Gene Section
Review

A2M (alpha-2-macroglobulin)

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Abstract

Alpha-2-Macroglobulin (A2M) was first recognized as a broad-spectrum protease inhibitor and is a pan-proteinase inhibitor that can mechanically inhibit all proteinase families. It plays an important role in the clearance of proteinases from circulation, regulation of fibrinolysis, coagulation and complement activation. A2M is also known to act as a transport/carrier protein. In general, A2M is produced by the liver as an acute-phase protein during stress conditions and then secreted into the blood and extracellular environments where it functions. It is also locally produced by macrophages, fibroblasts, and epithelial cells. A2M gene mutations play a role in the pathogenesis of diseases such as Alzheimer's disease, parkinson's disease, and prostate cancer.

Keywords
Alpha-2-Macroglobulin (A2M), Pan-proteinase inhibitor, Alzheimer Disease, Parkinson's Disease

Figure 1. Genomic location of A2M (Chromosome 12 - NM_001347425 (GRCh38.p13 Primary Assembly).
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Figure 2. Chromosomal Location of A2M (https://www.genecards.org/). Cytogenetic Location of A2M: 12p13.31, which is the short (p) arm of chromosome 12 at a position 13.31 (UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38) Assembly).

Identity

Other names
Alpha-2-Macroglobulin, C3 And PZP-Like Alpha-2-Macroglobulin Domain-Containing Protein 5, Alpha-2-M, CPAMD5, FWP007, S863-7, A2MD

HGNC (Hugo): A2M

Location: 12p13.31

Local order:
shown in Chromosome 12 - NM_001347425 (GRCh38.p13 Primary Assembly)

DNA/RNA

Note
The A2M gene is 48,446 bp long (according to UCSC, GRCh38/hg38), located on the minus (-) strand and spans 37 exons (NCBI Homo sapiens Annotation Release 109).

Transcription
The gene has 13 transcripts (Table 1)

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Table 1. Transcripts of the human A2M gene (Ensemble, GRCh38.p12).

Figure 3. Numbers and illustrative sizes of exons of human A2M. (http://atlasgeneticsoncology.org/)
Pseudogene

A related pseudogene so-called Alpha-2-macroglobulin pseudogene 1 (A2MP1) with 9 exons has been identified in chromosome 12p13.31.

Protein

Alpha-2-Macroglobulin (A2M) is a protein-coding gene (https://www.genecards.org/cgi-bin/carddisp.pl?gene=A2M&keywords=A2M). The human A2M is a 720 kDa soluble glycoprotein composed of four identical 180 kDa (1451 amino acid) subunits, each of which is encoded by a single-copy gene on chromosome 12 (Kovacs, 2000). A2M protein is a plasma proteinase inhibitor and binds with the amyloid beta peptide (A beta) specifically and preserves the A beta peptides in a soluble condition, preventing fibril formation (Zamani et al., 2016). The protein encoded by this gene is a protease inhibitor and cytokine transporter (https://www.genecards.org/cgi-bin/carddisp.pl?gene=A2M&keywords=A2M). It uses a bait-and-trap mechanism to inhibit a broad spectrum of proteases, including trypsin, thrombin, and collagenase. It can also inhibit inflammatory cytokines, and it thus disrupts inflammatory cascades (https://www.ncbi.nlm.nih.gov/gene/2). This protein has a peptide stretch, called the bait region which contains specific cleavage sites for different proteinases. When a proteinase cleaves the bait region, a conformational change is induced in the protein which traps the proteinase. The entrapped enzyme remains active against low molecular weight substrates whereas the activity against high molecular weight substrates is greatly reduced. Following cleavage in the bait region, a thioester bond is hydrolyzed and mediates the covalent binding of the protein to the proteinase (https://www.uniprot.org/uniprot/P01023). Similar to other alpha-macroglobulins such as complement components C3 and C4A and the PZP (PZP alpha-2-macroglobulin like), A2M has an extraordinary binding capacity for a variety of ligands. In the plasma, this allows the alpha-macroglobulins to function as defense barriers against foreign peptides (Kovacs, 2000).

