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Analyzing Patterns of De Novo Mutations in Genetic Disorders: Insights of a Comprehensive Database

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Abstract:- De novo Mutations (DNMs) are genetic alterations that occur in a family member for the first time either due to a mutation in the parent's germ cells or a mutation that arises in the embryo during its division. Unlike somatic mutations, de novo mutations can be passed down from one generation to another. De novo mutations have been shown to be an essential cause of several neurodevelopmental disorders, early-onset genetic disorders, and late-onset psychiatric disorders: autism, spectrum disorders, schizophrenia, intellectual disabilities, and coffin-siris syndrome. To analyze such mutations and their association with genetic diseases, researchers often look for patterns. These patterns pinpoint the exact base that may have been replaced and make the task of studying the disease easier . Unlike somatic mutation patterns that have been widely studied in oncology and various other fields since the early 2000s, de novo mutation patterns on the other hand have only been a more recent form of study. Our study aims to explore and analyze patterns associated with DNMs in causing various genetic conditions using the de novo mutation database published by the University of Washington in 2018.

I. INTRODUCTION

De novo mutations, or mutations that develop in the parent's germline and then pass on to their offspring, are a significant contributor in causing various genetic disorder. Research on de novo mutation has shed light on the underlying mechanisms that explain the emergence of such diseases[1].

De novo mutations are now widely acknowledged to constitute the primary source of an array of genetic conditions, such as congenital anomalies, intellectual disability, and neurodevelopmental disorders[1]. Despite their significance, most de novo mutations associated with various genetic disorders are still unknown.

Preliminary investigations have revealed intriguing findings, suggesting that de novo mutations exhibit diverse patterns in different genetic diseases. While some disorders exhibit distinct mutational hotspots or recurrent mutations, others display a more random distribution of de novo mutations across the gene (for single gene disorders). These observations hint at the presence of unique disease-specific mechanisms[2]. The need to comprehend the intricate interactions between mutations in genes and disease susceptibility led to the selection of this research topic.

In this study, we aim to look for commonalities and differences among diverse genetic disorders by evaluating the patterns of de novo mutations reported in a free available database of University of Washington in year 2018.[3] It serves the purpose to identify patterns within the vast collection of de novo mutation caused disorders, drawing on data from a comprehensive database, and adding onto the ongoing and published research on specific disease-related de novo mutation patterns. Understanding these patterns can help reveal the underlying biological processes and pathways that are involved in the emergence of disorders. Additionally, the discovery of recurring patterns can help in identifying potential targets for developing therapeutics and diagnostic markers.

II. RESULTS

The resulting analysis provides insights into the distribution of de novo mutations across different genetic disorders, allowing for comparison and identification of patterns.

