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## Insilico Analysis of Alpha-1 Antitrypsin Pathway in Ischemic Stroke Patients

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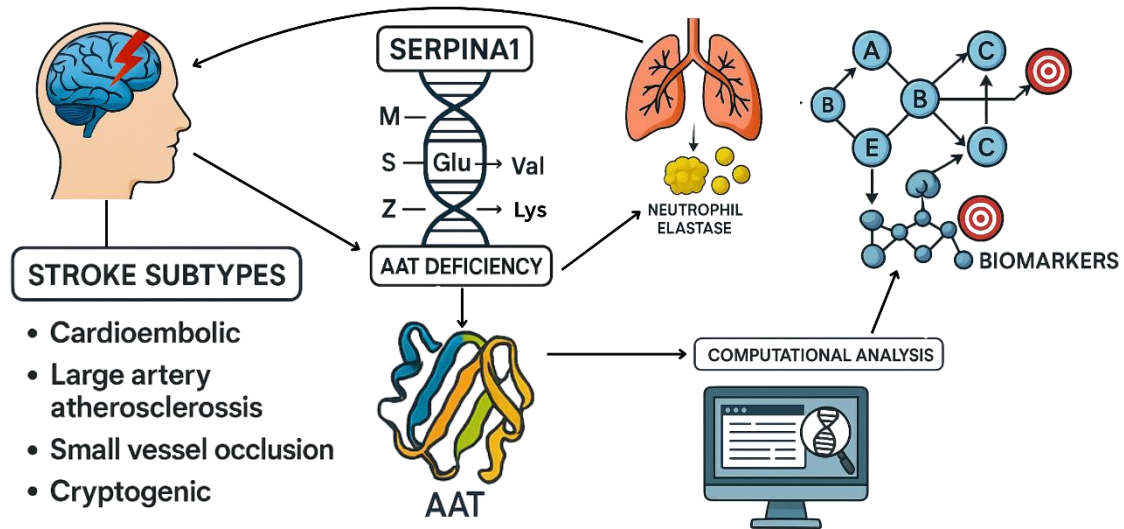
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### Abstract

Ischemic stroke is related to the low oxygen supply to the brain cells. It is subdivided into cardioembolic stroke, large artery atherosclerosis stroke, small vessel occlusion and cryptogenic stroke. Its development is correlated to the genetic variations of the SERPINA1 gene that produces variants such as Z-allele variant where glutamic acid is replaced with lysine, S-allele variant where glutamic is replaced by valine and the normal M-allele variant which leads to the synthesis of less amount of AAT coupled with its deficiency and lowering of AAT activity against the neutrophil elastase that degrades elastin in the lung tissue reducing the permeation of oxygen to the blood stream. In this study, various computational tools such as Heartbio portal, genotype-tissue expression platforms have been employed to retrieve data that relate to the stroke. The pathways in which SERPINA1 participates are identified and the genes involved in them with a regulation activity relating to the stroke were analyzed. The identified genes can be applied as biomarkers to trace the potential development of the stroke in patients with cardiovascular diseases, diabetes, obesity and others. Additionally, the genes can be employed in the therapeutical treatments of the stroke patients.

**Keywords:** SERPINA1, Alpha-1 Antitrypsin, Cardioembolism, large artery atherosclerosis, Alpha-1 Antitrypsin Deficiency.

## Graphical Abstract



## 1. Introduction

An ischemic stroke involves a blockage in blood flow in human brain. If blood flow doesn't return quickly enough, an ischemic stroke will cause permanent brain damage or even cause death.

The blockage of blood flow is raised by a blood clot or a piece of fatty plaque which is broken off from the inside of a blood vessel. Ischemic stroke may have symptoms like drooping muscles on one side of the face, numbness on one side of the face or in one arm or leg, weakness or paralysis in one arm, leg, or side of the body, loss of sensation and abnormal sensations on one side of the body and also neck stiffness. Ischemic stroke can be caused by atherosclerosis, clotting disorders, atrial fibrillation, high cholesterol (hyperlipidemia), Type2 diabetes and also microvascular ischemic disease. Medications and treatments used for ischemic stroke are thrombolytic drugs, endovascular mechanical thrombectomy, stroke rehabilitation.

### 1.1 Sub types of ischemic strokes

Ischemic stroke is subdivided into four categories as [2]:

**Large artery atherosclerosis:** This describes the progressive building of plaque in the largest artery of body (aorta). This occurs in the neck and the head region responsible for approximately 15% of ischemic stroke. Plaque is a sticky substance made up of cholesterol, fat, calcium and other material caused by factors such as smoking, unhealthy diet, or genetic predisposition. Patients with high blood pressure, high cholesterol level, high fat content, obesity, diabetes and

some forms of inflammation are subjective to large artery atherosclerosis while the factor of genetic predisposition describes the tendency of physical or mental cords or disorder to be able to be inherited by the next generation resulting from specific genetic variations that are often inherited from a parent.

