

# Schizophrenia

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Schizophrenia is an extreme mental disease that is hereditary. Schizophrenia arises from an individual's DNA and goes on to affect a family for generations. Approximately 2 million Americans have been affected in some way by the presence of Schizophrenia. Understanding schizophrenia is very important to the development of new drugs and treatment options. Studies have shown a mutation in neuronal PAS domain protein 3, a dysregulated expression in focal adhesion kinase (FAK) and a mutation in two endocannabinoid receptors are some of the causes of schizophrenia. New innovative research involving stem cells and neuroproteomics are now developing in the study of schizophrenia. Further research on schizophrenia can give a better understanding on the molecular level at what is going on in the brain. Research will also allow for more effective drug therapy with fewer side effects.

Schizophrenia is developed in the brain. The neurons in schizophrenic patients make fewer connections than neurons found in healthy patients. One gene that has recently been found to cause schizophrenia is neuronal PAS domain protein 3 (NPAS3)(Yu). A mutation in NPAS3 causes the gene to function improperly and severely affect brain development (Macintyre). The NPAS3 mutations were studied in a family that had a long history of mental disorders. The NPAS3 controls the information that is translated from DNA to messenger RNA which allows

for healthy neurons in the brain to consistently develop. Two experiments were completed to better understand where the NPAS3 mutation occurs and what the mutation does to change the function of the protein (Yu).

Experimental methods to find the mutation consisted of polymerase chain reaction (PCR) and capillary electrophoresis. The mutation happens when the DNA base pair is changed from G to A, this in turn changes the amino acid from valine to isoleucine (NPAS3-V304I). The mutation was discovered on exon 8 at base pair 910. The second experiment was done to understand what effect the mutation had on the protein. Green fluorescent proteins (GFP) were used on NPAS3 and NPAS3-V304I to identify the affected of the mutation through western blotting. Using mice as subjects, constructs that had the GFP were placed invitro and then cells from the mice were assayed for neurite outgrowth. The end result showed a significant decrease of neurite outgrowth in the mice that had the mutated NPAS3(Yu).

Patients with schizophrenia have demonstrated dysregulated expression of gene in focal adhesion kinase (FAK) signaling. To better understand the signaling of FAK, male patients with schizophrenia and male patients without schizophrenia were studied. FAK is very important in the regulation of cell migration and cell adhesion. The experiments conducted in this paper determined whether neurosphere derived cells from schizophrenia patients had altered cell mobility and adhesion. The cells from the patients were assayed for motility and adhesion. They were then analyzed for FAK proteins. The proteins were then tagged with green fluorescent proteins and monitored by time lapse imaging in increments of 10 minutes for 70 minutes. The proteins of the healthy controlled patients had cells that demonstrated fast disassembly of focal adhesions. Focal adhesions are protein complexes that connect the cytoskeleton of the cell to the extracellular matrix. The focal adhesions are in a constant state of flux to transmit signals to

different cells. The cells that did not demonstrate fast disassembly of focal adhesion were from the unhealthy patients. The altered FAK signaling is a mutated gene expression found in schizophrenia patients (English).

Since schizophrenia is a hereditary disease, an additional study was performed on two endocannabinoid receptors found in schizophrenia; CB1 and CB2. These receptors have been located in the brain as well as other parts of the body. A study was done between tagged nucleotide polymorphisms (SNPs) in the gene CNR2 encoded for CB2 receptor. The study was done on postmortem brain tissue and an allelic comparison was done on the SNPs. The data showed that there is a high relation between the two SNPs and CNR2. The R63, C, and R63-C alleles were identified as being significantly increased in patients with schizophrenia compared to those without schizophrenia. The patients with Q63 allele were the controlled patients. The R63 alleles significantly lowered the response to the CB2 ligand. The results demonstrated, that patients had a lower reception from CB2 receptors had a higher risk of schizophrenia (Ishiguro).

Schizophrenia is difficult to study because the disease affects the neurons in the brain. In order to properly study the neurons in the brain, they must be alive. Until recently the only ways to study neurons in the brain were brain imaging, post-mortem pathology, and genetic studies of patients. There have been recent breakthroughs in the study of schizophrenia using stem cells. Historically, research was only viable if conducted on deceased brain tissue. Researchers are now able to use the stem cells to study live neurons. At Salk Institute, human-induced pluripotent stem cells were used to study live neuron cells from schizophrenia patients. The stem cells will now allow a researcher to duplicate the cells. The fibroblasts of patients were reprogrammed to human induced pluripotent stem cells. This allowed a near endless source of cells that were identical to patient cells. Mice were then used to study the neuron outgrowth using the stem cells.

Various experiments were performed on the stem cells including assays for neuronal connectivity and neurite outgrowth, to compare to the expected results of human cells. The experiments revealed cells decrease neuron outgrowth in the cells (Brennand).

The living nerve cells can now be tested with different drug compounds to find which drug is able to work directly with the nerve cells. Understanding gene mutations in NPAS3 in schizophrenia patients on the molecular level can help identify new drugs for treatment. The understanding of NPAS3 can also lead to the understanding of other gene mutations found in similar mental illnesses such as bipolar disorder. The breakthrough of harvesting adult stem cells will be able to accelerate the research in genes related to brain function in schizophrenia as well as other mental disorders.

Neuroproteomics is the study of protein complexes that make up the nervous system. The study is important because it focuses on the specific way in which the proteins connect the neurons. There are two main quantitative methods of study; gel electrophoresis and non-gel-based liquid chromatography/mass spectroscopy base profiling. Schizophrenia brain proteins have been identified as white matter proteins and grey matter proteins. Using the methods in neuroproteomics the proteins can be separated in a fast and efficient way. Postmortem brain tissue proteins from schizophrenic patients are fluorescently labeled and placed through two-dimensional gel electrophoresis (2-DE). The 2-DE separates the gray and white matter proteins that are associated with schizophrenia (English).

Treatment of schizophrenia is very expensive and some of the drugs have extreme side effects. Most people that have schizophrenia are prescribed drugs to control the disease. Olanzapine is a drug that has been known to treat patients with schizophrenia, but the large problem with these drugs is they cause weight gain. A study was done with olanzapine and some

derivatives of olanzapine. The experiment was done on female Dawley-Spague rats that were seven years old. There were six rats for each drug. The rats then were separated into groups of three and given a dosage of 3 mg/kg or 6 mg/kg of one of the drugs each day. The rats were placed in cages and given food. The food and water consumption were monitored over a five week period. The data demonstrated weight gain and food increase on each group of rats. The control in this experiment was a group of three rats that were not given the olanzapine or one of its derivatives. Over the period of the five week period the mice slowly started to gain more weight. During the same period, the mice ingested increased amounts of food. The study showed that the olanzapine drug slowly caused the mice to gain weight and consume more food. The results of the experiment allows for greater understanding of why the mice gained weight and further support the development of a new drug designed to combat the processes that are related to weight-gain. The schizophrenia disease is developed from transcription factors and because transcription factors can control the metabolism, scientists can identify the close relationship between schizophrenia and therapy weight-gain. This experiment is an important step toward better drug therapy for schizophrenia patients (Somayeh).

Although there is a lot of mystery to the study of schizophrenia, research has shown that schizophrenia affects many areas of the brain. Mutations found in NPAS 3, FAK, endocannabinoid receptors are just a few of the cases associated with schizophrenia. The breakthrough of new research methods such as harvesting adult stem cells, and neuroprotometrics can accelerate the research in genes related to brain function in schizophrenia. This will then ultimately allow for better drug treatment with fewer side effects.

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