Expression

A2M gene is most commonly expressed in endocrine tissues, lung, liver and gallbladder, female tissues, and adipose and soft tissues. It is less expressed in the eye, pancreas, and blood.
**Localisation**
A2M is found in various cellular compartments such as extracellular region, extracellular space, cytosol, platelet alpha granule lumen, collagen-containing extracellular matrix, extracellular exosome, blood microparticle (https://www.ensembl.org/index.html).

**Function**
Human A2M is a homotetrameric plasma glycoprotein consisting of polypeptide chains of 720-kDa and 1451 residues (Doan and Gettins, 2007; Arandjelovic et al., 2007). A2M, the largest known proteinase inhibitor (Mr = 720,000), is present in high concentrations (2-5 μM) in plasma and extravascular areas (Krimbou et al., 2001). A2M was first recognized as a broad-spectrum protease inhibitor and is a pan-proteinase inhibitor that can mechanistically inhibit all proteinases (Arandjelovic et al., 2007; French et al., 2008). In addition, it can strongly but non-covalently and reversibly bind to several growth factors. Proteolytic cleavage of the bait region by bait proteinase leads to major conformational changes, resulting in proteinase compression. The bait region is a stretch consisting of roughly 30 residues located approximately in the middle of the polypeptide chain; it is a flexible region with many residue types giving a broad spectrum of cleavage sites (Doan and Gettins, 2007). It plays an important role in the clearance of proteinases from circulation, regulation of fibrinolysis, coagulation and complement activation (Krimbou et al., 2001). A2M is also known to act as a transport/carrier protein because it also binds to numerous growth factors and specific cytokines (Kim et al., 2018; Wyatt et al., 2014). A2M also transports numerous non-proteolytic proteins including APOE (apolipoprotein E) (Krimbou et al., 2001). A2M interacts with proteinases such as KLK (kallikrein), PLG (plasminogen), MMP2 (matrix metalloproteinase 2), and MMP9 (matrix metalloproteinase 9). In general, A2M is produced by the liver as an acute-phase protein during stress conditions and then secreted into the blood and extracellular environments where it functions. It is also locally produced by macrophages, fibroblasts and epithelial cells (Kim et al., 2018). Being a unique pan-protease inhibitor, A2M is also synthesized and secreted in the brain (Bacskaï et al., 2000). It can induce cell signalling by binding to the LRP1 (LDL receptor related protein 1) and/or other cell surface receptors (Arandjelovic et al., 2006). A tetrameric complex undergoes a conformational change when a bait region is separated by a protease. This both sterically traps the protease and then produces an active form of A2M (A2M*), which is a ligand for LRP1. Methylamine (ammonium derivative) administration causes the exact conformational change and is used experimentally to produce A2M*. LRP1 and LRP8 are the brain receptors for A2M*, which mediate clearance of protease/protease inhibitor complexes (Bacskaï et al., 2000).

**Homology**
The A2M gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, and frog (Table 2).
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Figure 6. The implication of A2M in coagulation and complement systems. A2M can neutralize a massive variety of proteinases (including serine, cysteine-, aspartic-, and metalloproteinases). It acts as an inhibitor of fibrinolysis by inhibiting PLG and KLK, and as a coagulation inhibitor by inhibiting F2 (coagulation factor II/thrombin). Data were taken from KEGG: Kyoto Encyclopedia of Genes and Genomes (https://www.genome.jp/kegg/) in April 2020.

Mutations

The most common type of mutation in the A2M gene is the missense/nonsense mutation, and there are 4 mutations in this category. In addition, 1 small deletion mutation and 1 splicing mutation type are seen. These mutations lead to the clinical manifestation of diseases such as Alzheimer's Disease (AD) (Saunders 2003; Liao 1998; Blacker 1998), Chronic Obstructive Pulmonary Disease (COPD) (Poller 1992), and Autism Spectrum Disorder (ASD) (Sanders 2012) (Table 3).
### Missense/nonsense: 4 mutations

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### Small deletions: 1 mutation

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### Splicing: 1 mutation

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</table>

### Table 3. A2M related mutations.

**Implicated in**

A2M protein has been reported to bind pro-inflammatory cytokines, TNF (tumor necrosis factor) and IL1A (interleukin 1 alpha), which play a central role in the pathogenesis of chronic inflammatory disorders, including Inflammatory Bowel Disease (IBD) and Rheumatoid Arthritis (RA). (Webb et al., 1998).

