Analyzing Missense Mutations of the MAPT/Tau Gene to Predict Variant Pathogenicity in Alzheimer's Disease

Tejas Shah

Hopkinton High School, 90 Hayden Rowe, Hopkinton, MA, 01748, USA; tshah@hillers.org

ABSTRACT: Alzheimer's Disease (AD) continues to affect millions of people and is a leading cause of death in the United States. This stands true mainly in light of the fact that the underlying mechanisms of AD are unclear and there is no effective method of preventing neurodegeneration. The Tau protein, however, has shown to play an important role in the pathogenesis of the disease. Mutations in the MAPT/Tau gene can lead to complications in the functionality of Tau, potentially fast-tracking AD development. The goal of this study was to investigate potential missense mutations in this gene in order to identify those that were most pathogenic. Since missense mutations carry unknown effects on protein function, they were closely examined. Several amino acid (AA) changes such as hydrophobicity, charge, and polarity were investigated. Of 109 reported missense mutations, 72 resulted in significant AA changes. Due to their unknown effects, additional criteria such as AA conservation and mutation location with respect to tubulin-binding domains were also factored in to investigate overall impact. Through this comprehensive methodology, three mutations that were more likely to carry deleterious effects and potentially causing AD susceptibility in individuals with these alterations were identified.

KEYWORDS: Biomedical and Health Sciences; Genetics and Molecular Biology of Disease; Alzheimer's Disease; Tau; Bioinformatics.

Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder associated with memory loss and dementia.[1] At least 5.8 million individuals over the age of 65 within the United States live with the illness today and there were more than 120,000 recorded mortalities in 2018 alone, making it the sixth leading cause of death in the nation.[2] There is no known cure for the disorder as of now, but the frequency of cases is rising exponentially per decade, making it increasingly important to further understand the underlying causes of the illness.

During initial stages of progression, AD targets areas of the brain that are responsible for controlling thought, memory, and language, including the hippocampus and the entorhinal cortex, making these structures vulnerable to atrophy.[3] This results in an inability to recall basic information such as recent events or familiar names. As the disease progresses, the patient may be unable to recognize friends and family. They may also have trouble with verbal communication including reading, writing, and in some cases, speaking. During late-stage AD, the patient will need around the clock care, and this can be very demanding of family members and/or caregivers.[4] The patient will eventually lose the ability to carry out essential tasks such as bathing, eating, or dressing and will be in constant need of attention.[5]

The exact cause of AD is unknown, but genetics is speculated to be one of the most prominent factors to be associated with the illness.[6] Mutations in the Microtubule Associated Protein Tau (MAPT/Tau) gene can affect the functioning of the Tau protein. In healthy brains, the protein is primarily responsible for microtubule assembly and construction.[7] Recent studies have also shown that Tau plays a vital role in cellular signaling, synaptic plasticity, and genomic stability. However, under certain conditions, it can become insoluble, resulting in synaptic dysfunction and eventually, neural cell death, often referred to as tauopathies. This process occurs in a wide range of neurodegenerative disorders, including AD and Parkinson's.[8] The amount of phosphate within the brain also has an impact on the behavior of the Tau protein. In healthy adults, the brain consists of 2 to 3 moles phosphate per mole of Tau, and its biological activity is suppressed by hyperphosphorylation. However, in the brains of Alzheimer's patients, Tau is hyperphosphorylated to approximately 3 to 4 times it should typically be. Because the function of the protein becomes compromised, abnormal Tau folding may occur, which can lead to a genesis of paired helical and straight filaments within neurons.[9] This prompts the formation of neurofibrillary tangles and Tau accumulation within synapses and can lead to synaptic blockage, inhibiting cellular communication and resulting in cell death.

Genetic mutations always occur in cells but are often harmless. Occasional mutations in gene sequences that encode for crucial amino acids can, however, have severe repercussions as they may alter the way the protein functions altogether. This study looked at the various missense mutations of the MAPT/Tau isoform 6 gene through the use of Geno2MP, an online software that searches a database of rare variants from exome sequencing data. Missense mutations were specifically targeted in this study due to their unknown effect on protein function and pathogenicity. Changes in hydrophobicity, charge, and polarity were determined, then analyzed through the addition of special criteria. The Clustal Omega server and NCBI

DOI: 10.36838/v3i4.13

were used to gauge AA conservation within the MAPT/Tau FASTA sequence in humans and other organisms including *Caenorhabditis elegans* (Ce), *Danio rerio* (Dr), *Drosophila melanogaster* (Dm), *Mus musculus* (Mm), *Rattus norvegicus* (Rn), and *Xenopus tropicalis* (Xt). This would allow for the determination of the importance of each mutation and formulate a more accurate conclusion on mutation significance. In an effort to further improve the accuracy and validity of the analysis, the four tubulin-binding domains to which some of these altered amino acids belong were also identified through use of databases such as MARRVEL (**M**odel organism **A**ggregated **R**esources for **R**are **V**ariant **E**xpLoration) and NCBI. Typically, AAs within these domains are known to be essential for protein functionality therefore mutations taking place here were more closely examined. A combination of all these factors were used while evaluating and identifying the most harmful missense mutations in the MAPT/Tau gene to see if they could potentially contribute to dementia and AD.

Methods

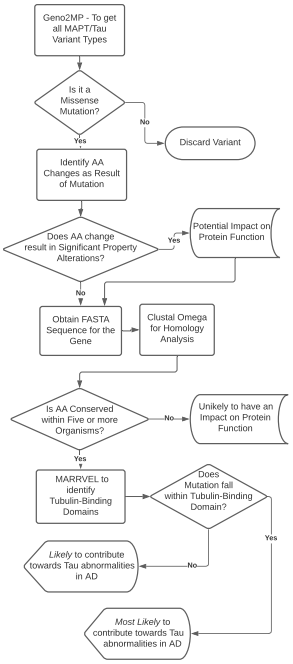


Figure 1: Workflow diagrams for identifying most deleterious mutations of the MAPT/Tau gene. Analysis was mutually exclusive.