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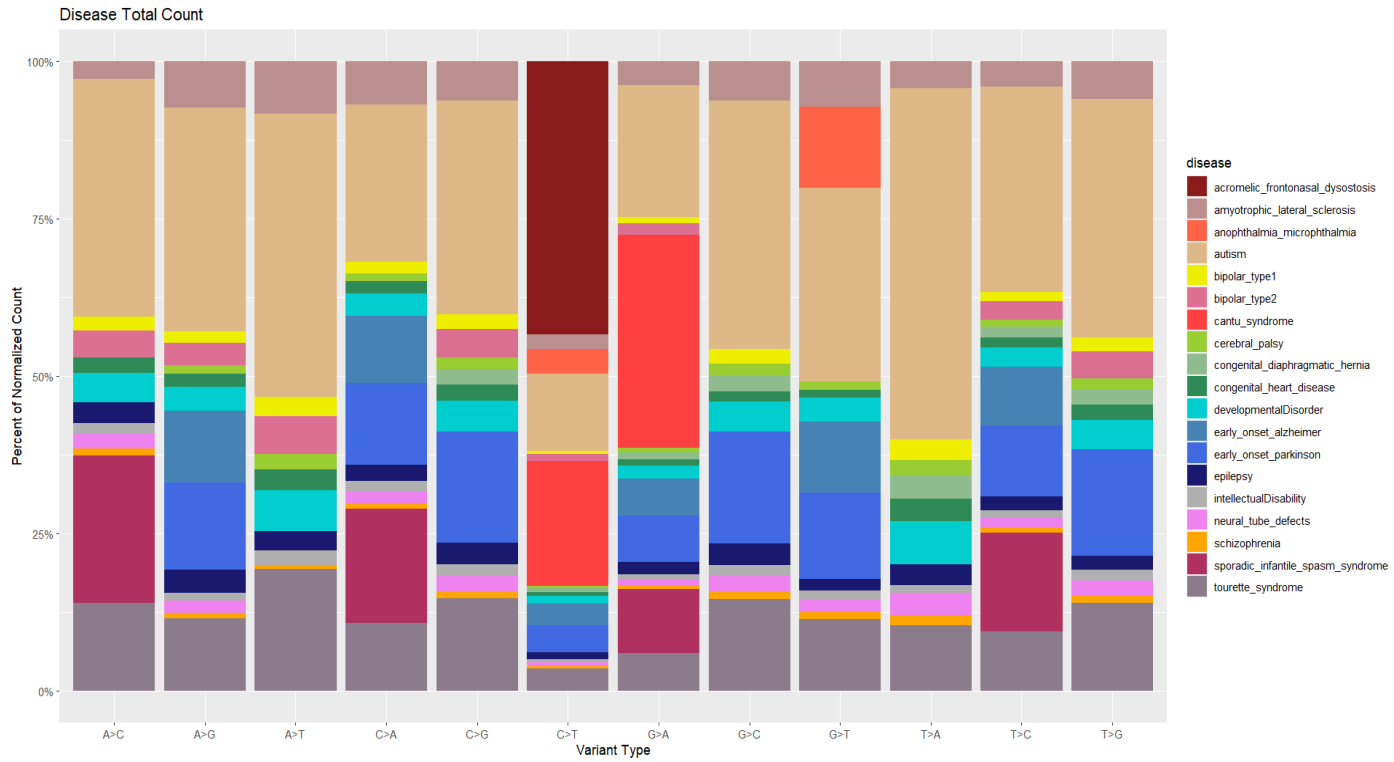

Fig 1: Disease Total Count is a graph visually depicting variant distribution in a combination of neurodevelopmental and neuropsychiatric disorders: some show no specific pattern, while acromelic frontonasal dysostosis exhibits a higher prevalence of C>T variants, and Cantu syndrome demonstrates significant proportions of C>T and G>A variations. A table of the same has been attached in the appendix.

Acromelic frontonasal dysostosis (AFND) is a rare genetic disorder characterized by facial and limb abnormalities which also lead to other complications such as intellectual disability[4]. The analysis of de novo mutations in Acromelic frontonasal dysostosis revealed a distinctive pattern, with a higher percentage of C>T mutations observed. Remarkably, all cases of Acromelic frontonasal dysostosis analyzed in this research demonstrated C>T variation, accounting for 100% of the mutations associated with this condition. (See Appendix A) This finding suggests a strong association between the C>T mutation and Acromelic frontonasal dysostosis, highlighting its potential role in the aetiology of this disorder. Moreover, these C>T mutations comprised approximately 46% of the overall C>T de novo mutations identified across all the other diseases.

Similarly, the investigation into Cantu syndrome unveiled a notable trend in the distribution of mutations. Interestingly, our results revealed that 45.5% of the Cantu syndrome cases presented C>T, while an equal proportion (45.5%) exhibited G>A variations. (See appendix A) These G>A mutations constituted around 30% of the total G>A mutations observed across all 15 samples. In a study investigating Cantú syndrome, a genetic cause was explored in a cohort of 14 individuals. The cohort consisted of seven simplex cases and seven familial cases. Simplex cases refer to individuals who are the only ones in their family affected by a particular disorder or condition. These cases typically occur sporadically and are not inherited from either parent.