**Animal Studies**

Umans et al. (1995) created mice lacking the A2M gene, which was viable, more resistant to endotoxins, produced normal litters, and demonstrated normal phenotype (Umans et al., 1995). Webb et al. (1996) showed that murine A2M binds TGFβ1 (tumor growth factor beta 1) and inhibits TGFβ-receptor interactions, suggesting that these results explain the endotoxin-insensitive phenotype of knockout mice (Webb et al., 1996). Zhang et al. (2017) evaluated whether the targeted A2M variants have an improved or similar function to wild-type (wt) A2M to alleviate cartilage degeneration in vivo. They observed that the targeted variants of A2M had a close chondroprotective effect with wt-A2M (Zhang et al., 2017). Cancer resistance is an important reason for the longevity of the naked mole-rat (Kurz et al., 2017). Recent liver transcriptome analysis revealed higher expressions of A2M and other cell adhesion molecules in naked mole-rat compared to wild mice that contribute to cancer resistance (Kurz et al., 2017). It is known that A2M decreases significantly in humans with age. Therefore, it is assumed that this event may facilitate tumor development. Upon this assumption, it was shown that A2M* modulates tumor cell adhesion, migration, and growth by inhibiting tumor-promoting signaling pathways, such as phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT) and small mother against decapentaplegic (SMAD) (Kurz et al., 2017). A2M* upregulates the expressions of tumor suppressor PTEN (phosphatase and tensin homolog), ITGB1 (integrin subunit beta 1), and CD44 but does not evoke epithelial-
mesenchymal-transition (EMT) events (Kurz et al., 2017).

**Prostate Cancer**

Prostate Cancer (PCa) cells produce a high level of differentiation marker for KLK3 (kallikrein related peptidase 3), just like normal prostate epithelial cells (Cumming et al., 2011). KLK3 is widely used as a biomarker to screen for PCa, to detect recurrence following local treatments, and to track response to systemic treatments in metastasis (Cumming et al., 2011; Kostova et al., 2018). Some studies have suggested that KLK3 may play a role in PCa pathology through various mechanisms, including changes in the invasive abilities of the PCa cell, gene expression, and morphology (Kostova et al., 2018). KLK3 has a serine protease chymotrypsin-like enzymatic activity and is a member of the glandular kallikrein family (Ezenwa et al., 2012). It has been shown that A2M and KLK3 can form a complex (Ezenwa et al., 2012; Stephan et al., 2014). A2M is the most abundant protease inhibitor in the blood also inhibiting many protease activities related to fibrinolytic action and inflammatory reactions. (Kanoh et al., 2008; Kanoh et al., 2011; Kanoh et al., 2012). It has also been reported that A2M can inhibit the activity of proteases and thus can inhibit the ability of cancers to infiltrate and metastasize (Kanoh et al., 2008; Kanoh et al., 2011; Kanoh et al., 2012). Compared with other protease inhibitors, KLK3 more easily reacts with A2M than in plasma (Kanoh et al., 2008; Kanoh et al., 2011; Kanoh et al., 2012). Serum KLK3 levels of PCa patients with A2M deficiency were significantly higher than PCa patients without A2M deficiency (Kanoh et al., 2008). The ratios of free KLK3 to total KLK3 (F/T ratios) of PCa patients with A2M deficiency were significantly lower than PCa patients without A2M deficiency. Therefore, patients with advanced PCa appear likely to have multiple bone metastases and increased serum KLK3 with A2M deficiency (Kanoh et al., 2008). On the other hand, serum A2M levels tend to decrease with the progression of PCa. In cases where serum KLK3 levels showed dramatic increases (>2,000 mg/dl), serum A2M levels tended to drop significantly (<20 mg/dl). The decrease in serum A2M levels may be brought about by the reticuloendothelial system rapidly removing many A2M-KLK3 complexes from the blood in PCa patients with extremely high levels of serum KLK3 (Kanoh et al., 2008).