Identifying Missense Mutations in the MAPT/Tau gene:

The online software, Geno2MP, was used to generate a list of all possible mutations and their properties within the MAPT/Tau isoform 6 gene (NP_001116538.2). Geno2MP is an online tool that searches a database for rare variants from exome sequencing data linked to phenotypic information from a variety of Mendelian gene discovery projects. The database contains information from more than 19,000 individuals that includes both persons affected by Mendelian conditions and unaffected relatives of these persons. A table containing all possible MAPT/Tau isoform 6 mutations was generated and then exported to Microsoft Excel, where further analysis took place. Data was then filtered by looking at the "fxnAnnotation" column, where only missense mutations were included, while the rest were discarded. Missense mutations were closely examined because their effects on the protein are still unclear as they could carry negative or negligible effects. Identifying these mutations would later allow for a closer look at what effects they can inflict on the overall functioning of the Tau protein. They were evaluated in terms of resulting AA property changes, AA conservation, and their locations with respect to tubulin-binding domains. Mutations that satisfied these criteria (Figure 2) were deemed likely to alter the function of the Tau protein and contribute towards AD pathogenesis.

Identifying specific Amino Acid (AA) changes:

Upon studying the "hgvsProteinVar" column in the table, specific AA changes, and their locations in the gene were identified. Following this process, the effects of these changes were then noted. The three properties that were investigated in this analysis were hydrophobicity, polarity, and charge. These properties were confirmed true with verified online tables and sources. A change in any of these factors as a result of a missense mutation could have potentially impaired the function of the Tau protein. If a change in AA property took place, the mutation was noted as significant in the next column. All 109 mutations were still taken to the next step of analysis even though some were found insignificant.

Gauging Gene Conservation :

The FASTA sequence of the MAPT/Tau isoform 6 gene in Homo Sapiens was obtained through NCBI and recorded. In order to determine conservation amongst *Homo sapiens* (Hs) and the other organisms, the FASTA sequences of *Caenorhabditis elegans* (Ce), *Drosophila melanogaster* (Dm), *Danio rerio* (Dr), *Mus musculus* (Mm), *Rattus norvegicus* (Rn), and *Xenopus tropicalis* (Xt) were also taken note of. These sequences (including Hs) were entered into Clustal Omega, an online tool that aligned the AA sequences to test the level of AA conservation amongst different organisms. With this alignment data, each AA from the table was investigated to see which were shared with the other organisms at their respective locations. If organisms shared one or more of the same AA in the same position, it was marked as conserved at that location.

Finding Altered AAs in Tubulin-Binding Domains :

The MAPT/Tau protein has four tubulin-binding domains. For each domain, AA sequences were found through the MARRVEL/DIOPT software for MAPT/Tau isoform X1. Typically, AAs within these domains are known to be essential for protein functionality so mutations taking place here were closely examined. These AA sequences were then identified within the MAPT/Tau isoform 6 gene and their beginnings and ends were defined. Then, it was investigated whether any of the reported mutations took place within the tubulin-binding domains.

Results

Reported MAPT/Tau mutations :

The MAPT/Tau gene on chromosome 17 has a reported 109 missense mutations that were found through the Geno2MP online database. Each of these reported muta

tions were from mRNA NM_001123066.3, the MAPT/Tau isoform 6 gene was used as a reference in this study. See Supplemental Table 1, for full list of identified missense mutations. These mutations were analyzed throughout the duration of this study.

Analysis of AA changes :

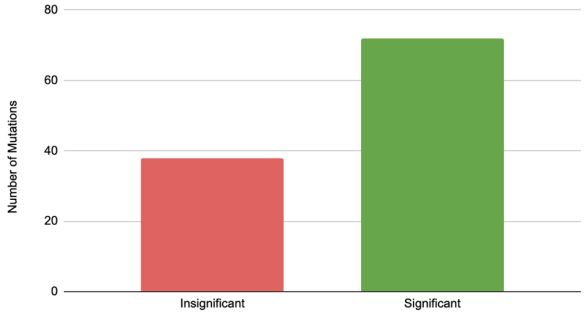


Figure 2: · Significance of Mutations· Of the 109 missense mutations reported, 72 were found to be significant based solely on resulting property alterations in hydrophobicity, polarity, and charge. 37 were said to be insignificant as they resulted in no changes in the traits listed above. For full list of mutation property changes, see Supplemental Table 2.

Missense mutations occur at a nucleotide level and can therefore lead to potential AA changes, causing certain alterations in protein function. The first mutation reported was G>A (guanine to adenine), which led to a change of the AA arginine (Arg) to histidine (His), (Supplemental Table 2). Three specific properties were investigated while evaluating AA changes that included hydrophobicity, polarity, and charge. Each AA property was determined and confirmed true through the use of verified sources.[10] Mutation #1 did not cause any changes in these properties, so it was marked as insignificant. The second mutation reported was G>T (guanine to thymine) and caused an AA change of arginine (Arg) to leucine (Leu). However, unlike the previous mutation, Mutation #2 was found to bring changes to the AA (Suplementel Table 2, Column 5), so it was marked as significant. This process was repeated several times in order to determine each mutation's theoretical impact on the protein and all findings are listed (Supplemental Table 2). Of the 109 identified missense mutations, 72 were found to alter the respective AA in regard to hydrophobicity, polarity, or charge and were therefore deemed significant (Figure 2).

AA Conservation amongst other organisms :

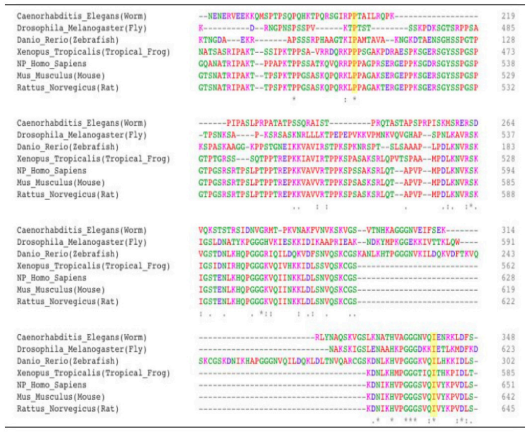


Figure 3: Segment of Aligned FASTA sequence of Ce, Dm, Dr, Hs, Mm, Rn, and Xt - Image captured from Clustal Omega. Red letters signify small and hydrophobic AAs, blue represents acidic AAs, magenta letters represent basic AAs, and green represents AAs with a hydroxyl, sulfhydryl, or amine functional group. An asterisk (*) indicates positions which have a single, fully conserved residue (See highlighted columns for fully conserved AAs from mutation list), a colon (:) indicates conservation between groups of strongly similar properties, a period (.) indicates conservation between groups of weakly similar properties.