Familial cases, on the other hand, refer to individuals who have a family history of the disorder. In these cases, the condition is passed down from one generation to another through genetic inheritance[5]. These findings suggest a significant involvement of both C>T and G>A mutations in the development of Cantu syndrome, underscoring their potential contribution to the pathogenesis of this disorder.

Among the several genetic diseases investigated, only Acromelic frontonasal dysostosis (AFND) and Cantu Syndrome exhibit discernible patterns that suggest the possible involvement of bias or an underlying mechanism. In the case of Amyotrophic Lateral Sclerosis, Autism Spectrum Disorder[6], and Tourette Syndrome, they show results that suggest no pattern at all. Tourette syndrome showcases about 8.1% mutation for all variants except the T>A variant which accounts for 4.1% mutations within the disease. (See Appendix A) autism spectrum disorder[6] showcases a variety of percentage mutations for each variant. Amyotrophic Lateral Sclerosis also shows a similar trend to autism spectrum disorder, where all variants show almost equal percentages of expression.

A few of the other diseases do not show an abundance of all variants; however, they share the percentage expression within a few variants. For example, Anophthalmia and microphthalmia are mainly caused by the prevalence of G>T and C>T mutations. Sporadic Infantile Spasm Syndrome exhibited a distribution of mutation types, between A>C, G>A, T>C and C>A variations. Interestingly, our analysis revealed that all four of these variants accounted for 13.6% of the mutations observed in cases of Sporadic Infantile Spasm Syndrome. Such varying results with no specific patterns are also observed in the other diseases analyzed in the research: Bipolar Type 1, Bipolar Type 2, Cerebral Palsy, Congenital Diaphragmatic Hernia, Congenital Heart Disease, Control, Developmental Disorder, Early Onset Alzheimer, Early Onset Parkinson, Epilepsy, Intellectual Disability, Mixed, Neural Tube Defects, and Schizophrenia.

The results showcase how certain genetic diseases like AFND and Cantu Syndrome show signs of patterns that could hint to specific targeting however, several other genetic diseases like Schizophrenia and Neural Tube Defects do not show such patterns and thus non-specific targeting. Therefore, indicating the association of de novo mutations with potential disease causing mechanisms in certain genetic disorders.

III. DISCUSSION

In our analysis, we observed that several diseases, including Tourette syndrome, Autism, amyotrophic lateral sclerosis (ALS), bipolar type 1, and developmental disorder, did not exhibit any discernible patterns in terms of mutation distribution. The data showed that, some variants showed prevalence in these diseases if not all. The percentage abundance for each variant remained about similar for each disease, thus, suggesting no potential bias for these diseases and suggesting that certain mutations target the human genes in a nonspecific manner[6].

Unlike most other disorders that show no specific pattern, anophthalmia/microphthalmia (AM) is the only disorder that shows less abundance of a variety of different variants. Rather, AM is only caused by 2 variants, the G>T and C>T variant. Only *SOX2* has been identified as a major gene associated with AM, primarily through de novo mutations. However, the underlying reasons for these non-specific mutations in *SOX2* remain largely unexplored, lacking any clear explanation or discernible trend. Understanding the non-specific pattern of AM is crucial for unraveling the complex processes involved in eye development. Focusing on developing treatment plans for AM would be far easier than the other disorders because it only revolves around the G>T and C>T variant and no other gene mutation via de novo mutation occurs. Future investigations focused on elucidating the genetic factors, regulatory elements, and signaling pathways associated with AM will contribute to a more comprehensive understanding of this condition.

However, these non-specific mutations also suggest the possibility of the De novo mutation not being a significant factor that could cause the disorder. A study pointed out how over a 1000 genes result in Autism Spectrum Disorder meaning that no one gene is likely to explain more than 1% of cases[7]. Another study further supported this suggestion by suggesting that most of the exonic de novo mutations observed within Autism Spectrum Disorder seem to have little connection to the disease, and those de novo mutations that are of potential risk are insufficient to cause disease[6].