**Cardioembolism:** This involves blood clot in the brain that occurs when the heart pumps rejected materials such as cell tissue debris, blood clot the brain where they get stuck causing the blockage of blood vessels making approximately 30% of ischemic stroke. The main factors such as fragments of calcifications that grow due to small deposits of calcium in the tissues, tumor tissue where by the tissue cells divide abnormally leading to blockage of the blood vessel or decrease in the diameter of blood vessels, tumors can be benign or malignant.

**Small vessel occlusion:** This subcortical stroke is caused by the blockage or leaking of a small, deeply located branch of a large artery in the brain, initially due to high blood pressure. This results into movement and /or sensation difficulties in some sides of body. With eventual deprivation of oxygen supply and nutrients to the brain, the brain cells will die off.

**Cryptogenic stroke:** This kind of stroke is further divided into two: stroke with determined etiology and stroke with undetermined etiology. It is a stroke that is identified as cerebral stroke of obscure or unknown origin. The main cause of this stroke is not quantifiable neither is identifiable and it contributes to around 25 – 40% of all ischemic strokes. It can be symptomized by body weakness or paralysis on one side, dizziness, speaking difficulties and also confusion.

### *1.2 Alpha-1 antitrypsin role in ischemic stroke*

Alpha-1 antitrypsin (AAT) is a protein belonging to the serpin superfamily encoded by the SERPINA1 gene in human, located on the long arm of chromosome 14 (14q32.1). Alpha-1 antitrypsin is produced in the liver and then it is transported throughout the body through the blood <sup>[18]</sup>.

AAT inhibits the enzyme neutrophil elastase which is released from white blood cells to fight infections providing protection to the lung tissue from neutrophil elastase which could cause damage lung tissue if not regulated through its digestive activity of the elastin found in the alveolar region of the lungs. Regulation of neutrophil elastase activity is critical to main tissue homeostasis and preventing tissue damage <sup>[18]</sup>.

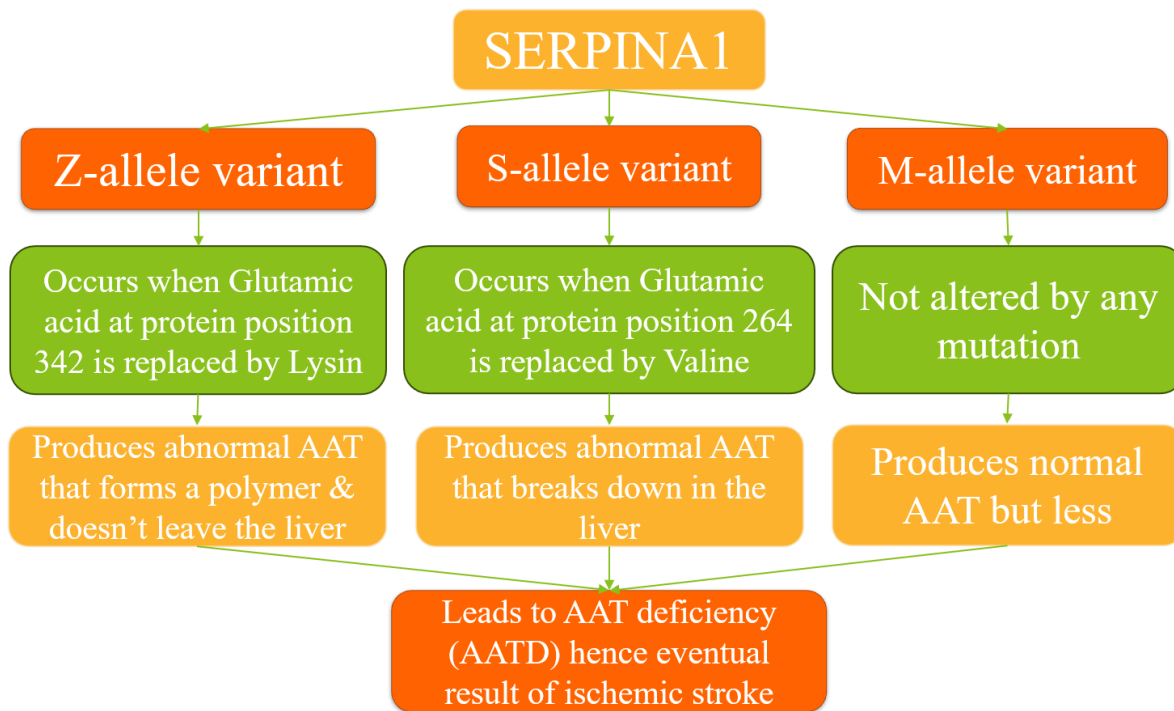


Figure 1 showing the three different variants of SERPINA1 which all contribute to AAT deficiency and hence to the development of stroke.

