 sequence fused to genomic sequences located at 22961 bp 3' to GOT1 and 79407 bp 5' to NK2 transcription factor related, locus 3 (NKX2-3). This may result in the dysregulation of NKX2-3, which lies adjacent to the breakpoint (Struski et al., 2008).

To be noted

miRNAs targeting human Nkx2-3

The top miRNAs binding the 3'-UTR of the human NKX2-3 transcript were identified using TargetScan v6.2 (Lewis et al., 2005) and Miranda algorithm v4.0 (Betel et al., 2006) with parameters of >8-mer matches with mirSVR scores <= -1 and PhastCons score >= 0.6 BP. Identified miRNAs included members of the miR-92a microRNA precursor family of highly conserved miRNAs (miR-25, miR-92a, miR-92b and miR-363). The miR-92a family plays an important role in regulating mammalian organs including heart and lungs, and immune system, formation of blood vessels, and development of endothelial cells. Inhibition of miR-92a can enhance angiogenesis and viability of endothelial cells (Zhang et al., 2014). miRNA92a family and miRNA-32 affect expression of endothelial Kruppel-like factors KLF2 and KLF-4, possibly though regulation of Nkx2-3 expression (Loyer et al., 2014).

Epigenetic modification of genetic variant

Rs11190140 is a C/T variation followed by G. The C allele is in a CG dinucleotide. The C is subjected to methylation. The genetic variation and epigenetic modification affect the NFAT transcription factor binding to the DNA, T< nonmethylated C< methylated C (John et al., 2011).

Nkx2-3 allelic expression imbalance in human IBD colonic mucosa

Arai et al. 2011 (Arai et al., 2011) examined the expression of Nkx2-3 mRNA from colonic mucosa from Japanese patients with IBD. Allelic expression ratios of NKX2.3 mRNA transcribed from risk haplotype to the non-risk haplotype in the involved mucosa from 10 IBD patients were significantly higher than the allelic ratio of respective genomic DNA ($p = 0.00195$) (Arai et al., 2011). This observed allelic expression imbalance supports the idea that the risk haplotype of NKX2.3 confers susceptibility to UC through increasing expression of NKX2.3 mRNA in the colonic mucosa.

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