The non-specific distribution of mutations in these genetic diseases suggests a complex aetiology involving many genetic and environmental factors. Several other research papers have also suggested the role of environmental factors in the expression of phenotypes for neurodevelopmental disorders and late-onset psychiatric phenotypes[1]. These findings align with the multifactorial nature of these disorders, where genetic susceptibility interacts with environmental influences to influence disease manifestation.

In contrast to the above-mentioned diseases, certain patterns emerged in other disease forms, as highlighted in the results section. For instance, Acromelic frontonasal dysostosis showed a notable prevalence of C>T variants, while Cantu syndrome exhibited a higher frequency of both C>T and G>A variations. These specific patterns of mutations observed in certain diseases indicate that they are targeted in a more specific manner. The observed unique patterns of mutations in these diseases may suggest similar genetic mechanisms.

Cantu Syndrome, is a rare condition, where in about "three dozen affected individuals have been reported in the medical literature[8]."Certain research studies have found that through exome sequencing on one proband-parent trio and three unrelated cases, all probands contained a heterozygous mutation in the *ABCC9* gene. De novo analysis of candidate genes identified 15 potential mutations, but only the *ABCC9* mutation (c.3460C>T) was validated in affected individuals[5]. The findings from that report highlight the involvement of the ATP-sensitive potassium channel in disease development. They also suggest an underlying reason for the potential bias of the specific targeting of the C>T variant that was also identified in this research paper.

The prevalence of Acromelic frontonasal dysostosis (AFND) worldwide remains uncertain, with "at least 100 recorded cases reported[9]". AFND encompasses three types caused by mutations in ALX3, ALX4, and ALX1 genes, encoding transcription factors that regulate gene activity. AFND type 2 (FND2) follows an autosomal dominant pattern and can also result from de novo mutations. Notably, individuals with a single copy of the mutated ALX4 gene may exhibit enlarged foramina in the parietal bones. The role of *ZSWIM6*, a gene associated with AFND, remains poorly understood, but a missense substitution is believed to disrupt a conserved sin3-like domain and affect hedgehog signalling[9].

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However, a comprehensive molecular-developmental explanation for AFND's specific malformation pattern is lacking, and although AFND shows a C>T variant pattern, the underlying reason or potential bias remains unknown.

The presence of distinct mutation patterns in certain genetic disorders suggests the involvement of specific shared genetic mechanisms, potentially indicating common underlying pathways or networks involved in disease development[2]. Insights for targeted treatment approaches could be gained from understanding the precise molecular mechanisms and genetic relationships linked to these disorders. However, no such findings have been discovered yet, so further research into these diseases is required.

IV. MATERIALS AND METHODS

This research project focused on identifying and analyzing patterns in genetic diseases caused by De Novo Variants using a publicly available database file from the University of Washington, specifically the non-SSC Samples file (denovo-db.non-ssc-samples.variants.v.1.6.1.tsv.gz.)[10] This database is freely available on the internet and has been used to identify the mutations that cause 21 disorders: Acromelic Frontonasal Dysostosis, Amyotrophic lateral sclerosis, anophthalmia microphthalmia, autism, bipolar type 1, bipolar type 2, Cantu syndrome, Cerebral Palsy, Congenital diaphragmatic hernia, Congenital heart disease, control, Development Disorder, Early Onset Alzheimer, Early Onset Parkinson, Epilepsy, Intellectual Disability, Mixed, Neural Tube Defects, Schizophrenia, Sporadic Infantile Spasm Syndrome, and Tourette syndrome. Recent advancements in whole-exome and whole-genome sequencing techniques have enabled the assessment of thousands of genetic variants. To facilitate the study of de novo variations, denovo-db was created as a comprehensive database assembled from published literature. While the database encompasses various phenotypes, it particularly emphasizes neurodevelopmental disorders. The information in denovo-db has been carefully curated to include relevant details such as functional annotation, CADD scores, and validation status, supporting genetic research endeavors.[11]

The data in the database was filtered to suit the purpose of observing patterns for the research paper beginning with the removal of columns not required such as the function class column and Coding DNA size column, for the course of the research. The retained columns for analysis and pattern recognition include SampleID (primaryID), Study Name, Primary Phenotype, Num probands, Num controls, PubMedID, Position, and Variant. A new column under the name Study size was created by summing the Num controls and Num probands columns.