Mutations in the SERPINA1 gene are associated with alpha-1 antitrypsin deficiency, which is a genetic disorder distinguished by low levels of alpha-1 antitrypsin in the blood <sup>[22]</sup>. This protein also functions as a part of innate antiviral immunity. Any Defects in this gene can cause the deficiency of plasminogen activator inhibitor-1 (PAI-1 deficiency), and high concentrations of this gene product are connected with thrombophilia.

More than 100 variants of SERPINA gene have been connected with a condition, Alpha 1 Antitrypsin deficiency. AAT deficiency results in the development of lung diseases such as Emphysema, Chronic Obstructive Pulmonary Disease (COPD), Bronchiectasis and it can also predispose individual to liver diseases like Liver cirrhosis, Liver failure. Diagnosis of AAT deficiency involves blood tests to measure the levels of AAT and identifying any genetic mutations in the SERPINA1 gene <sup>[18]</sup>.

### 1.3 Literature review

Ischemic stroke occurs when the blood supply to the part of the brain is blocked or reduced, this will cut down the supply of oxygen and nutrients supply to the brain which will leads to the

brain death, ischemic stroke is caused by the blocked artery in the brain where the blood vessel is narrowed or blocked which will reduce the blood flow.

Zhang et al. found out that ischemic stroke is a heterogeneous condition influenced by a combination of genetic and environmental factors. Ischemic stroke involves two critical stages including the disruption of cerebral blood supply, and the subsequent development of cerebral tissue hypoxia and necrosis [28].

Ilaria et al. found out that low alpha 1 antitrypsin serum level, resulting from variations in SERPINA1 causes alpha-1 antitrypsin deficiency (AATD), the most frequently found variants in AATD, with the Z variant present in most individuals diagnosed with AATD. However, there are many other less frequent variants known to contribute to lung and/or liver disease in AATD [3].

During the absence of AAT, there is an imbalance of proteinases and anti-proteinases, which leads to the progression of emphysema and deterioration of lung function, resulting in chronic obstructive pulmonary disease. These events start with the loss of electrical function and progresses to disturbance of membrane function with calcium influx leading to calcium-dependent excitotoxicity, generation of reactive oxygen species.

## 2. Methodology and tools used

### 2.1 Materials

The materials that were required for retrieval of datasets about the stroke included alpha-1 antitrypsin protein sequence as well as Serpina1 gene sequence.

### 2.2 Tools used

**PDB:** The Protein data Bank provides three-dimensional data about proteins such as their three-dimensional structures for large biological molecules like proteins and nucleic acids. The information/data uploaded to the database is first verified authentic scientifically and mostly obtained from experiments using methods such as X-ray crystallography, Nuclear Magnetic Resonance (NMR) spectroscopy, cryo-electron microscopy and others. The database is accessed through its website <http://www.rcsb.org/> and all data can be accessed by use of keywords or accession numbers through search or advanced search options.

**GenBank Database:** This is a DNA database that provides open access to annotated collection of all publicly available nucleotide sequences and their protein translations on the GenBank result page. It provides all information about genes and their proteins which can be accessed through use of keywords especially gene names. GenBank is accessed through its website address <http://www.ncbi.nlm.nih.gov/genbank> .

**GTEX:** Genotype-Tissue Expression provides all kind of information about the gene expression in various tissues, sex of people, gender, and also age brackets to provide the activity track of the gene activity and any of the genetic variations can be studied and determined. It also exploits the use of WGS, WES and RNAseq methods for the obtaining of molecular data of the genes. The database can be accessed through its website address <https://www.gtexportal.org/>

**UniProt:** The Universal Protein database (UniProt) is a freely accessible protein database that provides the protein sequence, function and others derived from the genome sequencing projects. The database can also be accessed through <https://www.uniprot.org/>

**PathCards:** This database is found under the collection of Pathway Unification database. It is an integrated database of human biological pathways and their annotations. It can be accessed through the website address <https://pathcards.genecards.org/> using the names of the genes inserted into the search option provided.

**Heartbio Portal:** The portal employs limma to determine genes that are expressed differently across experimental conditions and variants found in known protein product correlated with various phenotypes. The database is accessed through its website address <https://www.heartbio.portal.com/> and results are retrieved with use of a keyword search.

### 2.3 Methods and protocol

**UniProt:** The website is accessed through its address and the name of the protein – Alpha-1 antitrypsin – was used to retrieve the details of AAT.

**PDB:** The protein structural data for the ATT derived from *Homo sapiens* using X-ray crystallography was observed and analyzed.

**GenBank:** The data about the SERPINA1 gene was obtained for *Homo sapiens* species, retrieved and analyzed.

**GTEX:** The gene expression in bulk and single tissue was observed and analyzed using the Expression PCA (Principal Component Analysis).

