Ji RR, Serebriyskaya T, Natalia Kuzkina N. Genetic Landscape of aHUS: A Comprehensive Analysis of Genetic Variants Reported in The Literature. J Rare Dis Res Treat. (2018) 4(1): 13-51

www.rarediseasesjournal.com

Journal of Rare Diseases Research & Treatment

Research Article Open Access

Genetic Landscape of aHUS: A Comprehensive Analysis of Genetic Variants Reported in The Literature

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Article Info

Article Notes

Received: October 4, 2018

Accepted: December 19, 2018

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Keywords

Genotype-phenotype

Allelic frequency

aHUS

Alternative complement pathway

Pathogenicity

Abstract

Genetic information provides important guidance for long-term management of patients with atypical hemolytic uremic syndrome (aHUS), an extremely rare disease that primarily affects a patient's kidney. To better understand the phenotypic impact of variants identified in aHUS patients, we systematically mined the National Library of Medicine database for case studies of aHUS patients with identifiable genetic variants. Allelic variants from 10 genes (C3, CFB, CFH, CFI, CFHR1, CFHR3, CFHR5, DGKE, CD46/MCP, and THBD) associated with aHUS were collected from 1652 patients. We analyze the enrichment of genetic variants in this "literature cohort" compared with a reference population, the Genome Aggregation Database (gnomAD). We also used a number of tools to predict the pathogenicity of the variants, attempting to reconcile all the results using the protein structure and conservation data. In total, we identified 447 unique genetic variants: 301 of these were not present in the gnomAD database and thus have "moderate" evidence of pathogenicity; 33 variants have "strong" evidence of pathogenicity by enrichment analysis. This study showcases an *in silico* framework that patient data aggregation and a large scale sequencing database provided a novel opportunity to understand genotype-phenotype associations in aHUS. This framework can be efficiently applied to other rare diseases where data are sparse to help improve the diagnosis and management of these patients.

Abbreviations: aHUS: atypical hemolytic uremic syndrome; gnomAD: Genome Aggregation Database; CD46/MCP: cluster of differentiation 46/membrane cofactor protein; CFH: complement factor H; CFI: complement factor I; CFB: complement factor B; C3: complement component 3; ACMG: American College of Medical Genetics; AF: allele frequency; CFHR1: complement factor H-related protein 1; CFHR3: complement factor H-related protein 3; CFHR5: complement factor H-related protein 5; DGKE: diacylglycerol kinase epsilon; THBD: thrombomodulin; MEDLINE: Medical Literature Analysis and Retrieval System Online; VEP: variant effect predictor; SIFT: sorts intolerant from tolerant substitutions; PROVEAN: protein variation effect analyzer; FATHMM: functional analysis through Hidden Markov Models

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a disease characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.[1] aHUS is extremely rare. Although the precise incidence and prevalence are unknown, it is estimated that aHUS affects 1–2 individuals per million inhabitants in the United States.[2] aHUS can occur at any age, from the neonatal period to adulthood, although the onset appears to be more frequent in childhood than adulthood.[3] In childhood, aHUS affects males and females equally.[4] In adulthood, however, there is a preponderance in females affected and pregnancy can be a triggering event.[5]

aHUS is caused by chronic, uncontrolled activation or dysregulation of the alternative pathway of complement.[6] Unlike the classical and lectin pathways of complement, the alternative pathway is continually activated and closely regulated by a number of complement regulatory proteins (such as complement factor H [CFH], complement factor I [CFI], and CD46/membrane cofactor protein [MCP]), so that host cells are not damaged.[3] In most patients with aHUS, it has been demonstrated that the excessive activation of complement can result from mutations in any of the regulatory proteins or production of neutralizing autoantibody of these proteins, for example, anti-factor H antibodies.[7,8]

Although not required for diagnosis of aHUS, information on pathogenic complement mutations can be used to establish the cause of disease with accuracy, as well as to guide long-term disease management decisions and effective treatment.[9-11] Approximately 20% of patients experience extrarenal manifestations, including central nervous system, cardiac, gastrointestinal, distal extremity, and severe systemic organ involvement.[4,8,10] The ongoing risk of these manifestations varies among genotypes. For example, patients having mutations in *C3*, complement factor B (CFB), and CFH are particularly at risk for developing cardiovascular complications.[12]