For each disease (Primary Phenotype), the data was divided into separate subsets referred to as filtered_df(y+1), where ‘y’ represented a chronological numbering from 0 – 18. The count function was applied to the Primary Phenotype, Study Name, Study Size, and Variant columns within each subset to tally the different types of de novo point mutations associated with each disease, for example, the C>T variant or the T>A variant. This data was then normalized to eliminate redundant data and standardize data due to varying sample sizes and merged with the corresponding subset to generate a new table that allows us to compare the prevalence of mutations across the disorders on a level playing field.

To eliminate duplicate data, the table was aggregated, and the information was organized into three columns: Variant Type, Disease Name, and Total Count. All the tables were combined into a single data frame. The data frame was then converted to a percentage bar plot (Figure 1) that compared the abundance of variants in one disorder while simultaneously comparing the abundance of one variant for all disorders.

V. CONCLUSION

Our research findings demonstrate the complicated landscape of mutational trends in de novo mutations across a range of disorders. While some diseases clearly show the prevalence of mutational patterns, as seen in Cantu syndrome and Acromelic frontonasal dysostosis, many other genetic diseases do not show patterns at all such as Schizophrenia, Bipolar Type 1, and Tourette Syndrome.

In the long run, a better comprehension of the mutational patterns in de novo mutations will have impact on diagnostic procedures, individualized treatments, and genetic counseling in addition to improving our understanding of the aetiology of disease. Continued research in this area will help to manage and treat genetic illnesses better, which will eventually assist the people and families afflicted by these conditions.

It may be possible to get important insights into the pathogenic mechanisms at play by understanding these specific and non-specific mutation patterns in various genetic diseases. It might clarify the relationship between genetic components, molecular processes, and disease manifestation. Furthermore, these findings highlight the significance of considering the heterogeneity of mutational landscapes across various diseases, emphasizing the need for additional research to identify potential therapeutic targets and develop personalized treatment strategies based on mutation profiles.