**PathCards:** The genes pathways were identified and used to obtain information in the Heartbio portal.

**Heartbio Portal:** The datasets from this portal were retrieved through use of the genes' names from the pathways in PathCards. The genetic association datasets, differential expression of genes in relation the stroke and genetic variants were studied and analyzed.

### 3. Results



Figure 2 represents the three-dimensional structure of the alpha-1 antitrypsin protein. The protein consists of only one chain. On the right-side, protein AAT structure is visualized in PvMol with a retrieval code as 1HP7.

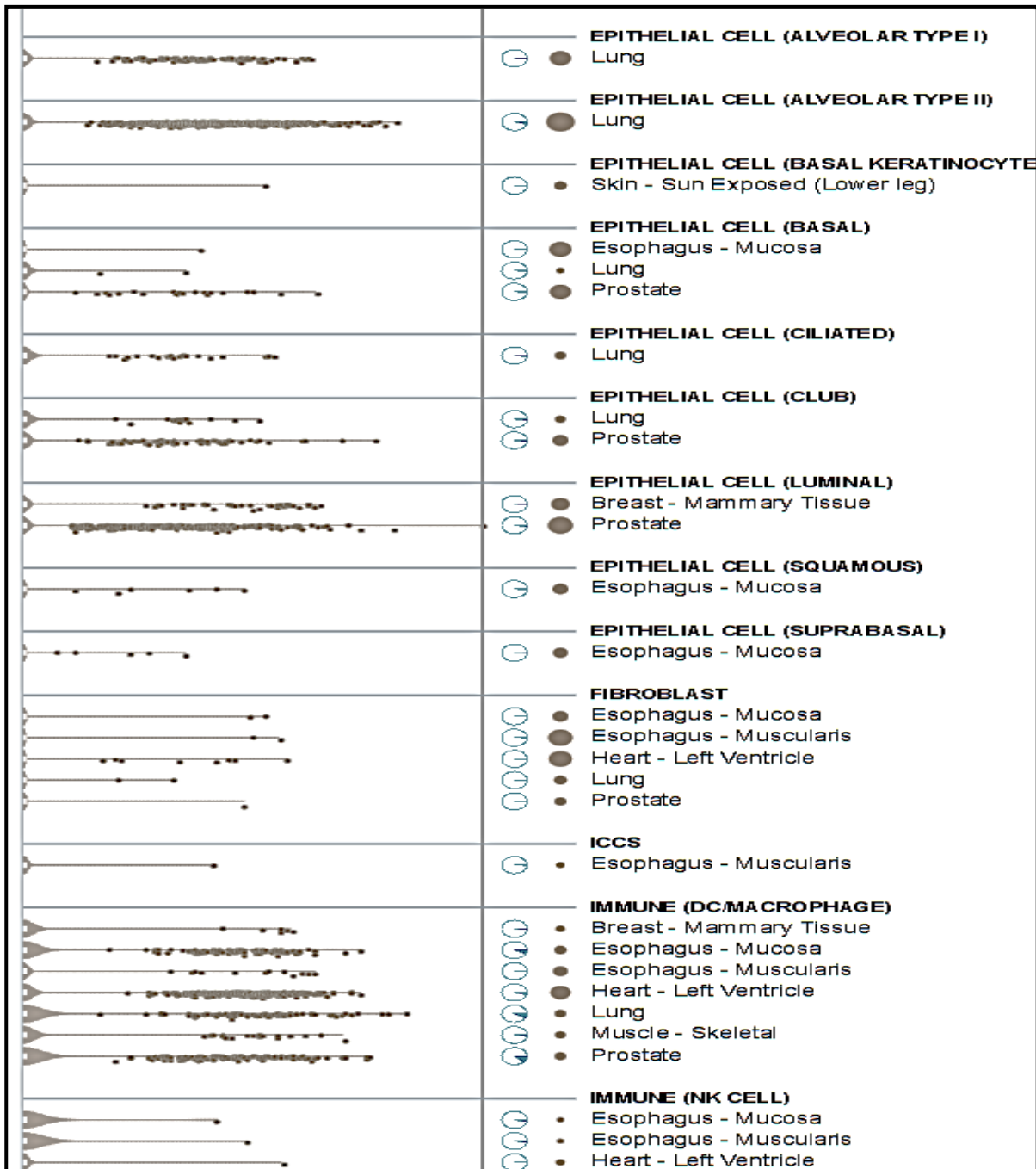


Figure 3 depicts the expression of the serpinal gene in single tissue. It can be observed that bars corresponding to epithelial cell (alveolar region) around lungs and also in Dendritic cells (DC) / macrophages of the immune system due to the immune participation of the protein product (AAT) of the serpinal gene.