In approximately 30–50% of individuals with aHUS, no mutation in a complement gene and no autoantibodies can be detected.[7,8] However, recent literature exploring larger panels and new high-throughput sequencing technology show that other genes and pathways such as the coagulation pathway are also associated with aHUS.[13] Nonetheless, many variants identified in patients are classified as variants of unknown clinical significance.[14] Interpretation of these variants is difficult because: (1) some functional assays may be less reliable in predicting the impact of variants on protein function than others; (2) the rarity of the disease hinders the aggregation of a sufficiently large patient cohort; (3) incomplete penetrance is the norm in these patients.[14,15]

The standards and guidelines published in 2015 by the American College of Medical Genetics (ACMG) lay out an extensive framework of evidence for interpretation of sequence variants, including guidance for using population data and computational and predictive tools.[14] By definition, causal genetic variants are enriched in patient populations as compared with reference populations. This principle has been exploited in genome-wide association studies to identify genes implicated in common diseases.[16] In rare diseases, similar analyses can be utilized to assess pathogenicity of rare genetic variants if their allele frequencies (AFs) in patient populations and reference/control populations can be estimated. Large population databases such as the Genome Aggregation Database (gnomAD),[17,18] containing 123 136 exome sequences and 15 496 whole-genome sequences of unrelated individuals from a wide variety of large-scale sequencing projects, now make it possible to obtain AFs of rare variants in reference populations. However, lack of a large patient cohort makes estimating variant AFs in patients with rare diseases challenging.

To overcome this difficulty, we created a "literature cohort" of more than 1600 patients with aHUS by compiling all case studies in MEDLINE. The allelic variants of 10 genes (namely, C3, CD46/MCP, CFB, CFH, complement factor H-related protein 1 [CFHR1], complement factor H-related protein 3 [CFHR3], complement factor H-related protein 5 [CFHR5], complement factor I [CFI], diacylglycerol kinase epsilon [DGKE], and thrombomodulin [THBD]) known to be associated with aHUS,[3,19] along with the patient characteristics, were compiled and stored together in a relational database. We assessed the pathogenicity of genetic variants in the 10 genes with bioinformatic, statistical, and structural analyses.

Materials And Methods

Literature Mining and Variant Annotation

MEDLINE was searched systematically through April 30, 2017, for all case reports of patients with aHUS with identifiable genetic variants in any of the 10 genes known to be associated with aHUS: C3, CD46/MCP, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, DGKE, and THBD.[3,19] If reported, information about the patients' relatives was also recorded. When possible, genetic variants were annotated with patient demographics (e.g., genetic ancestry, age, sex), as well as specific disease characteristics such as onset, severity, etc. All data were stored in a relational database to allow data retrieval using structured query language.

To account for repeated-case reporting in the literature, patients were first matched based on age, sex, onset, genetic ancestry, and variant information. Potential matches were manually checked before being merged. In cases where one or more of the fields (e.g., age, sex, onset, genetic ancestry) were missing, the original articles were double-checked to ensure that they referenced each other and came from the same source (i.e., authors). All matches had to have the same genetic variant(s). We designated the resulting cases the "aHUS literature cohort."

Variant Pathogenicity Analysis (Enrichment Analysis)

For every variant (e.g., allele A) present in both the aHUS literature cohort and the gnomAD reference population,[17] a two-by-two contingency table can be constructed:

	allele A	non-allele A
individual with aHUS	count in literature cohort	count in literature cohort
individual without aHUS	count in gnomAD	count in gnomAD

A right-tailed Fisher exact test was performed to evaluate whether allele A was enriched in the aHUS literature cohort as compared with that in the reference population gnomAD (i.e., non-aHUS population). *P* values were Bonferroni-corrected to account for multiple tests performed.

The same analysis was performed comparing the variants' AF in the non-Finnish European subgroup (63 369 subjects) from gnomAD and that of patients of non-Finnish European ancestry (1261 patients) in the literature cohort.