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REFERENCES

[1]. R. Acuna-Hidalgo, J.A. Veltman, A. Hoischen, New insights into the generation and role of de novo mutations in health and disease. *Genome Biology*, **17(1)**. (2016).
[2]. J. Gauthier, F.F. Hamdan, G.A.Rouleau, A Strategy to Identify de Novo Mutations in Common Disorders such as Autism and Schizophrenia. *Journal of Visualized Experiments: : Jove*, e2534, doi:10.3791/2534 (2011).
[3]. denovo-db, Seattle, WA https://denovo-db.gs.washington.edu/denovo-db/Usage.jsp
[4]. Acromelic frontonasal dysostosis - About the Disease - Genetic and Rare Diseases Information Center. (n.d.). https://rarediseases.info.nih.gov/diseases/5539/acromelic-frontonasal-dysostosis
[5]. B.W.M. van Bon, C. Gilissen, D.K. Grange, R.C.M. Hennekam, H. Kayserili, H. Engels, H. Reutter, J.R. Ostergaard, E. Morava, K. Tsiakas, B. Isidor, M.L. Merrer, M. Eser, N. Wieskamp, P. de Vries, M. Steehouwer, J.A. Veltman, S.P. Robertson, H.G. Brunner, B.B.A. de Vries, A. Hoischen, Cantú Syndrome Is Caused by Mutations in ABCC9. *American Journal of Human Genetics*, **90(6)**, 1094–1101. (2012).
[6]. B.M. Neale, Y. Kou, L. Liu, A. Ma'ayan, K.E. Samocha, A. Sabo, C. Lin, C. Stevens, L. Wang, V. Makarov, P. Polak, S. Yoon, J. Maguire, E.L. Crawford, N.G. Campbell, E.T. Geller, O. Valladares, C. Schafer, H. Liu, T. Zhao, G. Cai, J. Lihm, R. Dannenfelser, O. Jabado, Z. Peralta, U. Nagaswamy, D. Muzny, J.G. Reid, I. Newsham, Y. Wu, L. Lewis, Y. Han, B.F. Voight, E. Lim, E. Rossin, A. Kirby, J. Flannick, M. Fromer, K. Shakir, T. Fennell, K. Garimella, E. Banks, R. Poplin, S. Gabriel, M. DePristo, J.R. Wimbish, B.E. Boone, S.E. Levy, C. Betancur, S. Sunyaev, E. Boerwinkle, J.D. Buxbaum, E.H. Cook Jr, B. Devlin, R.A. Gibbs, K. Roeder, G.D. Schellenberg, J.S. Sutcliffe, M.J. Daly, Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature*, **485(7397)**, 242–245. (2012).
[7]. S. De Rubeis, X. He, A.P. Goldberg, C.S. Poultney, K. Samocha, A.E. Cicek, Y. Kou, L. Liu, M. Fromer, S. Walker, T. Singh, L. Klei, J. Kosmicki, S. Fu, B. Aleksic, M. Biscaldi, P.F. Bolton, J.M. Brownfeld, J. Cai, N.G. Campbell, A. Carracedo, M.H. Chahrour, A.G. Chiocchetti, H. Coon, E.L. Crawford, L. Crooks, S.R. Curran, G. Dawson, E. Duketis, B.A. Fernandez, L. Gallagher, E. Geller, S.J. Guter, R.S. Hill, I. Ionita-Laza, P.J. Gonzalez, H. Kilpinen, S.M. Klauck, A. Kolevzon, I. Lee, J. Lei, T. Lehtimäki, C. Lin, A. Ma'ayan, C.R. Marshall, A.L. McInnes, B. Neale, M.J. Owen, N. Ozaki, M. Parellada, J.R. Parr, S. Purcell, K. Puura, D. Rajagopalan, K. Rehnström, A. Reichenberg, A. Sabo, M. Sachse, S.J. Sanders, C. Schafer, M. Schulte-Rüther, D. Skuse, C. Stevens, P. Szatmari, K. Tammimies, O. Valladares, A. Voran, L. Wang, L.A. Weiss, A.J. Willsey, T.W. Yu, R.K.C. Yuen, The DDD Study, Homozygosity Mapping Collaborative for Autism, UK10K Consortium, The Autism Sequencing Consortium, E.H. Cook, C.M. Freitag, M. Gill, C.M. Hultman, T. Lehner, A. Palotie, G.D. Schellenberg, P. Sklar, M.W. State, J.S. Sutcliffe, C.A. Walsh, S.W. Scherer, M.E. Zwick, J.C. Barrett, D.J. Cutler, K. Roeder, B. Devlin, M.J. Daly, J.D. Buxbaum, Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*, **515(7526)**, 209–215. (2014).
[8]. Cantú syndrome: MedlinePlus Genetics. (n.d.). https://medlineplus.gov/genetics/condition/cantu-syndrome/#frequency
[9]. National Organization for Rare Disorders. Frontonasal Dysplasia - Symptoms, Causes, Treatment | NORD. https://rarediseases.org/rare-diseases/frontonasal-dysplasia/. (2023).
[10]. denovo-db download, Seattle, WA https://denovo-db.gs.washington.edu/denovo-db/Download.jsp
[11]. About denovo-db, Seattle, WA https://denovo-db.gs.washington.edu/denovo-db/

