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GENOMIC VIEW ON EPILEPSY AND AUTISM CANDIDATE GENES

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ABSTRACT:

The most frequently linked behavioural and neurological disorders to epilepsy are common complex disorders. Numerous disease-associated genes were discovered as a result of extensive parallel sequencing of individual or cohort genomes and exomes. Here, we evaluate the potential genes for epilepsy with an emphasis on exome and gene panel data. The findings demonstrate that, along with the analysis of genes expressed in the brain and the post synaptic proteome.

1. Candidate genes for non-metabolic epilepsies and autism are frequently AT-rich, and

2. Genes implicated in synaptic processes and developmental brain diseases typically have large transcript sizes and local AT-richness.

These findings suggest that essential candidate genes for epilepsy and autism are preferentially located in late-replicating, GC-poor chromosomal regions (isochores). These findings suggest that the genetic changes causing various brain illnesses are restricted to responsive chromatin regions containing important genes for the brain. These findings suggest that essential candidate genes for epilepsy and autism are preferentially located in late-replicating, GC-poor chromosomal regions (isochores). These findings suggest that the genetic changes causing various brain illnesses are restricted to responsive chromatin regions containing genes essential for the proper functioning of the brain.

Keywords: Remote sensing, Climate change, Artifcial Intelligence, Carbon emissions, Ocean acidification

I. INTRODUCTION

Early on, it was determined that epilepsy and autism spectrum disorder (ASD) were neurological disorders. About 30% of people who have either ASD or epilepsy also have the other. The majority of children with co-occurring ASD and epilepsy, according to studies on ASD and epilepsy, are caused by the same brain

pathology. Up to 2% of people will receive an epilepsy diagnosis at some point in their lives, making it one of the most widespread complex neurological conditions that affect people. Epilepsy is thought to affect 65 million people globally. Although many illnesses cannot fit neatly into one specific category, epilepsy is divided into subcategories based on what the major cause is believed to be. Seizures, the main epileptic symptom, can result from insults such brain damage from an accident or an infection, or they might have a hereditary basis or be a symptom of another condition. Genetic epilepsies and ASD can be divided into the following categories depending on how they are transmitted:

1. Mendelian, in which a single gene serves as the primary determinant, and
2. non-Mendelian or complex, in which multiple genes and/or epigenetic factors are involved.

II. LITERATURE SURVEY

ASD, often known as Asperger syndrome or Rett syndrome, is a neurodevelopmental illness that represents the severe end of the autism spectrum disorders. A parallel examination of autism candidate genes may be relevant because intellectual disability affects over 70% of people with autism, whereas it affects at least 25% of people with epilepsy. This is because multiple biological pathways are anticipated to overlap. Recently, the genetic aetiology of ASD has been better understood because to findings from exome sequencing. Many of the relevant genes produce proteins that are involved in transcriptional control, chromatin remodelling, and synapse development. Along with histone-modifying enzymes, voltage-gated ion channels, FMRP-associated genes, and genes expressed during embryogenesis are also included in this group. Notably, 10%–20% of people with fragile X syndrome also have epilepsy. Double strand break repair can result in chromosomal DNA loss or gain in addition to base-pair substitutions, single nucleotide variations, and minor frame shift changes. These copy number variants (CNVs) are important contributors to genomic diseases. CNVs are thought to make up a sizable fraction of human genetic variations and play a significant role in the hereditary predisposition to prevalent diseases, especially neuropsychiatric illnesses. Genome-wide analyses have shown that schizophrenia, autism spectrum disorder, and epilepsy are all associated with rare CNVs that change genes involved in neuron-developmental pathways. From an evolutionary perspective, CNV-related genetic diseases (dosage imbalances) seem to be extremely penetrant and subject to significant negative selection. In order to analyse basic characteristics such as gene size, base composition, and pathway enrichment of putative epilepsy and autism genes, we used data from many specialist resources and general databases in this work. We also contrast these genes' compositional characteristics with those of genes expressed in the brain and with the postsynaptic proteome.

III. METHOD

By searching the literature using the keywords "epilepsy, gene, and exome" in PubMed, we were able to first gather all the genes connected to epilepsy that were discovered using exome sequencing. Using "epilepsy" as the phenotype and "pathogenic" as the feature, ClinVar was searched again to provide a list of genes related to epilepsy. The core autism candidate list, which includes high-confidence genes, provided the autism candidate genes. We combined additional public datasets that will be described in the next section for consolidation purposes. The genes expressed in the brain that are being negatively selected are used. The proteome of the postsynaptic was obtained. A non-redundant set of human genes with HUGO protein coding entries was gathered via ensemble annotation. The complete exon plus intron gene sequence is used to calculate the gene's GC percentage and size. We used the Kruskal-Walli's rank sum test tool in the R Project for Statistical Computing Isochores chromosomal coordinates to check for changes in GC% distributions between the examined gene sets. For each of the gene sets that were evaluated, Gene Ontology pathway enrichment was carried out, and a p-value for enrichment was determined using the hypergeometric test based on the number of genes included in both the predefined set and our selected gene list. Only enrichments that are really significant are shown.