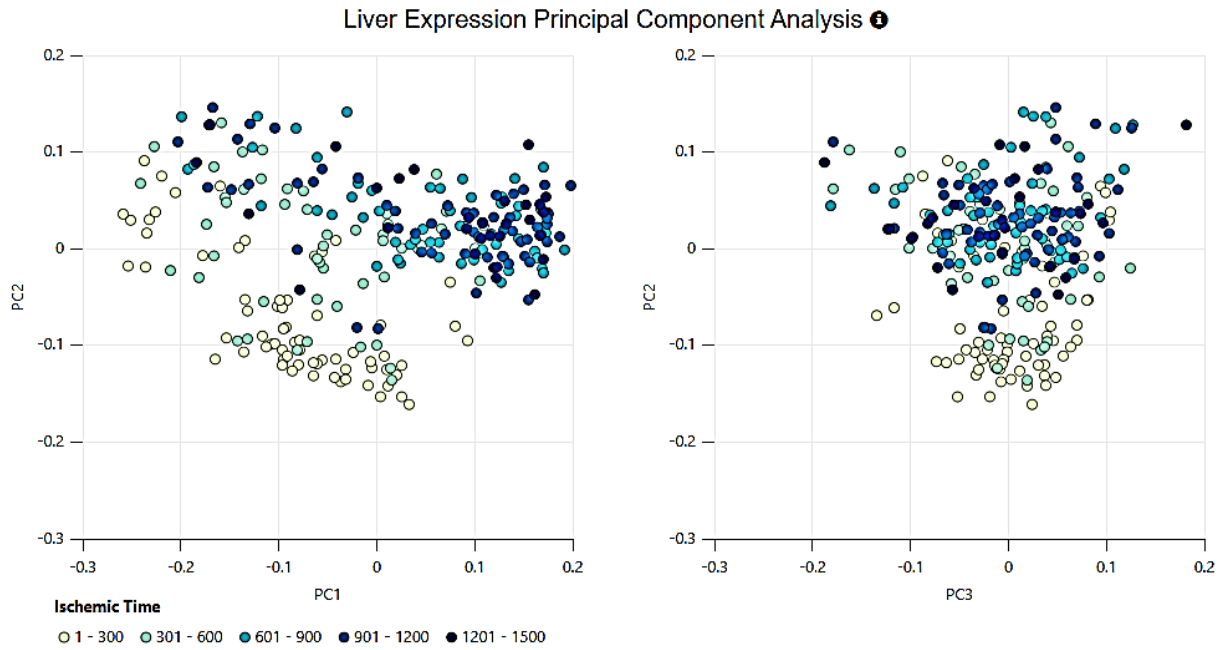


Figure 4 showing the expression of serpinA1 during ischemic time.

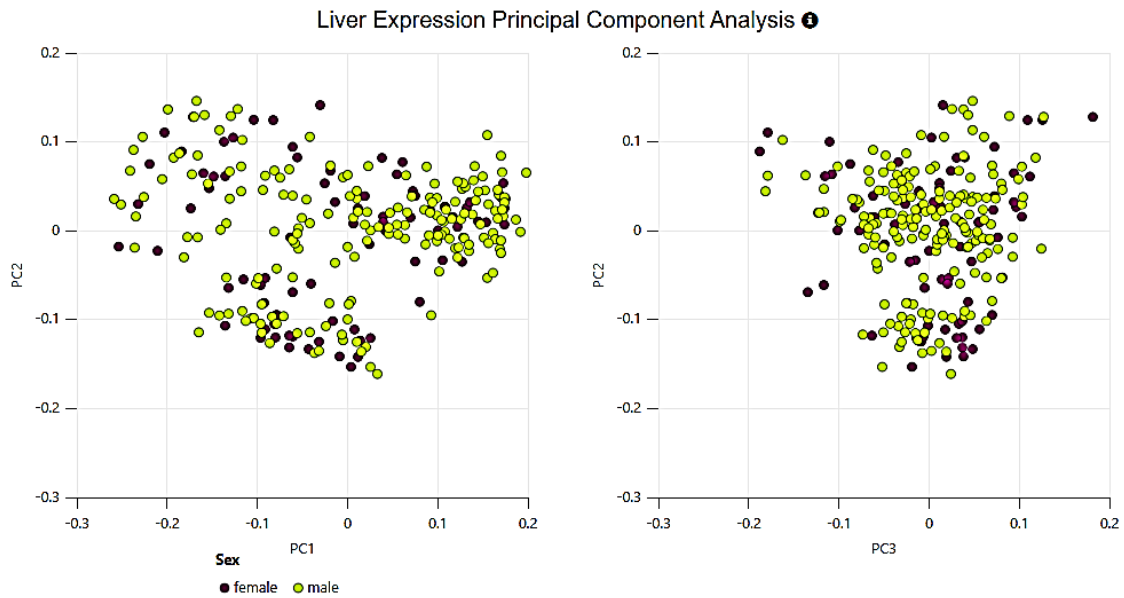


Figure 5 showing the expression of serpinA1 during ischemic time for male and female.