Conservation is an important feature of AAs in a protein as it can be very useful for evaluating the cruciality of certain missense mutations. An essential AA is expected to be highly conserved amongst organisms, while relatively less important AAs are not as conserved. Significant changes in conserved AAs are more likely to alter the functioning of the protein because crucial AAs are at greater risk of resulting in property changes. In order to analyze the most important AA changes, then aligned the MAPT/Tau FASTA sequence of *Caenorhabditis elegans* (Ce), *Drosophila melanogaster* (Dm), *Daniorerio* (Dr), *Mus musculus* (Mm), *Rattus norvegicus* (Rn), *Xenopus tropicalis* (Xt), and *Homo sapien* (Hs) using the online software Clustal Omega (Figure 3). Of the 109 mutations, 83 were found to be conserved in at least one or more of the listed organisms (Supplemental Table 3), however only Mutation #91, Mutation #92, and Mutation #102 were conserved in all five (Table 1)

Table 1: Fully Conserved AAs from Mutation List. Within the 109 missense mutations, it was found that only three AAs were fully conserved amongst all tested organisms. For a full list of AA conservation, see Supplemental Data Table 3, Appendix 1.

Mutation #	hgvsProteinVar	hgvsAlleleChange	AA Conserved?	AA Conserved in...
91	p.(P512S)	C>T	Yes	Ce, Dm, Dr, Mm, Rn, Xt
92	p.(P512H)	C>A	Yes	Ce, Dm, Dr, Mm, Rn, Xt
102	p.(I643T)	T>C	Yes	Ce, Dm, Dr, Mm, Rn, Xt

Mutations Within Tubulin-Binding Domains :

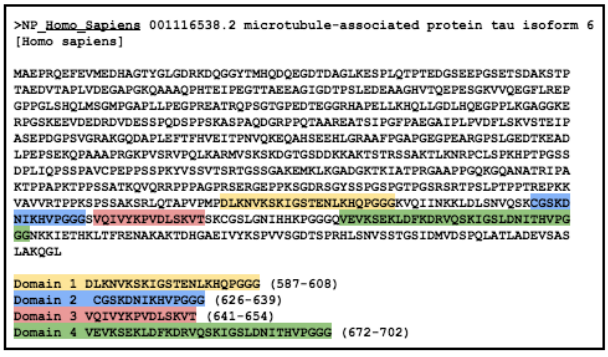


Figure 4: The four tubulin-binding domains of MAPT/Tau isoform 6 marked in its FASTA sequence (Source: NCBI/Protein). Domains are represented with corresponding colors. Domain 1 (587-608) is highlighted in yellow; Domain 2 (626-639) is highlighted in blue; Domain 3 (641-654) is highlighted in red; and Domain 4 (672-702) is highlighted in green.

The MAPT/Tau protein has four tubulin-binding domains, highlighted in Figure 3. It was found that only Mutation #101, #102, and #103 fall into one of these domains (Table 2). Mutations within these domains were explicitly inspected because AAs found within functional domains are known to be more essential for protein functionality.

DOI: 10.36838/v3i4.13

Table 2: Mutations that took place in tubulin-binding Domains. Of the 109 different missense mutations, it was determined that only three (101-103) took place in the tubulin-binding domain. Mutation #101 occurred in Domain 2, Mutation #102 occurred in Domain 3, and Mutation #103 occurred in Domain 4. None of the recorded missense mutations took place in Domain 1.

Mutation#	hgvsAlleleChange	hgvsProteinVar	Domain of the Mutation
101	G>A	p.(V635I)	Domain 2
102	T>C	p.(I643T)	Domain 3
103	G>A	p.(V698I)	Domain 4

Discussion

In this study, an approach to predict the pathogenicity of possible MAPT/Tau missense mutations was developed. It was found that depending on the type of mutation and its location in the gene, the overall effects may vary. AA changes were analyzed in the context of polarity, hydrophobicity, charge, and conservation amongst various organisms. Specific AA changes were investigated based on their position in the different functional domains of the protein. This information could be used to predict the probability of having a damaged or impaired Tau protein and could further help in predicting the risk of AD occurrence in individuals. This general bioinformatics approach can be replicated to predict the occurrence of other genetic diseases/illnesses by utilizing the gene sequence of an affected protein. This technique could be used to predict certain cancers with a known genetic component and other proteins that play a role in AD such as amyloid beta.

A total of 109 missense mutations were analyzed in the MAPT/Tau gene and 72 of them were determined to be significant based on changes in their corresponding AA (Figure. 1). Mutation #101 (p.(V635I)), Mutation #102 (p.(I643T)), and Mutation #103 (p.(V698I)) were the only alterations that were found to occur within a tubulin-binding domain. Furthermore, Mutation #102 was the only variant change determined to be both significant and fully conserved amongst these three. Significance in this context refers to property changes in AAs as a direct result of a mutation. To test for overall significance on protein function and the vitality of the AA, conservation was also evaluated. Since the AA Isoleucine was fully conserved at its location (p.643), Mutation #102 is more likely to carry a deleterious effect on the overall functionality of the Tau protein. It is important here because based of this evidence, it can be concluded that Mutation #102 will most likely alter AA function, potentially impairing the functionality of the protein.

Mutation #91 (p.P512S)) and Mutation #92 (p.P512H)) were also found to be both fully conserved and significant based on property changes. However, unlike Mutation #102, neither belonged to a tubulin-binding domain. Because fully conserved AAs are more likely to alter the overall functionality of the protein and these mutations were determined to be significant, changes are more likely to carry through. Therefore, it was concluded that Mutation #91 and #92 also carry a high probability of damaging the Tau protein and can potentially lead to AD.