Furthermore, the genetic analysis of one patient with A2M deficiency showed no mutation in the A2M gene. These results suggest that A2M deficiency develops from the A2M catabolism in patients with androgen-dependent advanced PCa and serum A2M levels may be an indicator of disease progression in addition to KLK3 levels (Kanoh et al., 2012).

**Acute Lymphoblastic Leukemia**

Many studies have shown coagulation and/or fibrinolysis abnormalities in approximately 50% of malignant patients and over 90% of those who have developed metastases. (Kwon et al., 2008; Bick, 1992; Luzzatto and Schafer, 1990; Hillen, 2000). The expression levels of A2M associated with fibrinolysis have been shown to increase differently in bone marrow plasma samples of acute lymphoblastic leukemia (ALL) patients (Braoudaki et al., 2013). A2M protein was three-fold upregulated in the serum of B cell-ALL patients, and its level of expression decreased significantly after induction therapy (Cavalcan et al., 2016). However, compared with serum samples from control patients, no significant changes in expression levels of A2M were observed. Therefore, A2M can be considered as a candidate biomarker of B cell-ALL and for evaluation of the response to induction therapy in patients (Cavalcan et al., 2016). A recent study also identified A2M as a candidate biomarker for the diagnosis of B-cell ALL by serum proteomic analysis (Guo et al., 2019).

**Fetal Lung Interstitial Tumor**

Fetal Lung Interstitial Tumor (FLIT) is very rare (Onoda et al., 2014) and an infantile pulmonary lesion that occurs predominantly in newborns (Tanaka et al., 2017). Onoda et al. (2014) characterized a novel chromosomal rearrangement resulting in A2M and ALK (ALK receptor tyrosine kinase) gene fusion in a patient with FLIT (Onoda et al., 2014). The corresponding chimeric gene was subsequently confirmed by sequencing, including the genomic breakpoint between intron 22 and 18 of A2M and ALK, respectively. The Discovery of A2M as a novel ALK fusion partner, together with the involvement of ALK, provides new insights into the pathogenesis of FLIT and suggests the potential for new therapeutic strategies based on ALK inhibitors (Onoda et al., 2014). Tanaka et al. (2017) suggested that these infantile pulmonary lesions containing a chimeric A2M/ALK gene should be categorized as a specific type of inflammatory myofibroblastic tumor that develops only in newborns and infants (Tanaka et al., 2017).

**Alzheimer’s Disease**

Human studies suggest that A2M may have a key role in neuroinflammatory response to AD pathogenesis (Varma et al., 2017). This evidence includes the co-localization of A2M with amyloid plaques and proteomic studies with increased plasma A2M concentration in AD patients compared to controls (Bauer et al., 1991; Thal et al., 1997). AD is characterized by the formation of senile plaques and neurofibrillary nodes in the brain (Selkoe and Hardy, 2016; Yuan et al., 2013). Since A beta is the main component of senile plaques, the genes encoding
proteins implicated in the A beta clearance (LRP1 and A2M) were proposed as risk factors for AD and Sporadic Alzheimer's disease (SAD) (Yuan et al., 2013). A2M is a serum pan-protease inhibitor in AD, based on its ability to mediate clearance and disruption of A beta through the primary neuronal LRP1 for APOE (Blacker et al., 1998; Cater et al., 2019). Due to its roles in APOE and APP (amyloid beta precursor protein) metabolism in the brain, A2M and is considered a risk factor for AD (Zill et al., 2000).

