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Review

UTS2 (urotensin 2)

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Abstract

Review on UTS2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Keywords: UTSII, Urotensin2

Identity

Other names: PRO1068, U-II, UCN2, UII

HGNC (Hugo): UTS2

Location: 1p36.23

DNA/RNA

Description

The human UTS2 gene is an active cyclic heptapeptide and encodes a mature peptide. This gene is located on the reverse strand of chromosome 1. It consists of an open reading frame (ORF) having 372 nucleotides which encodes 124 amino acids. Its size is about 14.3 kDa and has an isoelectric point 7.67.

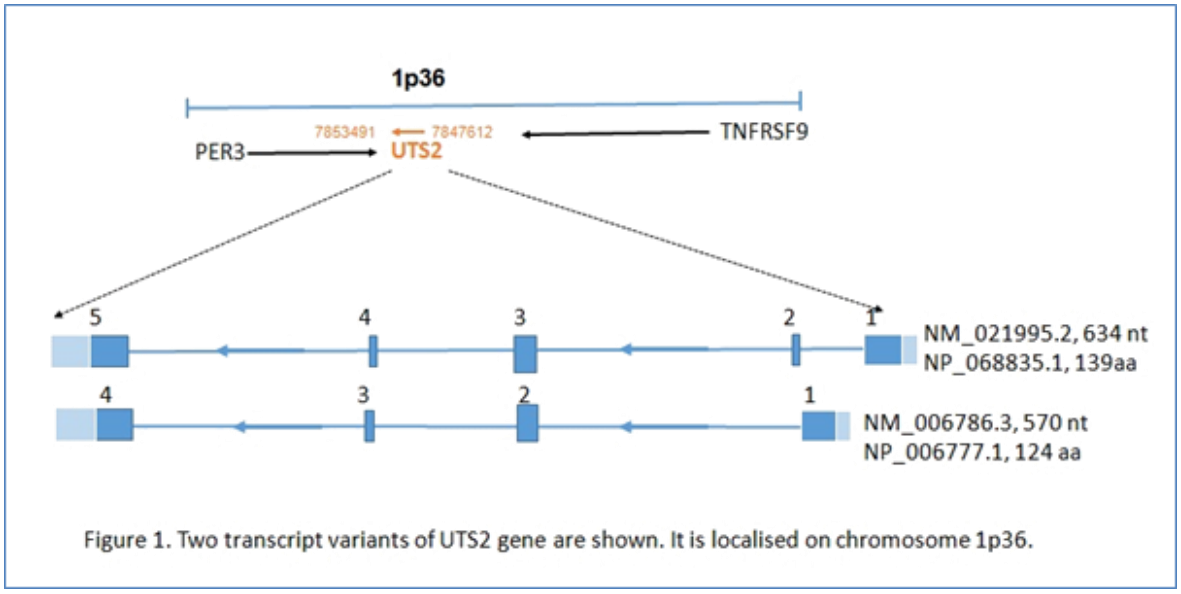

Figure 1. Two transcript variants of UTS2 gene are shown. It is localised on chromosome 1p36.

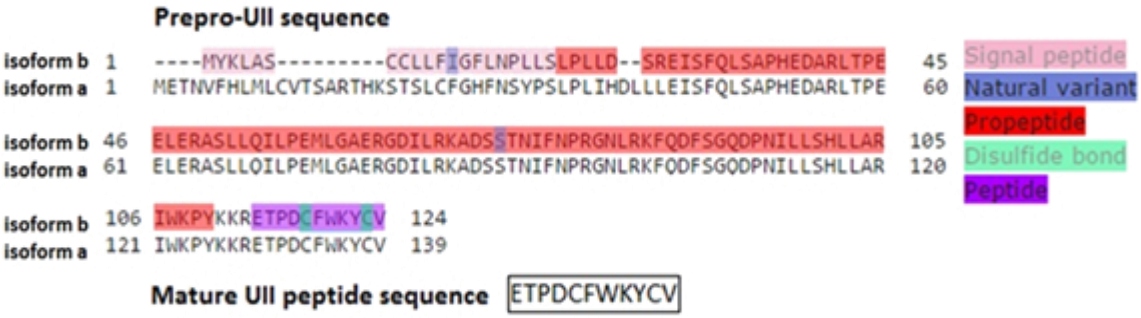

Figure 2. Prepro-UII and mature UII peptide sequences are shown. The signal peptide, natural variant, propeptide, disulfide bond and peptide regions are also highlighted in different colours.

The mature peptide for both transcript variants (TV1 and TV2) is known to be identical but has different amino-terminal end as compared to transcript variant 1. The two most common transcript variants (TV1 and TV2) are shown in Figure1. The third transcript variant is known to be putative protein coding. It has a transcript length of 1601 bps with a translational length of 139 residues and has a total of 7 exons with 6 coding exons. UII is most abundantly expressed in the central nervous system, for example in the brainstem and spinal cord. Apart from the CNS, UII mRNA is also expressed in the liver, kidney, cardiomyocytes, coronary and in multiple endocrine glands (Ames et al., 1999, Nothacker et al., 1999).

Pseudogene

There is no pseudogene for UTS2.

Protein

Description

Urotensin II is known to be a potent vasoactive peptide in humans and in several other animal models. It is a cyclic peptide of 12 amino acids. The cyclic region of the peptide (Cys-Phe-Trp-Lys-Tyr-Cys) of UII is evolutionary conserved but the N-terminal region of UII is highly variable (Conlon, 2000, Conlon, 2008). U-II is known to be the endogenous ligand of an orphan G-protein-coupled receptor (GPR 14). In humans, UTS2 originated from a large precursor molecule i.e prepro-U-II and is encoded by a gene on chromosome 1p36. The prepro and mature UII peptide sequences are shown in Figure2. Two splice variants of the precursor are known, one consist of124 amino acids while the other has 139 amino acids. Actually human UTS2 derived from post-translational processing of two different precursors, which are alternate splice variants (Ames et al., 1999, Coulouarn et al., 1998). Ensembl mentions a third transcript variant that is known to be putative protein coding. It has a translational length of 139 amino acids. UTS2 is having a molecular mass of approximately 14.3 kDa and has an isoelectric point 7.67.

The amino acid sequence of UTS2 is highly conserved across several vertebrates and shares structural similarity to somatostatin. Due to the structural similarities between U-II and somatostatin, it was wrongly interpreted that UTS2 shared binding sites with somatostatin. The human GPR14 (G-Protein-Coupled Receptor-14) has been found out to function as a UTS2 receptor (Ames et al., 1999, Liu et al., 1999, Mori et al., 1999, Nothacker et al., 1999). It is also known as sensory epithelium neuropeptide like receptor (SENR) (Tal et al., 1995). This receptor was later called the urotensin receptor (UTR) because of the high selectivity of GPR 14 for UTS2(Liu et al., 1999). The binding of U-II with UTR is functionally coupled to calcium mobilization.

Expression

UTS2 is widely distributed and is found in a variety of different tissues. In humans it has been found in the heart (Matsushita et al., 2001), kidney (Matsushita et al., 2001, Shenouda et al., 2002, Totsune et al., 2003), liver (Totsune et al., 2003, Coulouarn et al., 1998) and in the brain and spinal cord of several other species. However the distribution of UTS2 is somewhat unusual as it is found in motor neurons of the spinal cord and motor nuclei in the brain (Coulouarn et al., 1998, Dun et al., 2001). The pre-pro UTS2 has been found to co-localize with androgen receptors in motor nuclei (Pelletier et al., 2002). Immunohistochemistry for the UII peptide reveals its presence in the neuronal cell soma of the brain and spinal cord (Ames et al., 1999, Chartrel et al., 1996, Dun et al., 2001). UTS2 is also shown to be expressed in pancreas (Totsune et al., 2003). There is very high expression of UTS2 proteins in cerebral cortex, hippocampus, lateral ventricle and cerebellum of CNS. It is also highly

expressed in pancreas, duodenum, small intestine, placenta and thyroid gland. UII is moderately expressed in gall bladder, stomach, colon, kidney, testis, prostate, breast, lung, heart muscle, bronchus. It has low expression in skin, soft tissue and bone marrow. But it has not been detected in oral mucosa, adipose tissue, skeletal muscle and smooth muscle.

Localisation

UTS2 has primarily extracellular localisation. This protein is found mainly in the human spinal cord generally in motoneurons.

Function

UTS2 (U-II) is a well known vasoactive hormone whose action is mainly dependent on seven transmembrane spanning G-protein-coupled receptor called GPR14 (Onan et al., 2004). UII play an indispensable role in the physiological regulation of several organ systems especially within the cardiovasculature. It is known to be the most potent mammalian vasoconstrictor possessing both vasoconstrictor and vasodilatory action properties as well as profibrotic and antiapoptotic activity (Langham & Kelly, 2013).

UTS2 possesses several cardiovascular actions such as potent vasoactive and cardiac inotropic and hypertropic properties (Douglas et al., 2002). It activates the G protein-coupled receptor UTS2R and thus exerts various cardiovascular effects and has a role in the pathophysiology of atherosclerosis (Segain et al., 2007).

It negatively regulates blood pressure. U-II is supposed to have several behavioral activities as it occurs in the central nervous system and is widely distributed in the brain.

It has been shown in studies conducted in rodents that central administration of U-II stimulates locomotion, stimulates anxiety and depressive-like conditions, provokes feeding activity and increases the duration of paradoxical sleep episodes (do Rego et al., 2008). UII also exerts a wide range of actions in other systems, such as proliferation of vascular smooth muscle cells, fibroblasts, and cancer cells (Wu et al., 2010, Lin et al., 2004, Ross et al., 2010). In addition it also increases foam cell formation, chemotaxis of inflammatory cells, and inotropic and hypertrophic effects on heart muscle, inhibits insulin release (Saez et al., 2011), modulates glomerular filtration (Langham & Kelly, 2013) and release of catecholamines and may help in the regulation of food intake and the sleep cycle (Huitron-Resendiz et al., 2005).

Guidolin et al. stated that urotensin-II has an angiogenic role (Guidolin et al., 2010). Furthermore endogenous urotensin II has a role in erectile functioning by selectively modulating its mechanism through eNOS (Bianca et al., 2012).

Homology

UTS2 is a partial homologue of somatostatin and shares structural similarity to somatostatin. It was also demonstrated that both rat and mouse homologs share sequence homology with human prepro UTS2 (Coulouarn et al., 1999). All the known homologs of UTS2 are known to share a highly conserved cyclic region in the peptide which predicts that this region has a functional significance.

Mutations

Different genetic polymorphisms in UTS2 and their association with diseases:

Several single nucleotide polymorphisms (SNPs) in genes encoding for urotensin II (UTS2) are known and have been well studied. According to the US National Center for Biotechnology Information (NCBI) database, over 60 single nucleotide polymorphisms (SNP) have been noted in the human UTS2 gene. Three of these SNP show amino acid changes in the UTS2 gene sequence. The well known SNP, 143G>A (T21M, rs228648) in the UTS2 gene is found to be associated with type 2 diabetes in Han people residing in northern China (Suguro et al., 2007, Zhu et al., 2002) while the other SNP, 3836C>T (S89N, rs2890565) has association with higher plasma insulin level, insulin resistance, and susceptibility of developing type 2 diabetes in Hong Kong Chinese and Japanese (Ong et al., 2006, Suzuki et al., 2004, Wenyi et al., 2003). The SNP, 3836C>T is supposed to be a functional SNP as it has association with higher plasma UTS2 level (Ong et al., 2006). Recently it has been found that Thr21Met (T21M) polymorphisms of the UTS2 gene were associated with higher risk of developing Behcet's disease as well as Systemic Sclerosis (Oztuzcu et al., 2013, Pehlivan et al., 2012). Both Thr21Met (T21M) and Ser89Asn (S89N) polymorphisms of the UTS2 gene have been found to be pathologically associated with the risk of developing diabetes and Diabetic Retinopathy (Okumus et al., 2012). The exchange of serine instead of asparagine at amino acid position 89 changes the structure of UTS2. Due to this, mutation at this particular point is likely to form immature UII peptide that might cause several pathological conditions (Okumus et al., 2012).

Implicated in

Breast cancer

In a recent study, Balakan et al. (2014) found that U-II and UTR mRNA is being expressed in the breast tissue and breast cancer tissue. Consequently they found an association of UTS2 with menopausal status, and extra-nodal and lymphatic invasion in breast cancer patients (Balakan et al., 2014).

Atherosclerosis

Atherosclerosis is vascular inflammation which is chronic in nature and results in the deposition of lipid and leucocyte in the arterial wall (Loirand et al., 2008). In hypertensive patients, plasma U-II level is found to be positively correlated with carotid atherosclerosis (Suguro et al., 2007) as well as in patients with coronary artery isease (Heringlake et al., 2004)

Metabolic syndrome

UTS2 is considered to give rise to the metabolic syndrome and its components, like hyperglycemia, hypertension, insulin resistance and inflammation. It has a role in inflammation by effecting ingestive behavior. Plasma UTS2 level has a positive correlation with systolic blood pressure and insulin resistance (Cheung et al., 2004, Ong et al., 2006, Suguro et al., 2007). The two well known disorders i.e hypertension and insulin resistance are known to occur together as components of the metabolic syndrome (Reaven G.M, 1988).

Behcet's disease

Oztuzcu et al. (2013) described that Thr21Met (T21M) polymorphisms of the UTS2 gene is known to be associated with Behcet's disease (BD) in Turkish population (Oztuzcu et al., 2013).

Diabetes Mellitus and Diabetic Retinopathy

An association between Thr21Met and Ser89Asn polymorphisms of the UTS2 gene, Diabetes Mellitus and Diabetic Retinopathy has been found by Okumus et al. (Okumus et al., 2012).

Systemic Sclerosis

Pehlivan et al. (2011) suggested that Thr21Met, but not Ser89Asn has an important role in the development of Systemic Sclerosis, and a powerful indicator of severe skin and lung involvement in patients with Systemic Sclerosis (Pehlivan et al., 2012).

Renal disease

Totsune et al. (2001) reported higher levels of plasma UTS2 i.e an increase in three fold and two fold in patients with renal dysfunction, with and without dialysis respectively as compared with healthy control (Totsune et al., 2001). This indicated a role of UTS2 in renal function.

Congestive Heart Failure

It has been found that myocardial UII is significantly expressed in heart samples taken from patients with congestive heart failure as compared to controls, which was inversely correlated with ejection fraction (Douglas et al., 2002).

Type 2 diabetes mellitus

Wenyi et al. reported the association of S89N polymorphism in the UTS2 with the development of Type 2 diabetes, via insulin sensitivity, in Japanese subjects (Wenyi et al., 2003).

Pre-eclampsia.

ElSharkawy et al. showed the elevation of UTS2 in the serum of PE patients which could be correlated to the severity and/or progression of the disease. The UTS2 genotype frequencies between patients and control groups showed a significant difference, which implies a potential benefit for UTS2 gene or level in serum as a diagnostic or prognostic indicator in pre-eclampsia (ElSharkawy et al., 2014). Endothelial nitric oxide synthase (eNOS) (Glu298Asp) and UTS2 (UTS2 S89N) gene polymorphisms are promising markers for early prediction of preeclampsia in Egyptian females (El-Sherbiny et al., 2013).

Schizophrenia

Higher UTS2 expression was found in schizophrenia patients suggesting that UTS2 level may be a probable candidate related to the pathology of the disease (Bulbul et al., 2014).

To be noted

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