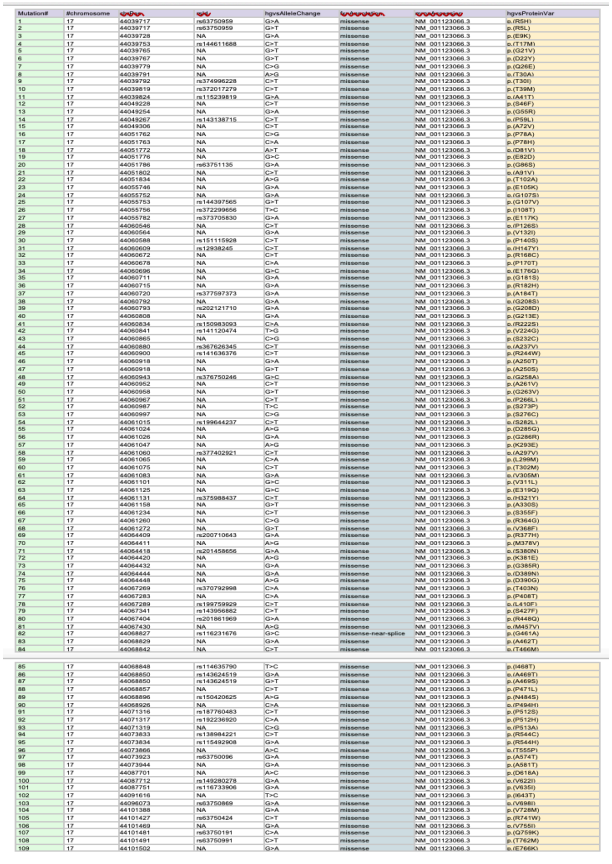
Several other mutations were noted as significant as well, however they did not all meet the conservation threshold, nor did they belong to a tubulin-binding domain. Significant property changes alone, are not always enough to considerably alter protein functionality. This needs to be taken into account along with AA conservation to obtain a more accurate result as to which mutations can be most deleterious.

Conclusion

Three missense mutations that were likely to damage the functionality of the Tau protein were identified. Mutation #91, #92, and #102 were fully conserved and brought changes to AA properties. Alterations as such in the MAPT/Tau gene could potentially increase the risk of developing Tau abnormalities and ultimately, AD. These specific changes can be detected early on through methods of gene analysis to predict AD occurrence and prevent or delay symptoms. By using this approach, there is a hope to pave the way for better understanding the underlying mechanisms of AD and predict its development in patients by looking at changes in relevant gene sequences.

Supplemental Data :

Supplemental Table 1: Geno2Mp Generated Missense Mutation list. It was discovered that there were 109 reported missense mutations in this specific gene. This table was found in the online database Geno$_2$MP. It includes Mutation Number (#), Chromosome number (#), Chromosome position (chrPos), Reference SNP cluster ID (rsID), Allele Change (hgvsAlleleChange), Type of Mutation (fxnAnnotation), mrnaAccession, and the AA change and as a result of an alteration at the numbered locations(hgvsProteinVar). The symbols included here are change (>), adenine (A), cytosine (C), guanine(G), thymine (T), and position (p.). The mutation numbers shown here are constant throughout the entire analysis.



Mutation#	#chromosome	chrPos	rsID	hgvsAlleleChange	fxnAnnotation	mrnaAccession	hgvsProteinVar
1	17	44039717	rs63750959	G>A	missense	NM_001123066.3	p.(R5H)
2	17	44039717	rs63750959	G>T	missense	NM_001123066.3	p.(R5L)
3	17	44039728	NA	G>A	missense	NM_001123066.3	p.(E9K)
4	17	44039753	rs146611688	C>T	missense	NM_001123066.3	p.(T17M)
5	17	44039765	NA	G>T	missense	NM_001123066.3	p.(G21V)
6	17	44039767	NA	G>T	missense	NM_001123066.3	p.(D21Y)
7	17	44039779	NA	C>G	missense	NM_001123066.3	p.(Q26E)
8	17	44039791	NA	A>G	missense	NM_001123066.3	p.(T30A)
9	17	44039792	rs374996228	C>T	missense	NM_001123066.3	p.(T30I)
10	17	44039819	rs372017279	C>T	missense	NM_001123066.3	p.(T39M)
11	17	44039824	rs115239819	G>A	missense	NM_001123066.3	p.(A41T)
12	17	44049228	NA	C>T	missense	NM_001123066.3	p.(S46F)
13	17	44049254	NA	G>A	missense	NM_001123066.3	p.(G55R)
14	17	44049267	rs143138715	C>T	missense	NM_001123066.3	p.(P59L)
15	17	44049306	NA	C>T	missense	NM_001123066.3	p.(A72V)
16	17	44051762	NA	C>G	missense	NM_001123066.3	p.(P78A)
17	17	44051763	NA	C>A	missense	NM_001123066.3	p.(P78H)
18	17	44051772	NA	A>T	missense	NM_001123066.3	p.(D81V)
19	17	44051779	NA	G>C	missense	NM_001123066.3	p.(E82D)
20	17	44051786	rs63751135	G>A	missense	NM_001123066.3	p.(G86S)
21	17	44051802	NA	C>T	missense	NM_001123066.3	p.(A91V)
22	17	44051834	NA	A>G	missense	NM_001123066.3	p.(T102A)
23	17	44055746	NA	G>A	missense	NM_001123066.3	p.(E105K)
24	17	44055752	NA	G>A	missense	NM_001123066.3	p.(G107S)
25	17	44055753	rs144397565	G>T	missense	NM_001123066.3	p.(G107V)
26	17	44055756	rs372209655	T>C	missense	NM_001123066.3	p.(Y108T)
27	17	44055782	rs373705830	G>A	missense	NM_001123066.3	p.(E117K)
28	17	44060546	NA	C>T	missense	NM_001123066.3	p.(R126S)
29	17	44060564	NA	G>A	missense	NM_001123066.3	p.(V132I)
30	17	44060588	rs151115928	C>T	missense	NM_001123066.3	p.(P140S)
31	17	44060609	rs12938245	C>T	missense	NM_001123066.3	p.(H147Y)
32	17	44060672	NA	C>T	missense	NM_001123066.3	p.(R168C)
33	17	44060678	NA	C>A	missense	NM_001123066.3	p.(P170T)
34	17	44060696	NA	G>C	missense	NM_001123066.3	p.(E176Q)
35	17	44060711	NA	G>A	missense	NM_001123066.3	p.(G181S)
36	17	44060715	NA	G>A	missense	NM_001123066.3	p.(R182H)
37	17	44060720	rs377597373	G>A	missense	NM_001123066.3	p.(A184T)
38	17	44060792	NA	G>A	missense	NM_001123066.3	p.(G208S)
39	17	44060793	rs202121710	G>A	missense	NM_001123066.3	p.(G208D)
40	17	44060808	NA	G>A	missense	NM_001123066.3	p.(G213E)
41	17	44060834	rs150983093	C>A	missense	NM_001123066.3	p.(P222S)
42	17	44060841	rs141120474	T>G	missense	NM_001123066.3	p.(V224G)
43	17	44060865	NA	C>G	missense	NM_001123066.3	p.(S232C)
44	17	44060880	rs367626345	C>T	missense	NM_001123066.3	p.(A237V)
45	17	44060900	rs141636376	C>T	missense	NM_001123066.3	p.(R244W)
46	17	44060918	NA	G>A	missense	NM_001123066.3	p.(A250T)
47	17	44060918	NA	G>T	missense	NM_001123066.3	p.(A250S)
48	17	44060943	rs376750246	G>C	missense	NM_001123066.3	p.(G258A)
49	17	44060952	NA	C>T	missense	NM_001123066.3	p.(A261V)
50	17	44060958	NA	G>T	missense	NM_001123066.3	p.(G263V)
51	17	44060967	NA	C>T	missense	NM_001123066.3	p.(P266L)
52	17	44060987	NA	T>C	missense	NM_001123066.3	p.(S273P)
53	17	44060997	NA	C>G	missense	NM_001123066.3	p.(S276C)
54	17	44061015	rs189644237	C>T	missense	NM_001123066.3	p.(S282L)
55	17	44061024	NA	A>G	missense	NM_001123066.3	p.(D285G)
56	17	44061026	NA	G>A	missense	NM_001123066.3	p.(G286R)
57	17	44061047	NA	A>G	missense	NM_001123066.3	p.(K293E)
58	17	44061060	rs377402921	C>T	missense	NM_001123066.3	p.(A297V)
59	17	44061065	NA	C>A	missense	NM_001123066.3	p.(L299M)
60	17	44061075	NA	C>T	missense	NM_001123066.3	p.(T302M)
61	17	44061083	NA	G>A	missense	NM_001123066.3	p.(V305M)
62	17	44061101	NA	G>C	missense	NM_001123066.3	p.(V311L)
63	17	44061125	NA	G>C	missense	NM_001123066.3	p.(E319Q)
64	17	44061131	rs375988437	C>T	missense	NM_001123066.3	p.(H321Y)
65	17	44061158	NA	G>T	missense	NM_001123066.3	p.(A330S)
66	17	44061234	NA	C>T	missense	NM_001123066.3	p.(S355F)
67	17	44061260	NA	C>G	missense	NM_001123066.3	p.(R364G)
68	17	44061272	NA	G>T	missense	NM_001123066.3	p.(V368F)
69	17	44064409	rs200710643	G>A	missense	NM_001123066.3	p.(R377H)
70	17	44064411	NA	A>G	missense	NM_001123066.3	p.(M378V)
71	17	44064418	rs201458656	G>A	missense	NM_001123066.3	p.(S380N)
72	17	44064420	NA	A>G	missense	NM_001123066.3	p.(K381E)
73	17	44064432	NA	G>A	missense	NM_001123066.3	p.(G385R)
74	17	44064444	NA	G>A	missense	NM_001123066.3	p.(D389N)
75	17	44064448	NA	A>G	missense	NM_001123066.3	p.(D390G)
76	17	44067269	NA	C>A	missense	NM_001123066.3	p.(T403N)
77	17	44067283	NA	C>A	missense	NM_001123066.3	p.(P408T)
78	17	44067289	rs199759929	C>T	missense	NM_001123066.3	p.(L410F)
79	17	44067341	rs143956882	C>T	missense	NM_001123066.3	p.(S427F)
80	17	44067404	rs201961969	G>A	missense	NM_001123066.3	p.(R449Q)
81	17	44067430	NA	A>G	missense	NM_001123066.3	p.(M457V)
82	17	44068827	rs116231676	G>C	missense-near-splice	NM_001123066.3	p.(G461A)
83	17	44068829	NA	G>A	missense	NM_001123066.3	p.(A462T)
84	17	44068842	NA	C>T	missense	NM_001123066.3	p.(T466M)
85	17	44068848	rs114635790	T>C	missense	NM_001123066.3	p.(I468T)
86	17	44068850	rs143624519	G>A	missense	NM_001123066.3	p.(A469T)
87	17	44068850	rs143624519	G>T	missense	NM_001123066.3	p.(A469S)
88	17	44068857	NA	C>T	missense	NM_001123066.3	p.(P471L)
89	17	44068896	rs150420625	A>G	missense	NM_001123066.3	p.(N484S)
90	17	44068926	NA	C>A	missense	NM_001123066.3	p.(P494H)
91	17	44071316	rs187760483	C>T	missense	NM_001123066.3	p.(P512S)
92	17	44071317	rs192236920	C>A	missense	NM_001123066.3	p.(P512H)
93	17	44071319	NA	C>G	missense	NM_001123066.3	p.(P513A)
94	17	44073833	rs138984221	C>T	missense	NM_001123066.3	p.(R544C)
95	17	44073834	rs115492908	G>A	missense	NM_001123066.3	p.(R544H)
96	17	44073866	NA	A>C	missense	NM_001123066.3	p.(T555P)
97	17	44073923	rs63750096	G>A	missense	NM_001123066.3	p.(A574T)
98	17	44073944	NA	G>A	missense	NM_001123066.3	p.(A581T)
99	17	44087701	NA	A>C	missense	NM_001123066.3	p.(D618A)
100	17	44087712	rs149280278	G>A	missense	NM_001123066.3	p.(V622I)
101	17	44087751	rs116733906	G>A	missense	NM_001123066.3	p.(V635I)
102	17	44091616	NA	T>C	missense	NM_001123066.3	p.(I643T)
103	17	44096073	rs63750869	G>A	missense	NM_001123066.3	p.(V698I)
104	17	44101388	NA	G>A	missense	NM_001123066.3	p.(V728M)
105	17	44101427	rs63750424	C>T	missense	NM_001123066.3	p.(R741W)
106	17	44101469	NA	G>A	missense	NM_001123066.3	p.(V755I)
107	17	44101481	rs63750191	C>A	missense	NM_001123066.3	p.(Q759K)
108	17	44101491	rs63750991	C>T	missense	NM_001123066.3	p.(T762M)
109	17	44101502	NA	G>A	missense	NM_001123066.3	p.(E766K)

Supplemental Table 2. Mutation Property Changes. : The AA changes were evaluated based on polarity, hydrophobicity, and charge. Specific AA changes are highlighted in yellow and corresponding property shifts are highlighted in blue. Mutation significance is specified by a green highlight, while insignificant mutations are marked in red. Columns without a highlight were generated by Geno$_2$MP, and the others were a result of the analysis.

Mutation#	hgvsAlleleChange	hgvsProteinVar	AA Change	AA Property Change	Is the AA change significant?
1	G>A	p.(R5H)	Arg>His	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Positive	No
2	G>T	p.(R5L)	Arg>Leu	Polar>Non-Polar; Hydrophilic>Hydrophobic; Positive>Uncharged	Yes
3	G>A	p.(E9K)	Glu>Lys	Polar>Polar; Hydrophilic>Hydrophilic; Neaative>Positive	Yes
4	C>T	p.(T17M)	Thr>Met	Polar>Polar; Hydrophilic>Hydrophilic; Uncharged >Uncharged	No
5	G>T	p.(G21V)	Gly>Val	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
6	G>T	p.(D22Y)	Asp>Tyr	Polar>Non-Polar; Hydrophilic>Hydrophobic; Nesative>Uncharaed	Yes
7	C>G	p.(Q26E)	Gln>Glu	Polar>Polar; Hydrophilic>Hydrophilic; Uncharged >Negative;	Yes
8	A>G	p.(T30A)	Thr>Ala	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
9	C>T	p.(T30I)	Thr>Ile	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
10	C>T	p.(T39M)	Thr>Met	Polar>Polar; Hydrophilic>Hydrophilic; Uncharaed >Uncharaed	No
11	G>A	p.(A41T)	Ala>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
12	C>T	p.(S46F)	Ser>Phe	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
13	G>A	p.(G55R)	Gly>Arg	Non-Polar>Polar; Hydrophobic>Hydrophilic; Uncharaed >Positive	Yes
14	C>T	p.(P59L)	Pro>Leu	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
15	C>T	p.(A72V)	Ala>Val	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
16	C>G	p.(P78A)	Pro>Ala	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
17	C>A	p.(P78H)	Pro>His	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
18	A>T	p.(D81V)	Asp>Val	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
19	G>C	p.(E82D)	Glu>Asp	Polar>Polar; Hydrophilic>Hydrophilic; Uncharged >Negative	Yes
20	G>A	p.(G86S)	Gly>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
21	C>T	p.(A91V)	Ala>Val	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
22	A>G	p.(T102A)	Thr>Ala	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
23	G>A	p.(E105K)	Glu>Lys	Polar>Polar; Hydrophilic>Hydrophilic; Negative>Positive	Yes
24	G>A	p.(G107S)	Gly>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
25	G>T	p.(G107V)	Gly>Val	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
26	T>C	p.(I108T)	Ile>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
27	G>A	p.(E117K)	Glu>Lys	Polar>Polar; Hydrophilic>Hydrophilic; Neaative>Positive	Yes
28	C>T	p.(P126S)	Pro>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
29	G>A	p.(V132I)	Val>Ile	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
30	C>T	p.(P140S)	Pro>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
31	C>T	p.(H147Y)	His>Tyr	Polar>Polar; Hydrophilic>Hydrophilic	No
32	C>T	p.(R168C)	Arg>Cys	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Uncharaed	Yes
33	C>A	p.(P170T)	Pro>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
34	G>C	p.(E176Q)	Glu>Gln	Polar>Polar; Hydrophilic>Hydrophilic; Negative>Uncharged	Yes
35	G>A	p.(G181S)	Gly>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
36	G>A	p.(R182H)	Arg>His	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Positive	No
37	G>A	p.(A184T)	Ala>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
38	G>A	p.(G208S)	Gly>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
39	G>A	p.(G208D)	Gly>Asp	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
40	G>A	p.(G213E)	Gly>Glu	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
41	C>A	p.(R222S)	Arg>Ser	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Uncharged	Yes
42	T>G	p.(V224G)	Val>Gly	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
43	C>G	p.(S232C)	Ser>Cys	Polar>Polar; Hydrophilic>Hydrophilic; Uncharaed>Uncharaed	No
44	C>T	p.(A237V)	Ala>Val	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
45	C>T	p.(R244W)	Arg>Trp	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
46	G>A	p.(A250T)	Ala>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
47	G>T	p.(A250S)	Ala>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
48	G>C	p.(G258A)	Gly>Ala	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
49	C>T	p.(A261V)	Ala>Val	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
50	G>T	p.(G263V)	Gly>Val	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
51	C>T	p.(P266L)	Pro>Leu	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
52	T>C	p.(S273P)	Ser>Pro	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
53	C>G	p.(S276C)	Ser>Cys	Polar>Polar; Hydrophilic>Hydrophilic; Uncharged>Uncharged	No
54	C>T	p.(S282L)	Ser>Leu	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
55	A>G	p.(D285G)	Asp>Gly	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
56	G>A	p.(G286R)	Gly>Arg	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
57	A>G	p.(K293E)	Lys>Glu	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Negative	Yes
58	C>T	p.(A297V)	Ala>Val	Non-Pola>Non-Polar; Hydrophobic>Hydrophobic	No
59	C>A	p.(L299M)	Leu>Met	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
60	C>T	p.(T302M)	Thr>Met	Polar>Polar; Hydrophilic>Hydrophilic; Uncharged>Uncharged	No
61	G>A	p.(V309M)	Val>Met	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
62	G>C	p.(V311L)	Val>Leu	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
63	G>C	p.(E319Q)	Glu>Gln	Polar>Polar; Hydrophilic>Hydrophilic; Negative>Uncharged	Yes
64	C>T	p.(H321Y)	His>Tyr	Polar>Polar; Hydrophilic>Hydrophilic	No
65	G>T	p.(A330S)	Ala>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
66	C>T	p.(S355F)	Ser>Phe	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
67	C>G	p.(R364G)	Arg>Gly	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
68	G>T	p.(V368F)	Val>Phe	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic; Positive>Positive	No
69	G>A	p.(R377H)	Arg>His	Polar>Polar; Hydrophilic>Hydrophilic	No
70	A>G	p.(M378V)	Met>Val	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
71	G>A	p.(S386N)	Ser>Asn	Polar>Polar; Hydrophilic>Hydrophilic; Uncharged>Uncharged	No
72	A>G	p.(K381E)	Lys>Glu	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Neaative	Yes
73	G>A	p.(G385R)	Gly>Arg	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
74	G>A	p.(D389N)	Asp>Asn	Polar>Polar; Hydrophilic>Hydrophilic; Neaative>Uncharaed	Yes
75	A>G	p.(D390G)	Asp>Asn	Polar>Polar; Hydrophilic>Hydrophilic; Neaative>Uncharaed	Yes
76	C>A	p.(T403N)	Thr>Asn	Polar>Polar; Hydrophilic>Hydrophilic; Uncharged>Uncharged	No
77	C>A	p.(P408T)	Pro>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
78	C>T	p.(L410F)	Lys>Phe	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
79	C>T	p.(S427F)	Ser>Phe	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
80	G>A	p.(R448Q)	Arg>Gln	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Uncharaed	Yes
81	A>G	p.(M457V)	Met>Val	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
82	G>C	p.(G461A)	Gly>Ala	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
83	G>A	p.(A462T)	Ala>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
84	C>T	p.(T466M)	Thr>Met	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
85	T>C	p.(I468T)	Ile>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
86	G>A	p.(A469T)	Ala>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
87	G>T	p.(A469S)	Ala>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
88	C>T	p.(P471L)	Pro>Leu	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
89	A>G	p.(N484S)	Asn>Ser	Polar>Polar; Hydrophilic>Hydrophilic; Uncharged>Uncharged	No
90	C>A	p.(P494H)	Pro>His	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
91	C>T	p.(P512S)	Pro>Ser	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
92	C>A	p.(P512H)	Pro>His	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
93	C>G	p.(P513A)	Pro>Ala	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
94	C>T	p.(R544C)	Arg>Cys	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Uncharaed	Yes
95	G>A	p.(R544H)	Arg>His	Polar>Polar; Hydrophilic>Hydrophilic; Positive>Positive	No
96	A>C	p.(T555P)	Thr>Pro	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
97	G>A	p.(A574T)	Ala>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
98	G>A	p.(A581T)	Ala>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
99	A>C	p.(D618A)	Asp>Ala	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
100	G>A	p.(V622I)	Val>Ile	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
101	G>A	p.(V635I)	Val>Ile	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
102	T>C	p.(I643T)	Ile>Thr	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
103	G>A	p.(V698I)	Val>Ile	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
104	G>A	p.(V728M)	Val>Met	Non-Polar>Polar; Hydrophobic>Hydrophilic	Yes
105	C>T	p.(R741W)	Arg>Trp	Polar>Non-Polar; Hydrophilic>Hydrophobic	Yes
106	G>A	p.(V755I)	Val>Ile	Non-Polar>Non-Polar; Hydrophobic>Hydrophobic	No
107	C>A	p.(Q759K)	Gln>Lys	Polar>Polar; Hydrophilic>Hydrophilic; Uncharaed>Positive	Yes
108	C>T	p.(T762M)	Thr>Met	Polar>Non-Polar; Hydrophilic>Hydrophobic; Uncharged>Uncharged	Yes
109	G>A	p.(E766K)	Glu>Lys	Polar>Polar; Hydrophilic>Hydrophilic; Uncharaed>Positive	Yes

