Integrative Genomics Analysis of Epilepsy & Autism in the Developing Brain

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Introduction

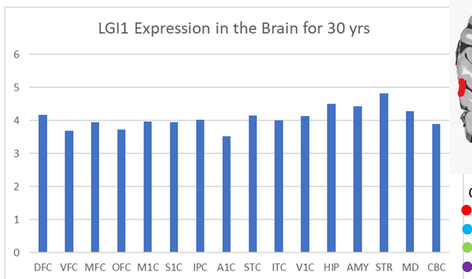
- Epilepsy is a neurological disease that occurs with an overload of sensory information which is caused by an overexcitation of neurons.
- Symptoms occur, such as seizures, which come in several forms and types.
- Additionally, severe autists also suffer non-epileptic seizures.
- In this study, we are utilising the LGI1 (Leucine-rich, glioma inactivated 1) gene, which was identified as a candidate gene for familial temporal lobe epilepsy with auditory features[1] to identify gene correlates in the developing brain.
- We use an integrative genomics approach to profile and analyse the genes correlated with epilepsy and autism.

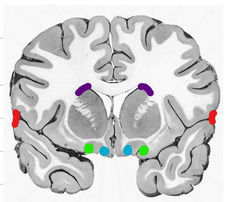
Methods

- A search of the Atlas of the Developing Human Brain: BRAINSPAN (http://www.brainspan.org/static/home) was performed to obtain gene expression data for LGI1 from 4 different brain regions. Genes with correlating expression patterns to LGI1 in the auditory cortex and the hippocampus were used in the subsequent analysis.
- Genes with correlating expression patterns to LGI1 from the auditory cortex and the hippocampus were compared to identify genes common to both brain regions.(http://bioinfogp.cnb.csic.es/tools/venny/)
- Relevant genes were filtered with Gene Ontology classification, Enrichment analysis and Clustering (https://david.ncifcrf.gov/).
- Protein interaction networks were created based on physical interactions from biochemical and genetic experimental data in order to find candidate genes relating to epilepsy and autism. (https://string-db.org/)
- Additional functional information for the genes of interest was obtained from NCBI.(https://www.ncbi.nlm.nih.gov/gene)

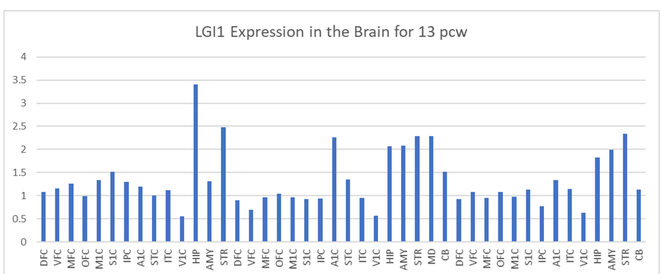
Results

Gene Expression Patterns



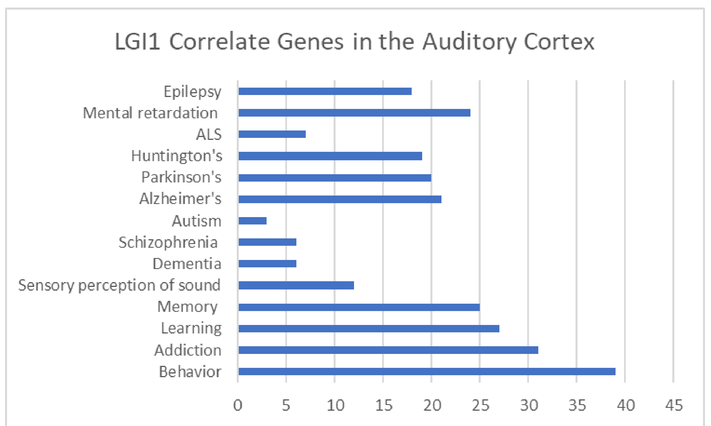


Coronal section of the brain:
- auditory cortex.
- Hippocampus.
- Amygdala.
- Striatum.



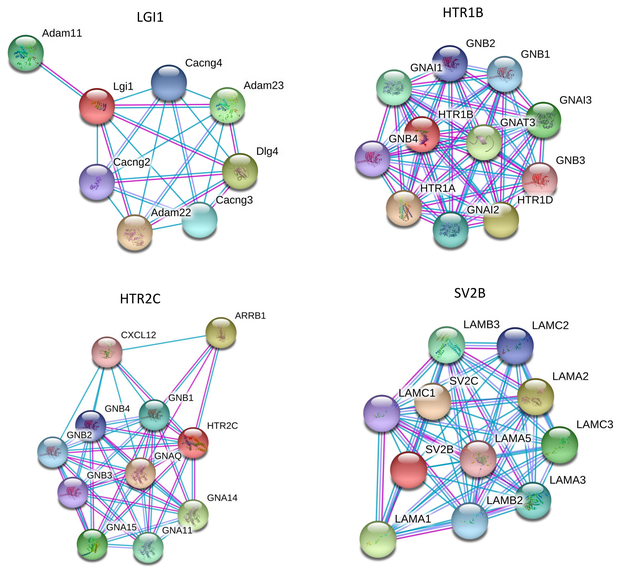
These graphs represent the value of LGI1 expression in the brain for different age groups. The columns above show the expression of LGI1 throughout different regions of a 30 year old brain. However, the age group that was used for this study was 13 post-conception weeks, due to the abundance of data. LGI1 expression was noted in the auditory cortex, as LGI1 is a known candidate gene for familial temporal lobe epilepsy with auditory features. The hippocampus, amygdala and striatum were also noted due to their high expression values.

