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Functional gene analysis to understand complex biological mechanisms in schizophrenia

Schizophrenia (SCZ) is a chronic debilitating psychiatric disorder affecting approximately 7 in 1000 people in their lifetime and ranked as one of the top 15 leading causes of disability worldwide. The symptoms of SCZ can be divided into positive symptoms (delusions, hallucinations and thought disorder), negative symptoms (inappropriate emotion, decreased motivation, poverty of speech and loss of interest) and cognitive symptoms (poor executive functioning, poor working memory and attention problems). These symptoms appear abruptly or may develop progressively usually in late adolescence or early adulthood but typically evolve into 'on and off 'cycles throughout life. Diseases such as high blood sugar, metabolic syndrome (cluster of 3 out of 5 findings: high blood sugar, high triglyceride level, low good cholesterol, obesity and high blood pressure), coronary heart disease (narrowing of blood vessels supplying heart) and chronic obstructive lung disease are higher in SCZ patients than the general population. They are also at increased risk of premature death and their life span reduced by 15–25 years than the general population. SCZ has a heritability estimate of 65–80% with various genetic studies during the past two decades identifying risk locations on chromosomes and candidate genes. To date 560 genes have been recognized in the literature or proposed in the causation and development of SCZ.

GeneAnalytics score	Disease	Total number of genes identified in disease from integrated databases	Number of matched genes from schizophrenia master list (%)
144.21	Schizophrenia	237	166 (27.3)
43.67	Attention deficit-hyperactivity disorder	69	43 (7.0)
42.6	Alcohol dependence	72	43 (7.2)
39.38	Psychotic disorder	39	37 (6.0)
37.57	Parkinson disease, late-onset	123	41 (6.7)
36.76	Alzheimer disease	556	41 (6.7)
36.69	Disease of mental health	60	37 (9.8)
36.53	Neuroblastoma	993	69 (11.3)
35.33	Autism spectrum disorder	116	39 (6.4)
34.1	Colorectal cancer	819	54 (8.8)

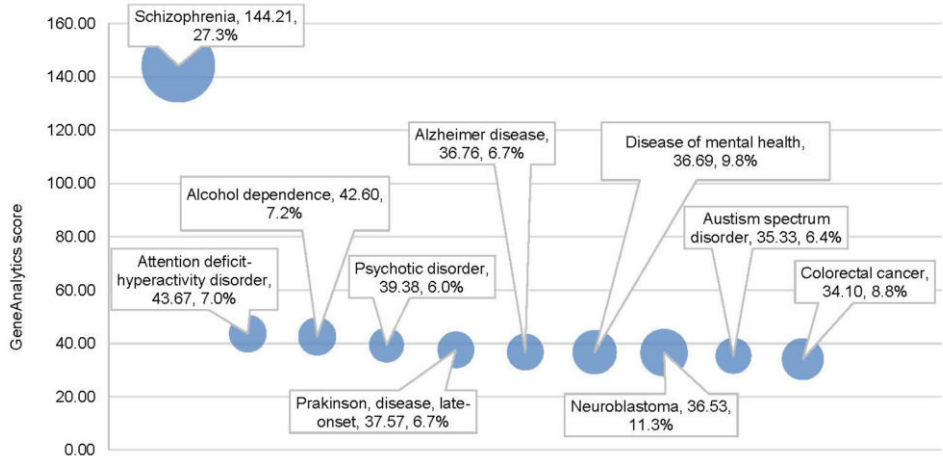

Fig. 1. Top ten categories of diseases associated with clinically relevant and known genes for schizophrenia.

In our research study, we used online databases to update the current list of 560 SCZ genes and identified 52 additional genes resulting in a total of 608. We used the web based GeneAnalytics profiling program and integrated genomic databases to create a molecular profile of the updated gene list to model their impact in select categories (tissues and cells, diseases (Fig. 1), pathways, biological processes, molecular functions, phenotypes (Fig. 2) and compounds) using the specialized GeneAnalytics program. The genes for SCZ were predominantly expressed in cerebellum, cerebral cortex, medulla oblongata, thalamus and hypothalamus. Psychiatric/behavioral disorders incorporating SCZ genes included Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder and Alcohol Dependence, Cancer and Alzheimer and Parkinson Diseases. Analysis of major biological pathways and mechanisms associated with SCZ genes identified glutamine receptors (eg. *GRIA1, GRIN2, GRIK4, GRM5),* serotonin receptors (eg.*HTR2A, HTR2C)*, GABA receptors (eg. *GABRA1, GABRB2),* calcium- related channel (eg. *CACNA1H, CACNA1B),* solute transporters (eg. *SLC1A1, SLC6A2)* and neurodevelopment (eg. *ADCY1, MEF2C, NOTCH2, SHANK3).* There was no single gene that overlapped in all the seven categories indicating heterogeneity and complexity in the genetic causation of SCZ.