Supplemental Table 3. AA Conservation Table : Within the 109 mutated AAs, 83 were found to be conserved within at least one or more of the tested organisms. The table was filtered to only display rows in which the AAs were conserved. Organisms that share an AA at their corresponding locations are listed in the column, highlighted in blue. Rows in which AAs were fully conserved amongst all organisms are highlighted in bright yellow. Columns without a highlight were generated by Geno$_2$MP, while the others were created through the analysis.

Mutation#	hgvsProteinVar	hgvsAlleleChange	AA Conserved?	AA conserved in..
1	p.(R5H)	G>A	Yes	Mm, Rn
2	p.(R5L)	G>T	Yes	Mm, Rn
5	p.(G21V)	G>T	Yes	Dm
8	p.(T30A)	A>G	Yes	Mm, Rn
9	p.(T30I)	C>T	Yes	Mm, Rn
12	p.(S46F)	C>T	Yes	Mm, Rn, Xt
13	p.(G55R)	G>A	Yes	Mm, Rn
14	p.(P59L)	C>T	Yes	Mm, Rn
15	p.(A72V)	C>T	Yes	Mm, Rn
16	p.(P78A)	C>G	Yes	Dm, Mm, Rn
17	p.(P78H)	C>A	Yes	Dm, Mm, Rn
18	p.(D81V)	A>T	Yes	Mm
19	p.(E82D)	G>C	Yes	Mm, Rn
20	p.(G86S)	G>A	Yes	Xt
21	p.(A91V)	C>T	Yes	Mm, Rn
22	p.(T102A)	A>G	Yes	Dm, Mm, Rn, Xt
23	p.(E105K)	G>A	Yes	Mm, Rn, Xt
24	p.(G107S)	G>A	Yes	Mm, Rn, Xt
25	p.(G107V)	G>T	Yes	Mm, Rn, Xt
26	p.(I108T)	T>C	Yes	Mm, Rn
28	p.(P126S)	C>T	Yes	Mm, Rn
29	p.(V132I)	G>A	Yes	Dm
30	p.(P140S)	C>T	Yes	Mm, Rn
31	p.(H147Y)	C>T	Yes	Rn
33	p.(P170T)	C>A	Yes	Mm, Rn
34	p.(E176Q)	G>C	Yes	Mm, Rn
37	p.(A184T)	G>A	Yes	Mm, Rn
38	p.(G208S)	G>A	Yes	Mm, Rn
39	p.(G208D)	G>A	Yes	Mm, Rn
40	p.(G213E)	G>A	Yes	Mm, Rn, Xt
42	p.(V224G)	T>G	Yes	Mm
43	p.(S232C)	C>G	Yes	Mm, Rn
44	p.(A237V)	C>T	Yes	Mm, Rn
48	p.(G258A)	G>C	Yes	Mm, Rn
49	p.(A261V)	C>T	Yes	Rn
50	p.(G263V)	G>T	Yes	Mm, Rn
51	p.(P266L)	C>T	Yes	Mm, Rn
52	p.(S273P)	T>C	Yes	Mm, Rn
53	p.(S276C)	C>G	Yes	Mm, Rn
54	p.(S282L)	C>T	Yes	Mm, Rn
56	p.(Q286R)	G>A	Yes	Mm, Rn
58	p.(A297V)	C>T	Yes	Mm, Rn
60	p.(T302M)	C>T	Yes	Mm, Rn
61	p.(V305M)	G>A	Yes	Dm, Mm, Rn, Xt
65	p.(A330S)	G>T	Yes	Rn
66	p.(V368F)	G>T	Yes	Mm, Rn, Xt
69	p.(R377H)	G>A	Yes	Mm, Rn, Dm
72	p.(K381E)	A>G	Yes	Xt
74	p.(D389N)	G>A	Yes	Mm, Rn
76	p.(T403N)	C>A	Yes	Rn
77	p.(P408T)	C>A	Yes	Ce, Dm, Mm, Rn
78	p.(L410F)	C>T	Yes	Mm, Rn
79	p.(S427F)	C>T	Yes	Dm, Dr, Mm, Rn
80	p.(R448Q)	G>A	Yes	Mm, Rn
81	p.(M457V)	A>G	Yes	Dr, Mm, Rn
82	p.(G461A)	G>C	Yes	Mm, Rn
83	p.(A462T)	G>A	Yes	Mm, Rn, Xt
84	p.(T466M)	C>T	Yes	Mm, Rn
85	p.(I468T)	T>C	Yes	Mm, Rn
86	p.(A469T)	G>A	Yes	Dr, Mm, Rn
87	p.(A469S)	G>T	Yes	Dr, Mm, Rn
88	p.(P471L)	C>T	Yes	Mm, Rn
89	p.(N484S)	A>G	Yes	Mm, Rn
90	p.(P494H)	C>A	Yes	Ce, Mm, Rn
91	p.(P512S)	C>T	Yes	Ce, Dm, Dr, Mm, Rn, Xt
92	p.(P512H)	C>A	Yes	Ce, Dm, Dr, Mm, Rn, Xt
93	p.(P513A)	C>G	Yes	Mm, Rn, Xt
94	p.(R544C)	C>T	Yes	Mm, Rn, Xt
95	p.(R544H)	G>A	Yes	Mm, Rn, Xt
96	p.(T555P)	A>C	Yes	Ce, Mm, Rn, Xt
97	p.(A574T)	G>A	Yes	Xt
98	p.(A581T)	G>A	Yes	Ce, Dr, Mm, Rn,
99	p.(D618A)	A>C	Yes	Dm, Dr, Mm, Rn, Xt
100	p.(V622I)	G>A	Yes	Ce, Dr, Mm, Rn, Xt
101	p.(V635I)	G>A	Yes	Ce, Dr, Mm, Rn
102	p.(I643T)	T>C	Yes	Ce, Dm, Dr, Mm, Rn, Xt
103	p.(V698I)	G>A	Yes	Mm, Rn
104	p.(V728M)	G>A	Yes	Mm, Rn, Xt
105	p.(R741W)	C>T	Yes	Mm, Rn, Xt
106	p.(V755I)	G>A	Yes	Mm, Rn
107	p.(Q759K)	C>A	Yes	Dr, Mm, Rn, Xt
108	p.(T762M)	C>T	Yes	Mm, Rn, Xt
109	p.(E766K)	G>A	Yes	Mm, Rn, Xt