Gene Profiling



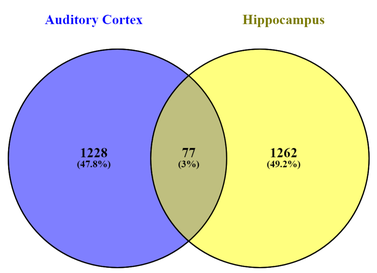
LGI1 and its correlates were entered into DAVID for Gene Ontology classification and the graph above shows the number of correlates relating to various behaviours and neurological conditions.

Interaction Network Analysis

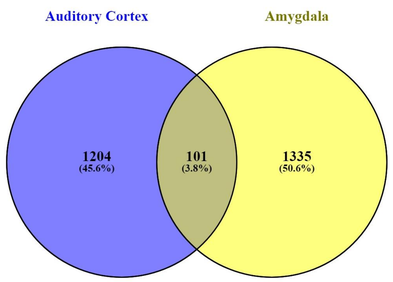


Protein interaction networks based on experimental evidence were constructed for several of the common genes with established relevance to epilepsy and behavior in order to identify additional genes of interest. Many of the network genes were of the same family and associated with ion channel activity, G-protein, serotonin, GABA, and dopamine signalling. Behavior, neurodevelopmental and neurological disorders associated with the network genes include: social behavior, exploratory behavior, grooming behavior, fear response, addiction, mental retardation, Alzheimer 's and Parkinson's

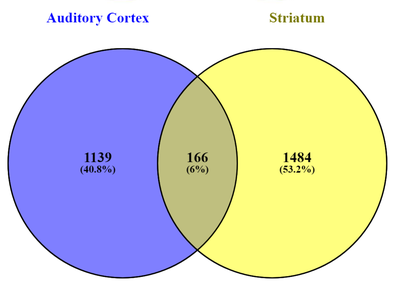
Common Genes



This Venn diagram represents the number of common genes between the LGI1 correlates expressed in both the hippocampus and the auditory cortex. Excluding probes, there were 1305 LGI1 correlates expressed in the auditory cortex and 1339 in the hippocampus, with 77 genes in common. Of these genes, 6 are associated with processes related to the synapse: synaptic transmission, synaptosome, and vesicle recycling



This Venn diagram represents the number of common genes between the LGI1 correlates expressed in both the amygdala and the auditory cortex. Excluding probes, there were 1305 LGI1 correlates expressed in the auditory cortex and 1436 in the amygdala, with 101 genes in common. Of these genes, 8 are associated with processes related to the synapse: synaptic transmission, neural synaptic plasticity, excitatory postsynaptic potential, and synaptic vesicle proteins



This Venn diagram represents the number of common genes between the LGI1 correlates expressed in both the striatum and the auditory cortex. Excluding probes, there were 1305 LGI1 correlates expressed in the auditory cortex and 1650 in the hippocampus, with 166 genes in common. Of these genes, 29 are associated with processes related to the synapse: synaptic transmission, neural synaptic plasticity, excitatory postsynaptic membrane, synaptic vesicle proteins, synaptosome, synapse assembly, immunological synapse, and vesicle recycling

Conclusions

- The purpose of the study was to identify genes of interest that may bridge the neurodevelopmental disorders, epilepsy and autism.
- To accomplish this, we implemented a strategy that targeted gene expression patterns in the primary auditory cortex in the developing brain.
- We identified many established genes related to epilepsy, cognitive function, behaviour and neurological disorders in the primary auditory cortex.
- Of the genes in the primary auditory cortex, 3 are associated with both epilepsy and autism/social behavior based on experimental data:(SLC9A9[2], SHANK3[3,4], and ANXA7[5]), providing support for the methodology used in this study.
- Expression patterns of LGI1 in the developing brain were most distinct for 3 brain regions at 13-15 pcw: Hippocampus, Amygdala and Striatum
- Comparing the LGI1/gene correlates for these 3 regions with the primary auditory cortex correlates at the same time period resulted in the identification of many genes with common function to LGI1 with respect to synaptic transmission and related synaptic processes.
- Take together, the genes of interest identified from this study provide a rationale basis for follow up experimental work to understand the link between epilepsy and autism.

References

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