It has been demonstrated that the incidence of A2M GG genotype in AD (8.1%) is more frequent than control groups (3.79%) and that homozygous A2M deletion (A2M DD) did not occur in control groups, but was observed in 5.21% of AD patients (Cacabelos, 2002). According to some studies, the A2M gene has two polymorphisms associated with AD independent from the APOE status (Zill et al., 2000; Poduslo et al., 2002). The first polymorphism that is a 5-base pair (bp) deletion in the 5' splice site of exon 18 resulting in exon skipping was found to be associated with the AD (Zill et al., 2000; Poduslo et al., 2002). The second polymorphism is a G>A point mutation (Zill et al., 2000) in exon 24 that leads to a Valin to Isoleucine exchange (Val1000Ile). It has been suggested that Val1000Ile polymorphism alters protein function as it occurs near the thioester region of the protein (Zill et al., 2000). This polymorphism has been reported to be associated with the late-onset AD form of the homozygous G allele, but other studies have not confirmed these results (Zill et al., 2000; Yuan et al., 2013).

Plasma A2M concentration is significantly associated with cerebrospinal fluid (CSF) markers of neuronal damage, which are total-tau and phosphorylated tau proteins (Seddighi et al., 2018). It has also been found that higher A2M concentration in basal serums of cognitively normal individuals is associated with greater risk of progression to clinical AD in men, indicating a gender-specific change in the inflammatory response in the early stages of AD pathogenesis (Seddighi et al., 2018). A2M gene and protein expressions in the brain were found to be significantly associated with the gene and protein expression levels of CAMK2B (calcium/calmodulin dependent protein kinase II beta), which is a well-characterized tau phosphatase so called calcineurin. By using a system-level approach that combines multiple tissue gene expression datasets with mass spectrometry-based proteomic analysis of brain tissue, the A2M gene network containing a RCAN1 (regulator of calcineurin 1), has been identified (Varma et al., 2017). These findings suggest that A2M is also associated with preclinical AD, reflecting early neuronal damage in the course of the disease and may respond to tau phosphorylation in the brain through RCAN1 and CAMK2B (Varma et al., 2017).

**Parkinson’s disease**

A2M is a component of Lewy bodies (LB), associated with a hallmark of Parkinson's Disease (PD) (Krüger et al., 2000). It has been reported that A2M can regulate proteolytic events in LB formation (Krüger et al., 2000). AG transition (rs669) at codon 1000 near the thioester region and 5 bp deletion (rs3832852) adjacent to the splice site at intron 17 in the A2M gene have been shown to transform the A2M protein structure and alter the protein function (Poller et al., 1992). Given the biological function of A2M in protein accumulation, some studies have investigated the relationships between A2M gene polymorphisms and PD risk (Benitez et al., 2010). Some studies have suggested that rs669 single nucleotide polymorphism (SNP) is associated with an increased risk of PD (Tang et al., 2002; Xiao and Zhang, 2006). However, in some studies, no relation was found between A2M polymorphisms and PD (Nicoletti et al., 2002). In a meta-analysis study investigating the relationship between rs669 and rs3832852 polymorphisms with PD risk, a total of 877 PD patients and 1296 controls from six studies were included (Guo et al., 2016). Odds ratio (OR) showed that rs669 polymorphisms were probably associated with increased PD risk only in dominant genetic models (OR = 1.41, CI = 1.03-1.92), especially in the Asian subgroup (OR = 1.97, CI = 1.03-3.75). Krüger et al. (2000) conducted a genetic study in a large sample of 328 German PD patients and 322 closely matched healthy controls (Krüger et al., 2000). By analyzing Val1000Ile polymorphism and a 5 bp deletion in the 5’ splice region of exon 18, they observed excess of homozygosity for the A2M deletion in early-onset PD patients (age at onset 50 years) (Krüger et al., 2000).

**Hepatic Fibrosis**

A2M is a well-known biomarker of hepatic fibrosis (HF) (Naveau et al., 1994; Calès et al., 2005; Ho et al., 2010). In the inflammatory or injured liver, increased A2M inhibits the catabolism of matrix proteins and thus causes HF (Tiggelman et al., 1996; Ho et al., 2010). While A2M binds to fibrinolytic enzymes, it cleaves at its thioester region (Rehman et al., 2013). The thioester cleavage may increase with HF development. Compared to healthy control serum, the thioester cleaved C-terminal end of A2M was found to change by more than two-fold in percentage spot volume only in cirrhotic serum analysed by 2D gel electrophoresis. The thioester-cleaved N-terminal end of A2M changed by more than two-fold mostly in cirrhotic serum and with fewer glycoforms in the serum of moderate HF patients. Uncleaved A2M was differentially expressed in all stages of HF. However further analysis of the thioester cleavage products may give
Osteonecrosis of Femoral Head

Diagnosis of Osteonecrosis of Femoral Head (ONFH) is complex due to the lack of reliable serum biomarkers (Ghale-Noie et al., 2018). The upregulation of the A2M gene has been reported in the glucocorticoid (GC)-induced ONFH rat model (Ghale-Noie et al., 2018). It has been suggested that A2M serum level is suitable as an indicative biomarker for glucocorticoid GC-induced ONFH in rodents and A2M may play a role in host repair response to GC-related effects (Carli et al., 2017).

According to Fang et al. (2019), A2M can be associated with steroid-induced necrosis of femoral head (SINFH) (Fang et al., 2019). Multiple pathological reactions occurring in SINFH and A2M can serve as a potential biomarker for SINFH diagnosis or a promising therapeutic target (Fang et al., 2019). The ONFH presumably directly or indirectly elevates A2M in the bloodstream. Therefore, the serum level of A2M might be used as a reliable diagnostic tool in clinical practice (Ghale-Noie et al., 2018).

Rheumatoid Arthritis

Inflammation is important in the pathogenesis of arthritis (Li et al., 2019). Early administration of intra-articular A2M may provide chondral protection in RA by reducing the presence of local catabolic proteases and inflammation levels (Li et al., 2019). The intra-articular A2M administration induced an anti-inflammatory response and slowed cartilage damage and bone resorption, suggesting that supplemental A2M may be a novel therapy for arthritis (Li et al., 2019). In a study where potential serum biomarkers for RA were determined by high resolution quantitative proteomic analysis, A2M protein was observed to be downregulated (Cheng et al., 2014). In the hospital-based case-control study conducted on the South Asian (134 RA cases, 149 controls) and Caucasian (137 RA cases, 150 controls) populations, the 5 bp deletion polymorphism of the A2M gene was examined (Ghelani et al., 2011). It was reported that the A2M locus shows an ethnically specific variation and maybe a useful marker for RA (Ghelani et al., 2011). A2M can inhibit the MMPs (matrix metalloproteinases), which are elevated in many chronic inflammatory diseases such as RA, and is considered as a potential inflammatory biomarker of MMP activity and RA (Wedekind et al., 2017).

Osteoarthritis

Osteoarthritis (OA) is an age-related and chronic degenerative disease that is characterized by the degradation of the extracellular matrix (ECM) of chondrocytes (Liu et al., 2019). It has been shown that A2M levels are lower in synovial fluid from patients with OA, and additional A2M injection reduces the progression of post-traumatic OA in rats (Wang et al., 2014). Synovial fluids of OA patients do not include the A2M levels required to inactivate the high concentrations of catabolic factors and the additional intraarticular A2M provides chondral protection in post-traumatic OA. Increasing evidence in this context showed that A2M is the most effective factor for cartilage protection as an active anti-inflammatory component of the platelet-rich plasma (PRP) injections (Orhurhu et al., 2020).

Chronic Obstructive Pulmonary Disease

A2M is speculated to play a role in regulating protease activity in the lung (Poller et al., 1989). The most common variation of the A2M gene is 5 bp deletion (Dimov and Vlaykova, 2010). Though rare, hereditary A2M deficiency has been associated with 20-30 times higher risk of COPD (Dimov and Vlaykova, 2010). The increased plasma concentrations of A2M was detected in smoking and non-smoking patients with COPD (96 individuals) compared to healthy controls (33 individuals) (Arellano-Orden et al., 2017). It was recently determined that the interactions of MiR-122-5p-A2M-LINC00987 / A2M-AS1 / linc0061 networks may play a key role in COPD irrespective of the smoking status. Moreover, A2M was suggested as a potential biomarker of COPD (Qian et al., 2018).