Acknowledgements

This project was made possible through the help and guidance of MSc. Zeynep Öztürk of whom I am extremely appreciative to. I would also like to thank my parents for their endless support in my education.

References

1. Durmaz A, Kumral E, Durmaz B, Huseyin A., Aslan G., Ozkinay F., Pehlivan S., Orman M., Cogulu O. Genetic factors associated with the predisposition to late onset Alzheimer's disease. Gene. 2019;707:212-215. doi:10.1016/j.gene.2019.05.030 https://pubmed ncbi.nlm.nih.gov/31102717/.
2. 2020 Alzheimer's disease facts and figures [published online ahead of print, 2020 Mar 10]. Alzheimers Dement. 2020;10.1002alz.12068 doi:10.1002/alz.12068 https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/alz.12068
3. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Becker JT. Age, Alzheimer disease, and brain structure. Neurology. 2009;73(22):18991905. doi:10.1212/WNL.0b013e3181c3f293 https://pubmed.ncbi nlm.nih.gov/19846828/
4. "Alzheimer's Disease | AD." MedlinePlus, U.S. National Library of Medicine, 8 June 2020, medlineplus.gov/alzheimersdisease.html https://medlineplus.gov/alzheimersdisease.html.
5. "Alzheimer Disease: MedlinePlus Medical Encyclopedia." Medlineplus.Gov, 2016, medlineplus.gov/ency/article/000760.htmlhttps://medlineplus.gov/ency/article/000760.htm
6. Bekris, Lynn M et al. "Genetics of Alzheimer disease." Journal of geriatric psychiatry and neurology vol. 23,4 (2010): 213-27. doi:10.1177/0891988710383571 https://www.ncbi.nlm.nih.gov pmc/articles/PMC3044597/
7. Barbier, Pascale et al. "Role of Tau as a Microtubule-Associated Protein: Structural and Functional Aspects." Frontiers in aging neuroscience vol. 11 204. 7 Aug. 2019, doi:10.3389/fnagi.2019.00204 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6692637/
8. Guo, T., Noble, W. & Hanger, D.P. Roles of tau protein in health and disease. Acta Neuropathol 133, 665–704 (2017). https://doi.org/10.1007/s00401-017-1707-9.

DOI: 10.36838/v3i4.13

9. Iqbal K, Liu F, Gong CX, Grundke-Iqbal I. Tau in Alzheimer disease and related tauopathies. Curr Alzheimer Res. 2010; 7(8):656-664. doi:10.2174/156720510793611592 https://pubmed.ncbi.nlm.nih.gov/20678074/
10. "IARC TP53 Database." Amino Acid Properties, p53.iarc.fr AAProperties.aspx. https://p53.iarc.fr/AAProperties.aspx. Online Tools Geno2MP, https://geno2mp.gs.washington.edu/Geno2MP/#/MARRVEL, marrvel.org/human/gene/4137. Microtubule-Associated Protein Tau Isoform 6 [Homo Sapiens] - Protein - NCBI. www.ncbi.nlm.nih.gov/protein/NP_001116538.2. Embl-Ebi. "Clustal Omega." EBI, www.ebi.ac.uk/Tools/msa/clustalo/.

Author

Tejas Shah, the first and corresponding author of this paper, is a senior (Grade 12), currently attending Hopkinton High School. He is ever grateful for having been able to pursue a project that relates to his passion of entering the field of medicine. Tejas hopes to conduct similar research as an aspiring neuroscience major in the near future.