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APPENDIX A

Sr. No	Variant. Type	pct	disease
1	C>T	100	acromelic_frontonasal_dysostosis
2	A>C	1.7	amyotrophic_lateral_sclerosis
3	A>G	5.2	amyotrophic_lateral_sclerosis
4	A>T	3.5	amyotrophic_lateral_sclerosis
5	C>A	5.2	amyotrophic_lateral_sclerosis
6	C>G	3.5	amyotrophic_lateral_sclerosis
7	C>T	5.2	amyotrophic_lateral_sclerosis
8	G>A	5.2	amyotrophic_lateral_sclerosis
9	G>C	3.5	amyotrophic_lateral_sclerosis
10	G>T	5.2	amyotrophic_lateral_sclerosis
11	T>A	1.7	amyotrophic_lateral_sclerosis
12	T>C	3.5	amyotrophic_lateral_sclerosis
13	T>G	3.5	amyotrophic_lateral_sclerosis
14	C>T	9.1	anophthalmia_microphthalmia
15	G>T	9.1	anophthalmia_microphthalmia
16	A>C	21.9	autism
17	A>G	25	autism
18	A>T	18.8	autism
19	C>A	18.8	autism
20	C>G	18.8	autism
21	C>T	28.2	autism
22	G>A	28.2	autism
23	G>C	21.9	autism
24	G>T	21.9	autism
25	T>A	21.9	autism
26	T>C	28.2	autism
27	T>G	21.9	autism
28	A>C	1.3	bipolar_type1
29	A>G	1.3	bipolar_type1
30	A>T	1.3	bipolar_type1
31	C>A	1.3	bipolar_type1
32	C>G	1.3	bipolar_type1
33	C>T	1.3	bipolar_type1
34	G>A	1.3	bipolar_type1
35	G>C	1.3	bipolar_type1
36	T>A	1.3	bipolar_type1
37	T>C	1.3	bipolar_type1
38	T>G	1.3	bipolar_type1
39	A>C	2.5	bipolar_type2
40	A>G	2.5	bipolar_type2
41	A>T	2.5	bipolar_type2
42	C>G	2.5	bipolar_type2
43	C>T	2.5	bipolar_type2
44	G>A	2.5	bipolar_type2
45	T>C	2.5	bipolar_type2
46	T>G	2.5	bipolar_type2
47	C>T	45.5	cantu_syndrome
48	G>A	45.5	cantu_syndrome
49	A>G	1	cerebral_palsy
50	A>T	1	cerebral_palsy
51	C>A	1	cerebral_palsy
52	C>G	1	cerebral_palsy
53	C>T	1	cerebral_palsy
54	G>A	1	cerebral_palsy

55	G>C	1	cerebral_palsy
56	G>T	1	cerebral_palsy
57	T>A	1	cerebral_palsy
58	T>C	1	cerebral_palsy
59	T>G	1	cerebral_palsy
60	C>G	1.4	congenital_diaphragmatic_hernia
61	C>T	1.4	congenital_diaphragmatic_hernia
62	G>A	1.4	congenital_diaphragmatic_hernia
63	G>C	1.4	congenital_diaphragmatic_hernia
64	T>A	1.4	congenital_diaphragmatic_hernia
65	T>C	1.4	congenital_diaphragmatic_hernia
66	T>G	1.4	congenital_diaphragmatic_hernia
67	A>C	1.4	congenital_heart_disease
68	A>G	1.4	congenital_heart_disease
69	A>T	1.4	congenital_heart_disease
70	C>A	1.4	congenital_heart_disease
71	C>G	1.4	congenital_heart_disease
72	C>T	1.4	congenital_heart_disease
73	G>A	1.4	congenital_heart_disease
74	G>C	0.9	congenital_heart_disease
75	G>T	0.9	congenital_heart_disease
76	T>A	1.4	congenital_heart_disease
77	T>C	1.4	congenital_heart_disease
78	T>G	1.4	congenital_heart_disease
79	A>C	2.7	developmentalDisorder
80	A>G	2.7	developmentalDisorder
81	A>T	2.7	developmentalDisorder
82	C>A	2.7	developmentalDisorder
83	C>G	2.7	developmentalDisorder
84	C>T	2.7	developmentalDisorder
85	G>A	2.7	developmentalDisorder
86	G>C	2.7	developmentalDisorder
87	G>T	2.7	developmentalDisorder
88	T>A	2.7	developmentalDisorder
89	T>C	2.7	developmentalDisorder
90	T>G	2.7	developmentalDisorder
91	A>G	8	early_onset_alzheimer
92	C>A	8	early_onset_alzheimer
93	C>T	8	early_onset_alzheimer
94	G>A	8	early_onset_alzheimer
95	G>T	8	early_onset_alzheimer
96	T>C	8	early_onset_alzheimer
97	A>G	9.8	early_onset_parkinson
98	C>A	9.8	early_onset_parkinson
99	C>G	9.8	early_onset_parkinson
100	C>T	9.8	early_onset_parkinson
101	G>A	9.8	early_onset_parkinson
102	G>C	9.8	early_onset_parkinson
103	G>T	9.8	early_onset_parkinson
104	T>C	9.8	early_onset_parkinson
105	T>G	9.8	early_onset_parkinson
106	A>C	1.9	epilepsy
107	A>G	2.6	epilepsy
108	A>T	1.3	epilepsy
109	C>A	1.9	epilepsy
110	C>G	1.9	epilepsy
111	C>T	2.6	epilepsy

112	G>A	2.6	epilepsy
113	G>C	1.9	epilepsy
114	G>T	1.3	epilepsy
115	T>A	1.3	epilepsy
116	T>C	1.9	epilepsy
117	T>G	1.3	epilepsy
118	A>C	1	intellectualDisability
119	A>G	0.8	intellectualDisability
120	A>T	1	intellectualDisability
121	C>A	1.3	intellectualDisability
122	C>G	1	intellectualDisability
123	C>T	1	intellectualDisability
124	G>A	1	intellectualDisability
125	G>C	1	intellectualDisability
126	G>T	1	intellectualDisability
127	T>A	0.5	intellectualDisability
128	T>C	1	intellectualDisability
129	T>G	1	intellectualDisability
130	A>C	1.4	neural_tube_defects
131	A>G	1.4	neural_tube_defects
132	C>A	1.4	neural_tube_defects
133	C>G	1.4	neural_tube_defects
134	C>T	1.4	neural_tube_defects
135	G>A	1.4	neural_tube_defects
136	G>C	1.4	neural_tube_defects
137	G>T	1.4	neural_tube_defects
138	T>A	1.4	neural_tube_defects
139	T>C	1.4	neural_tube_defects
140	T>G	1.4	neural_tube_defects
141	A>C	0.6	schizophrenia
142	A>G	0.6	schizophrenia
143	A>T	0.2	schizophrenia
144	C>A	0.6	schizophrenia
145	C>G	0.6	schizophrenia
146	C>T	1	schizophrenia
147	G>A	0.8	schizophrenia
148	G>C	0.6	schizophrenia
149	G>T	0.8	schizophrenia
150	T>A	0.6	schizophrenia
151	T>C	0.6	schizophrenia
152	T>G	0.6	schizophrenia
153	A>C	13.6	sporadic_infantile_spasm_syndrome
154	C>A	13.6	sporadic_infantile_spasm_syndrome
155	G>A	13.6	sporadic_infantile_spasm_syndrome
156	T>C	13.6	sporadic_infantile_spasm_syndrome
157	A>C	8.1	tourette_syndrome
158	A>G	8.1	tourette_syndrome
159	A>T	8.1	tourette_syndrome
160	C>A	8.1	tourette_syndrome
161	C>G	8.1	tourette_syndrome
162	C>T	8.1	tourette_syndrome
163	G>A	8.1	tourette_syndrome
164	G>C	8.1	tourette_syndrome
165	G>T	8.1	tourette_syndrome
166	T>A	4.1	tourette_syndrome
167	T>C	8.1	tourette_syndrome
168	T>G	8.1	tourette_syndrome