In Silico Pathogenicity Prediction

The pathogenicity of genetic variants was evaluated using four of the representative methods included in the Variant Effect Predictor (VEP) tool[20]: Sorts Intolerant From Tolerant substitutions (SIFT),[21] PROtein Variation Effect ANalyzer (PROVEAN),[22] Functional Analysis Through Hidden Markov Models (FATHMM),[23] and MutationTaster.[24] Default settings were used to run the software. The results were then classified as either "deleterious" with a value of "1," or "tolerated" with a value of "0" based on the specific criteria per method. For SIFT, the "deleterious" category included both predicted "deleterious" and "deleterious_low_confidence," otherwise "tolerated"; for PROVEAN, the "deleterious" category included predicted "damaging," otherwise "neutral" and in case of multiple predictions, more "damaging" results were required to be designated as "deleterious"; for FATHMM, the "deleterious" category included predicted "damaging," otherwise "tolerated," and in case of multiple predictions, more "damaging" results were required to be designated as "deleterious"; for MutationTaster, the "deleterious" category included both predicted "disease_causing_automatic" (A) and "disease_causing" (D), otherwise "tolerated," and in case of multiple predictions, more A/D results were required to be designated as "deleterious." In the end, the numeric values of the predictions were summed; thus, the final value represented how many methods made "deleterious" predictions.

Adjustment of AF in Patients With aHUS

Before statistical analyses were performed, the AFs of the variants in the aHUS literature cohort were adjusted by a factor of two because this cohort only included patients with identifiable genetic variants, who account for approximately 50% of the total aHUS patient population.

Results

Genetic Variants in the aHUS Literature Cohort Have Similar Distributions as in Reported Patient Cohorts

A systematic mining of the literature identified 1652 patients with aHUS with mutations in at least one of the 10 complement genes that have been shown to be associated with the disease.[3,19] This group of patients was designated as the aHUS literature cohort. **Table 1** contains a breakdown of the patients in the literature cohort by mutated genes (see column "Observed % Patient"). Because the literature cohort had only patients with identifiable genetic variants, who account for approximately 50% of the total aHUS patient population,[3,19] the patient percentages were adjusted by a factor of two.

Table 1 also contains the breakdown of patients by

Table 1. Summary of genetic variants identified in aHUS literature cohort

Gene	Patient Number	Observed % Patient [a]	Expected % Patient [b]	Unique Variant [c]	Variant in gnomAD
CFH	733	22.2	20-30	184	48
CFI	188	5.7	4-10	56	40
CD46	257	7.8	5-15	73	22
C3	234	7.1	2-10	58	17
CFB	65	2.0	1-4	21	3
DGKE	36	1.1		28	4
THBD	41	1.2	3-5	12	9
CFHR1	240	7.3		1	0
CFHR3	181	5.5		1	1
CFHR5	23	0.7		13	2
Total	**1652** [d]			**447**	**146**

[a] Adjusted by a factor of 2 to account for the fact that this cohort includes patients with identifiable genetic variants.

[b] Loirat C, Frémeaux-Bacchi V. 2011. *Orphanet J Rare Dis*, 6:60; Noris M, Remuzzi G. 2015. *Am J Kidney Dis*, 66(2):359-75.

[c] Excluding structural variants with no defined breakpoints.

[d] Total number of patients - some patients have variants in two or more genes.

CD46/MCP, membrane cofactor protein; *CFB*, complement factor B; *CFH*, complement factor H; *CFI*, complement factor I; *CFHR1*, complement factor H-related protein 1; *CFHR3*, complement factor H-related protein 3; *CFHR5*, complement factor H-related protein 5; *DGKE*, diacylglycerol kinase epsilon; *THBD*, thrombomodulin.

mutated genes from published aHUS cohort studies (see column "Expected % Patient").[19] It has been shown that CFH is the most frequently mutated gene in these patients, accounting for approximately 20% to 30% of the genetic predisposition to aHUS. Consistently, CFH was also the most-mutated gene in the literature cohort, with 733 cases, or approximately 22% of patients having one or more variant in this gene. Genetic variants observed in our cohort, such as C3 (7%), CD46/MCP (8%), CFB (2%), and CFI (6%), also showed similar mutation rates as that reported for the literature cohort. *DGKE* mutations have been identified in 5% to 27% of patients aged 1 year and younger.[25,26] In the literature cohort, there were 136 patients with a disease onset at or before 12 months. Twenty-four or 8.8% of these young patients had at least one DKGE variant. Only one gene, THBD, had a lower mutation rate in the literature cohort compared with its published mutation rates in patients with aHUS.