Inflammatory Bowel Disease

IBD comprises a group of disorders characterized by chronic intestinal inflammation with the main phenotypes being Crohn’s Disease (CD) and Ulcerative Colitis (UC) (Hansen et al., 2012). Proteases and protease inhibitors have considerable implications in IBD because of their contributions to the mucosal barrier function of the gut (Cleynen et al., 2011). The systematic review study presented the A2M as one of the top genes implicated in UC (Cleynen et al., 2011). It was observed that serum A2M protein amount decreased by 0.5-fold in IBD patients compared to non-IBD controls (Knutson et al., 2013). Recently, the divergent plasma concentrations of A2M protein have been identified in both subtypes (CD and UC) of IBD compared to controls (Di Narzo et al., 2019). In another study, 7668 peptides were analyzed to distinguish between stricturing CD and non-stricturing CD, in which only 16 peptides including A2M were found to be involved (Townsend et al., 2015).

Autism Spectrum Disorder

Previously whole-exome sequencing of 928 individuals, including 200 phenotypically discordant sibling pairs, revealed highly disruptive de novo mutations in brain-expressed genes associated with ASD (Sanders et al., 2012). A2M gene was proposed
as a risk factor with damaging severity score for transcript variant I (NM_000014) ASD (Sanders et al., 2012). A relationship between transposable element content and autism-risk genes including the A2M gene has also been shown (Williams et al., 2013). Moreover, the subjects with ASD exhibited a significantly higher expression level of the A2M (Cortelazzo et al., 2016; Abraham et al., 2019). Furthermore, A2M was associated with complement and coagulation cascades, indicating that these systems may be involved in the pathogenesis of ASD (Shen et al., 2019).

References


Bacskai BJ, Xia MQ, Strickland DK, Rebeck GW, Hyman BT. The endocytic receptor protein LRP also mediates neuronal calcium signaling via N-methyl-D-aspartate receptors Proc Natl Acad Sci U S A 2000 Oct 10;97(21):11151-6


Dimov D, Vlaykova T. Genetic factors in COPD: special attention on candidate genes encoding proteases/antiproteases and inflammatory mediators Trakia J Sciences 2010;8 Suppl 2:192-204 ISSN 1313-7050

Doan N, Gettins PG. Human alpha2-macroglobulin is composed of multiple domains, as predicted by homology with complement component C3 Biochem J 2007 Oct 1;407(1):23-30

Ezenwa EV, Tijani KH, Jeje EA, Soriyani OO, Ogunjimi MA, Ojewola RW, Ajei OA, Elnahas AR. The value of percentage free prostate specific antigen (PSA) in the detection of prostate cancer among patients with intermediate levels of total PSA (4 0-10.0 ng/ml) in Nigeria


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Qian Y, Mao ZD, Shi YJ, Liu ZG, Cao Q, Zhang Q. Comprehensive Analysis of mRNA-mRNA-IncRNA Networks in Non-Smoking and Smoking Patients with Chronic Obstructive Pulmonary Disease Cell Physiol Biochem 2018;50(3):1140-1153

Rehman AA, Ahsan H, Khan FH. α-2-Macroglobulin: a physiological guardian J Cell Physiol 2013 Aug;228(8):1665-75


Thal DR, Schober R, Birkenmeier G. The subunits of alpha2-macroglobulin receptor/low density lipoprotein receptor-related protein, native and transformed alpha2-macroglobulin and interleukin 6 in Alzheimer’s disease Brain Res 1997 Nov 28;777(1-2):223-7

Tiggesman AM, Boers W, Moorman AF, de Boer PA, Van der Loos CM, Rotmans JP, Chumleau RA. Localization of alpha 2-macroglobulin protein and messenger RNA in rat liver fibrosis: evidence for the synthesis of alpha 2-macroglobulin within Schistosoma mansoni egg granulomas Hepatology 1996 May;23(5):1260-7


Webb DJ, Wen J, Lysiak JJ, Umans L, Van Leuven F, Gonias SL. Murine alpha-macroglobulins demonstrate divergent activities as neutralizers of transforming growth factor-beta and as inducers of nitric oxide synthesis A possible mechanism for the endotoxin insensitivity of the alpha2-macroglobulin gene knock-out mouse J Biol Chem


A2M (alpha-2-macroglobulin)