GeneAnalytics score	Phenotype	Total number of genes identified in phenotype from integrated databases	Number of matched genes from schizophrenia master list (%)
101.93	Hyperactivity	271	59 (9.7)
81.27	Impaired coordination	309	55 (9.0)
81.16	Increased anxiety-related response	128	38 (6.2)
77.96	Hypoactivity	312	54 (8.8)
73.52	Decreased body weight	1145	103 (16.9)
72.75	Abnormal spatial learning	172	40 (6.5)
68.94	Reduced long-term potentiation	107	32 (5.2)
68.55	Decreased vertical activity	108	32 (5.2)
68.25	Abnormal serotonin level	32	21 (3.4)
63.16	Abnormal social investigation	64	25 (4.1)

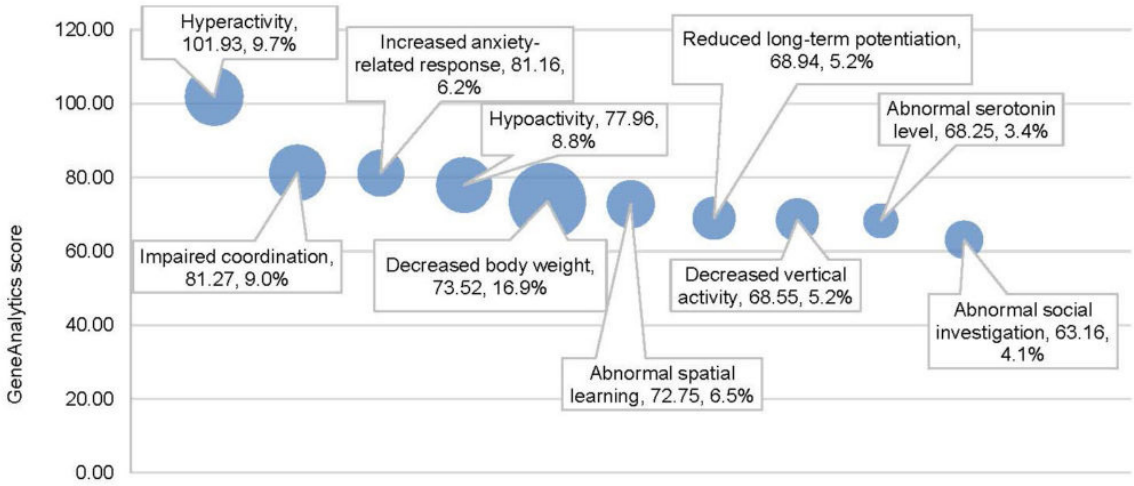

Fig. 2. Top ten categories of phenotypes associated with clinically relevant and known genes for schizophrenia.

The susceptibility to SCZ is due to the combined effects of ostensibly many genes in a given background creating a complex network increasing the probability of developing SCZ. A simple representation of the involved SCZ gene network include alterations in molecular function such as ion channel activity, ligand binding, receptor activity and a series of molecular functions impacting at the cellular level such as ion transport and synaptic transmission which collectively contribute to biological pathways leading to phenotypes or symptoms associated with SCZ including the response to drugs. Even though sleep disturbances and inflammation did not occupy top positions in the disease category, they did occupy the top positions in the pathway categories reflecting their strong underpinning in the development of SCZ. In conclusion, we compiled an updated master gene list of clinically relevant or proposed genes in SCZ from the medical literature. Our approach to interrogate SCZ genes and their interactions at various levels contributing to disease causation and development should increase our knowledge and possibly open new avenues for research and treatment approaches.

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