IV.RESULTS

Exome and ClinVar data

We thoroughly examined the exome sequencing contribution to this difficulty in an effort to identify any recurring, pertinent trends. In fact, when taking into account the total set of exome and

A distinct GO term enrichment is seen in the epilepsy risk genes obtained from ClinVar among the most enriched GO terms, the following are the most important:

1) the transmission of nerve impulse,

2) signalling in multicellular organisms,

3) a component of neurons,

4) a function of the nervous system,

5) a projection of neurons,

6) ion channel complex and

7) a transmembrane transporter complex.

According to what one may anticipate from a neurological condition, these pathways are suggestive of neuronal/synaptic core genes. Other GO terms are also noted, particularly genes associated with the learning term GO:0007612, which is enriched in genes like CHRNB2, CLN3, GRIN1, GRIN2A, and SYNGAP1, to mention a few. GO:0043038 for amino acid activation, which includes several tRNA synthetase genes, may be mentioned to highlight the diversity of pathways associated with epilepsy phenotypes. This pathway is likely to be unique to some syndromes associated with epilepsy, such as Alpers syndrome in the case of FRAS2 or mitochondrial encephalomyopathies in the case of TARS2 and VARS2.

Gene panel data

Gene panels intended for diagnosis have already begun to appear. Compared to exome or genome sequencing, they offer greater depth. This caused a paradigm shift in clinical genomics, a discipline that is "coming of age" and where genetic diagnoses is crucial. Three years ago, the first epilepsy gene panel was created. The panel contained 265 genes that, in accordance with Online Mendelian Inheritance in Man (OMIM), are thought to be involved in "monogenic disorders including epilepsy as a phenotypic feature." As a result, a search with this panel is limited to monogenic disorders where epilepsy may not be the primary symptom. GO terms like neurological system process, transmission of nerve impulse, and multicellular organismal signalling are significantly enriched at the junction of the exome plus ClinVar derived candidate genes and the EGP265 panel (22 genes); these GO terms are likely recapitulating important core epilepsy gene pathways. Finally, we wish to draw attention to the fact that 44 known epilepsy genes, four additional diagnostic panels, and the ClinVar-derived candidate genes all exhibit pathway enrichments.

Brain critical and synaptic genes

Reduced fecundity linked to severe mental diseases puts pressure on risk genes linked to conditions like autism, schizophrenia, mental retardation, and epilepsy. A class of exons known as brain critical exons (n = 3955) was defined by a recent study that combined exome and transcriptome data from large human population sets. These exons are highly expressed in brain tissues and, at the same time, exhibit suppressed accumulation of missense mutations, indicating that they are under purifying selection. Even though our collection of candidate genes for epilepsy revealed the lowest AT-bias, if just exome plus ClinVar candidates are taken into account, an increase in the AT-bias is seen. Surprisingly, the GC shift is

considerable when all candidates from the Epilepsy Gene Database are taken into account, or the "high confidence epilepsy genes." This pattern is much more pronounced for genes involved in synaptic activity, which is consistent with the finding that these genes tend to have relatively long introns.

V. CONCLUSION

We have demonstrated that the bulk of potential genes for autism and epilepsy differ structurally from the other human genes. An integrated genomic perspective with functional and evolutionary significance to some of the molecular activities of the brain is provided by the preferred positioning of synaptic and brain-critical genes in GC-poor chromosomal regions.

In actuality, the significant change in replication timing and expression throughout differentiation and development that is likewise exclusive to AT-rich genomic isochores is reminiscent of the striking decrease of TAD's (Topological Association Domains) boundary strength in AT-rich isochores of aged cells. Nuclear lamina, which is strongly connected with AT-rich sequences, and TADs are two inherent architectural features that may be hampered by higher order chromosome/chromatin structural changes caused by CNVs or SNVs.

In contrast to other brain cells like astrocytes or oligodendrocytes, where long genes are transcriptionally repressed, neural cells have a lower likelihood of being crucial for GC-rich/short intron genes, which are frequently linked to metabolic epilepsy pathways. Long genes (N100 kb) are dramatically repressed in Rett syndrome patients, and this repression is strongly correlated with mCpA (methylated CA dinucleotide) density, suggesting a further layer in the splicing mechanism of GCpoor genes that will be interesting to investigate. Combining these data may assist to reveal the underlying molecular mechanisms of brain and neurodevelopmental problems, particularly autism spectrum disorder and childhood epilepsy.

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