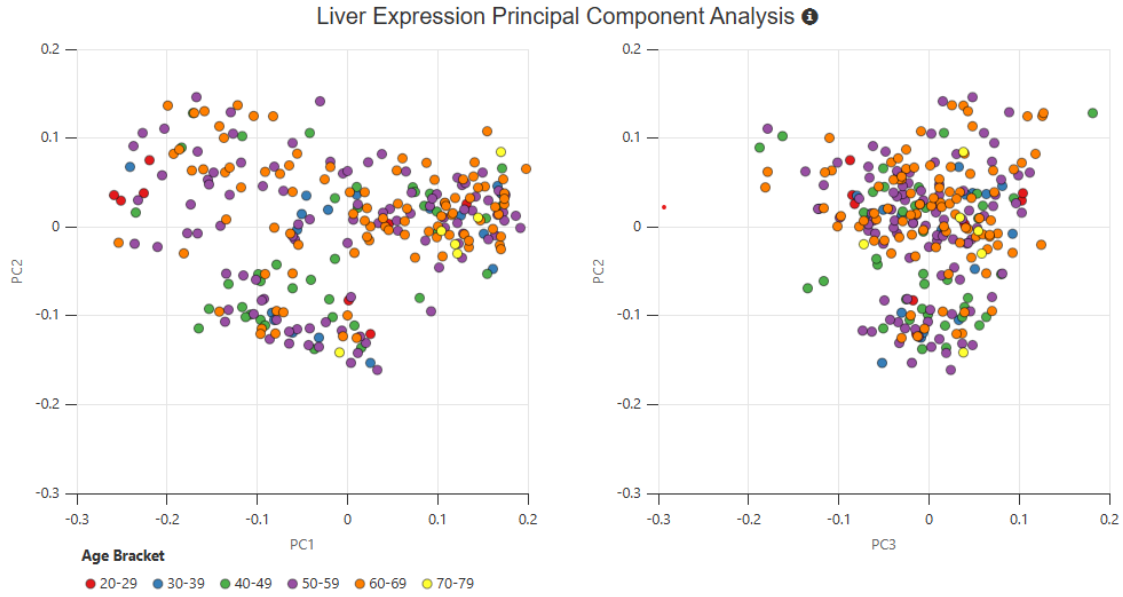


Figure 6 showing the expression of *serpina1* during ischemic time for different age brackets.