Most patients with aHUS have a mutation in only one gene and carry only one variant (**Figure 1A and 1B**). Among those patients who carry multiple genetic variants, the *CFH*, *CFHR1-5* gene cluster on chromosome 1 is usually involved. The high sequence homology among these genes predisposes this genomic region to gene conversions and genomic rearrangements.[27,28,29] Indeed, most of the variants in this region are structural variants with no defined breakpoints.

Consistent with the fact that aHUS is a rare disease, the majority of the variants collected were extremely rare. All but four of them had an AF ≤ 1% (**Figure 1C**). In the population database gnomAD,[17] which has sequence data for more than 138,000 individuals, 301 of the variants are not present (**Figure 1C**). According to ACMG guidelines, these 301 variants have moderate evidence for pathogenicity (PM2).[14] Given that the gene mutation rates in the literature cohort were in good agreement with those reported in the literature, we concluded that we could use this cohort to estimate AF in the aHUS population for a variant of interest.

Potentially Pathogenic Genetic Variants Were Identified by Enrichment Analysis

Although an identified variant in a causing gene can be suggestive of its pathogenicity, additional evidence such as functional/computational analysis is necessary to confirm the initial hypothesis. One approach is to examine whether such a genetic variant is statistically enriched in the patient population compared with a reference population. We employed this approach to evaluate the variants collected from a patient with aHUS and used the literature cohort and gnomAD[17] as the patient and reference populations, respectively.

For each of the 146 variants present in both the literature cohort and gnomAD (**Figure 1C**), a Fisher exact test was utilized to compare the AFs in both groups. Using a cutoff of Bonferroni-corrected *P* value of less than or equal to 0.05, 40 variants were found to be significantly enriched in the literature patient cohort (**Table S1**). An examination of the AFs in gnomAD showed that all of the 40 variants are extremely rare (AF ≤ 0.001). Clearly, enrichment analysis can be applied to all types of genetic variants; among the 40 variants statistically enriched in patients, there were 27 missense, six stop gained, four splice, and two frameshift variants and one insertion/deletion variant.

We also ran the analysis by matching the genetic ancestry of patient and reference populations. Because non-Finnish European was the only ethnicity well represented in the literature cohort (1261 patients) and gnomAD (63 369 individuals), the analysis was performed using this subpopulation. There were 100 variants remaining when

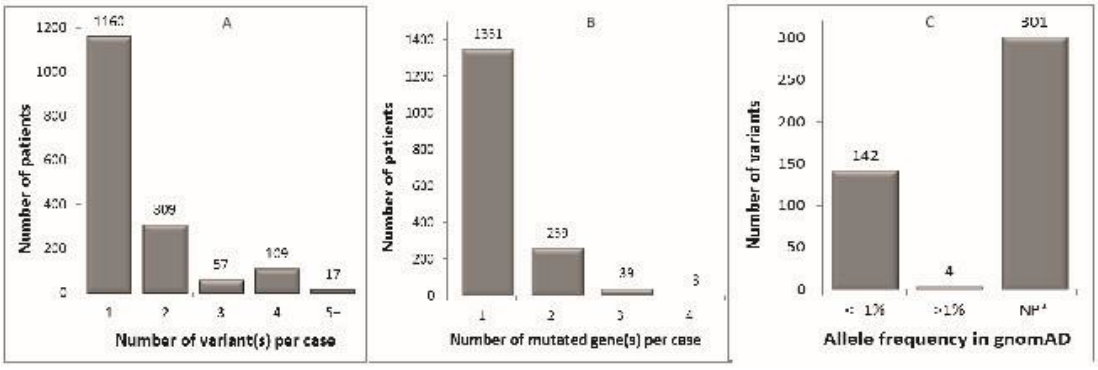

Figure 1: Distribution of genetic variants in aHUS literature cohort.
A. