|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **GENE** | **TRANSCRIPT** | **NAME** | **FUNCTION** | **REFERENCES** |
| *ADAM9* | NM\_003816 | ADAM metallopeptidase domain 9 | α-secretase | 1, 2, 3 |
| *ADAM10* | NM\_001110 | ADAM metallopeptidase domain 10 | α-secretase | 2, 3, 4, |
| *ADAM17* | NM\_003183 | ADAM metallopeptidase domain 17 | α-secretase | 2, 3, |
| *BACE1* | NM\_012104 | ß -site APP-cleaving enzyme 1 | ß-secretase | 5, 6 |
| *BACE2* | NM\_012105 | ß -site APP-cleaving enzyme 2 | ß-secretase | 7, 8, |
| *NCSTN* | NM\_015331 | nicastrin | γ-secretase | 9, 10, 11 |
| *PSENEN (PEN-2)* | NM\_172341 | presenilin enhancer γ secretase subunit | γ-secretase | 11, 12, |
| *APH1B* | NM\_031301 | APH1B γ secretase subunit | γ-secretase | 11, 13 |
| *APLP1* | NM\_001024807 | Aß (A4) precursor-like protein 1 | APP agonist cleaved by secretases | 14, 15 |
| *APBA1 (MINT1, X11A)* | NM\_001163 | Aß (A4) precursor protein-binding, family A, member 1 | It stabilizes APP and inhibits production of proteolytic APP fragments including the Aß | 16, 17, 18, |
| *LRRTM3* | NM\_178011 | leucine rich repeat transmembrane neuronal 3 | Aß production | 19, 20 |
| *GPR3* | NM\_005281 | G-protein coupled receptor 3 | It activates adenylate cyclase and modulates Aß production | 21 |
| *TTR* | NM\_000371 | transthyretin | Aß deposition | 22, 23, 24 |
| *SORL1* | NM\_003105 | sortilin-related receptor | APP recycling and vesicles trafficking | 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 |
| *ECE1* | NM\_001397 | endothelin converting enzyme 1 | intracellular degradation | 35, 36, 37 |
| *ECE2* | NM\_014693 | endothelin converting enzyme 2 | intracellular degradation | 35, 36, |
| *IDE* | NM\_004969 | insulin-degrading enzyme | Intracellular and extracellular degradation | 38, 39, 40, 41, 42 |
| *CST3* | NM\_000099 | cystatin C | Intracellular and extracellular degradation | 43, 44, 45, 46 |
| *CTSB* | NM\_001908 | cathepsin B | Intracellular and extracellular degradation | 43 |
| *CTSD* | NM\_001909 | cathepsin D | intracellular degradation | 47, 48 |
| *LYZ* | NM\_000239 | lysozyme | intracellular degradation | 49 |
| *MME (Neprylisin)* | NM\_000902 | membrane metallo-endopeptidase | extracellular degradation | 50, 51, 52, 53, 54 |
| *ACE* | NM\_000789 | angiotensin I converting enzyme | extracellular degradation | 55, 56, 57 |
| *MMP3* | NM\_002422 | matrix metallopeptidase | extracellular degradation | 58, 59, 60, 61 |
| *A2M* | NM\_000014 | α-2-macroglobulin | extracellular degradation | 62, 63, 64, 65, 66 |
| *PLAT* | NM\_000930 | plasminogen activator, tissue | extracellular degradation | 67, 68, 69, 70 |
| *MEP1B* | NM\_005925 | meprin A, β | extracellular degradation | 71, 72, 73, |
| *KLK6* | NM\_001012964 | kallikrein-related peptidase peptidase 6 | extracellular degradation | 74 |
| *LRP1* | NM\_002332 | Low density lipoprotein receptor-related protein 1 | extracellular clearance | 75, 76 |

**S1 Table. List of the 29 genes selected in our study**

**Bioinformatic**

Each of the samples in our dataset consisted of paired-end 100 base pair reads. We used the Burrows-Wheeler Aligner (BWA)77 to map the reads to the human genome (hg19/GRCh37). Following read mapping, we used SAMtools 78, Picard (<http://picard.sourceforge.net>), and the Genome Analysis Toolkit (GATK) 79,80 to refine the resulting alignments by removing duplicates, performing realignment around InDels, and recalibrating base quality scores. We then used the GATK’s UnifiedGenotyper to identify sequence variants, and subsequently filtered the variants and recalibrated variant quality scores 79. Our final dataset consisted of variant call format (VCF) files containing variants that passed all filters. Since our dataset consisted of a mix of exomes captured using different kits, and whole genome sequences, we employed a highly conservative approach to variant selection to increase our confidence that analyzed variants are true positives. We limited our dataset of variants to only those genomic regions we expected to have been sequenced in each of the exomes (based on capture probes used for exome library preparation) and whole genomes. Next, we compiled a list of all the variants present in at least a single sample. We examined each of the variants from the list of total variants in each sample, whether or not the variant was called by the GATK, and reassigned the genotype for that variant according to the following criteria: 1) If the variant was called by the GATK and passed all filters, we used the GATK genotype; 2) If no variant was called at the genomic position in question, we returned to the raw VCF file and if there were reads containing the variant, but the variant was not called because of failing filters or because only a small number of reads contain the variant, we set the genotype to missing for the sample and 3) if all the reads at this position for the sample indicated reference alleles, we set the genotype to homozygous reference. Resulting sequence files were converted to Plink format 81 using VCFTools 82. Lastly, we removed all variants not in our pre-defined list of candidate genes (*A2M* [NM\_000014], *ACE* [NM\_000789], *ADAM9* [NM\_003816], *ADAM10* [NM\_001110], *ADAM17* [NM\_003183], *APBA1* [NM\_001163], *APH1B* [NM\_031301], *APLP1* [NM\_001024807], *BACE1* [NM\_012104], *BACE2* [NM\_012105], *CST3* [NM\_000099], *CTSB* [NM\_001908], *CTSD* [NM\_001909], *ECE1* [NM\_001397], *ECE2* [NM\_014693], *GPR3* [NM\_005281], *IDE* [NM\_004969], *LRP1* [NM\_002332], *KLK6* [NM\_001012964], *LRRTM3* [NM\_178011], *LYZ* [NM\_000239], *MEP1B* [NM\_005925], *MME* [NM\_000902], *MMP3* [NM\_002422], *NCSTN* [NM\_015331] , *PLAT* [NM\_000930], *PSENEN* [NM\_172341], *SORL1* [NM\_003105], *TTR* [NM\_000371]) (**Table S1**). Remaining variants were annotated using ANNOVAR 83. Each variant was annotated with gene information (gene name, transcript ID, and transcript and protein positions of the variant), genomic location (exon, intron, UTR, intergenic, etc.), one or more variant classes (5’-UTR, 3’-UTR, intergenic, intronic, splice site, nonsynonymous, stop-gain, stop-loss, or synonymous), the 1000 Genomes minor allele frequency 84, dbSNP identifier85, and PolyPhen-2 86 and SIFT 87 functional predictions.

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