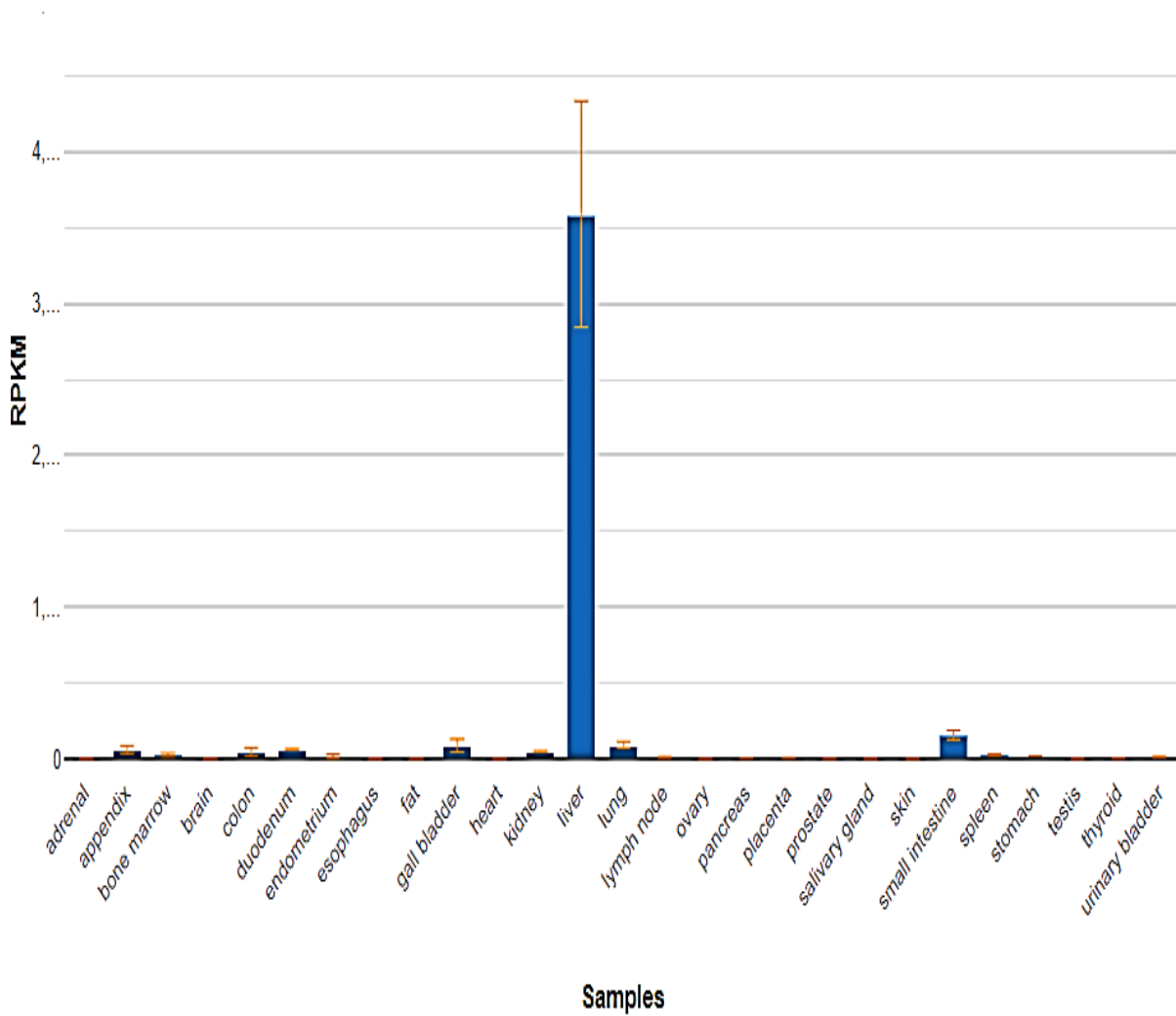


Figure 7 represent the graphical statistics data of the serpina1 gene expression in various tissues and organs. The liver happens to have the high gene expression of the serpina1 and this explains why AAT is synthesized in the liver cells and transported to the bloodstream by golgi transport pathway.

From the PathCards database, thirteen (13) pathways were identified related to ischemic stroke and AAT activity as discussed below.

#### 4. Discussion

Lung fibrosis pathway. The regenerative process following the damage of epithelial cells of the lung tissue especially at the alveolar region can lead to conditions known as pulmonary fibrosis [27]. These are usually induced by environmental and smoking-related activities. The process of replacing the damaged cells in order to maintain a barrier function and integrity as well as prevent blood loss involving clotting factors under a clotting cascade such as thrombin. With repeated cycles of damage and repair, there is development of chronic inflammation due to the neutrophilic response since neutrophil elastase promotes pro-MMP9 and inhibits the TIMP1 hence disrupting the balancing of protease and antiprotease equilibrium. The occurrence of lung fibrosis is due to increased and over-activation of parenchymal cells that act to elucidate wound healing, but eventually form excessive matrix at the alveolar region distorting the lung tissue architecture.

The genes such as Family with sequence 13 member A (FAM13A) gene that participates in cell proliferation due to its isoforms down-regulated by the Interleukin-1 Beta (IL-1B) and transforming growth factor (TGF-B1) where it is involved in the regulation of mesenchymal transition. The CEBPB gene expressed in parenchymal and mesenchymal cells has a transcriptional role to regulate between anti-inflammatory and pro-inflammatory signals during tissue repair, through the regulation of extracellular matrix degradation [15]. The CC chemokines such as eosinophil chemotactic factor CCL11 that binds to its cognate receptors CCR3 highly expressed in eosinophils and neutrophils have been associated with progressive pulmonary infiltration [8]. Similarly, CCR2 expression correlates with the increased fibrosis since its attenuation exhibits reduced fibrosis [20].

Embryonic and induced pluripotent stem cells and lineage-markers pathway. In this pathway, genes such as Activating Transcription Factor 2 (ATF2) which is a cAMP-dependent factor can translocate to the cytosol due to exposure to genotoxic stress thus impairing with mitochondrial-based cells leading to their death especially due to hypoxic stress [12]. The activity of ATF2 is regulated by the SOX family that includes SOX9, SOX1, SOX5 and others. The oncogenic LIM-Only transcription factor 2 (LMO2) expression in T-cells especially those still immature leads to the initiation of leukemia by providing self-renewal property through which the reactivation of hematopoietic stem cells-specific gene (García-Ramírez, Idoia et al., 2018), reducing the number of oxygen-carrying cells (red blood cells), white blood cells and/or platelets eventually decreasing the oxygen supply to body tissues [4].

On the other hand, LIMO4 has a regulation activity of lung epithelial cells proliferation especially in adults, however, it should be regulated also as it might contribute to cancer development [25]. GATA2 enhances the endothelial-to-hematopoietic transition (EHT) and also generation of hematopoietic stem cells (HSCs), therefore acting as a regulator of normal and leukemia cells [29]. CXCR4 encodes the receptor proteins that bind with ligands to stimulate multiple signaling pathways that elucidate hematopoiesis [19]. The receptor disrupts the blood-brain barrier and its down regulation inhibits brain metastasis formation. Hepatocyte nuclear

factor 1-beta (HNF-1B) provides instructions for the formation and development of the kidney, pancreas and liver of an embryo <sup>[26]</sup>. Any implications relating to liver's failure to produce normal AAT may have relation to HNF-1B expression.

P73 transcription factor network pathway involves a number of genes that coordinate with p73 to regulate its activity. It is a complex network that involves regulation of cellular activities/processes such as cell cycle arrest, damaged cells. The genes interacting with p73 have, among other functions, signaling duties, cell cycle regulation and therefore when the cell growth is not controlled to normal extent, there might develop cancer. Genes like HSF1 act to protect brain cells through promoting expression of heat shock proteins that safeguard the cell against stress-induced damage while RELA contributes to the regulation of inflammation in the brain regions which also promote cell survival, unlike genes such as BAK1, BAX and others that participate in cell's apoptosis <sup>[1],[7],[24]</sup>.

Nuclear receptors meta-pathway includes proteins that regulate expression of genes, usually activated by specific molecules such as hormones, lipids and xenobiotics binding. These are so important for cell development and differentiation <sup>[21]</sup>. The ALAS1 gene responsible for heme synthesis an essential molecule for oxygen transport in red blood cells and therefore low level of heme molecule correlates to low levels of oxygen supply to tissues, and if this happens in the brain region, ischemic stroke can be induced <sup>[10]</sup>. APOA gene family also has an indirect regulation of the risk of stroke due to their role in metabolism of triglycerides including cholesterol. Mutations in these genes such as APOA5, APOA2 can result to increased cholesterol levels which hinder vascular transport of blood and oxygen <sup>[16]</sup>.

Diseases of hemostasis pathway involves the genes whose expression can regulate hemostasis diseases occurrences that can increase the risk of stroke through affecting the blood clotting process. When the blood vessel gets injured, and there is a rapid formation of blood clots due to inherited or acquired factors, the clots may potentially block blood vessels leading to reduced blood flow towards the brain and consequential low oxygen supply hence stroke occurrence. Additionally, disorders/diseases like sickle cell disease and thrombocytosis may lead to abnormal functioning of platelets that block the cerebral arteries spearheading stroke outbreak <sup>[6]</sup>.

(Coat Protein complex II) COPII-mediated vesicle pathway as well as transport to the golgi and subsequent modification pathway are not directly connected to the stroke, however, the proteins of genes such as Sec24, Sec23 are involved in protein trafficking from the production cell to the target cells – in this case alpha-1 antitrypsin is formed in the liver and transported to the bloodstream <sup>[9]</sup>. Common issues that might happen during transport of the proteins such as protein unfolding that may lead to loss of function due to post translational modifications, impaired targeting of protein that helps it to be easily recognized, blockage of transport vesicles due to mutations in vesicle-forming proteins, can contribute to the dysfunction of the protein <sup>[5]</sup>.

Response to elevated platelet cytosolic  $\text{Ca}^{2+}$  pathway exhibits the role of increased platelet cytosolic  $\text{Ca}^{2+}$  in activation of clotting process whereby platelets undergo shape change releasing clotting factors, then clump together to form an aggregate that prevents bleeding [23]. When the abnormal blood clot is formed within the vessels supplying the brain, they tend to block those arteries leading to a decrease in blood flow as well as reduced oxygen supply leading to increased potentiality of ischemic stroke occurrence.

Insulin-like growth factors (IGFs) and their binding proteins are essential in the regulation of the cell survival, growth, and also differentiation of cells providing neuroprotection since the IGFBPs bind to IGFs to influence their transport through the body to the target tissue [14]. The decrease in levels of IGFs and signaling might lead to death of neural cells and brain tissue damage that may result into stroke.

Neutrophil degranulation pathway describes the process in which neutrophils release granules containing various substances. Among the granules, are the azurophil granules that contain the neutrophil elastase enzyme, and their release leads to sub sequential discharge of the enzymes into the bloodstream [12]. The enzymes digest the elastin of the lung tissue decreasing the permeability of oxygen leading to less oxygen supply to body cells, and in particular to the brain cells which in the due course may die contributing to the stroke.

## **5. Conclusion**

The ischemic stroke occurs when blood clot blocks the blood flow to the parts of the brain leading to cell death and tissue damage. The genes involved in inflammation, cell death and tissue repair regulate the stroke either upwards or downwards.

These genes might be either involved in promoting cell survival due to low levels by limiting brain tissue damage influence genes that are involved in repairing damaged brain tissue and formation of new neurons to express themselves. They also may be involved in anti-inflammatory processes that induce stroke-based inflammation.

The variations that happen in the SERPINA1 gene lead to the formation of less normal and more abnormal alpha-1 antitrypsin which leads to deficiency of the protein that eventually results in the increased activity of the neutrophil elastase on the elastin of lung tissues making the permeation of oxygen to bloodstream reduced, and eventually stroke outcome.

The studies indicate that people who have relatives with a background of stroke are susceptible to develop the stroke and therefore, their continuous health checkup about the stroke traits is highly advisable.

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NONE

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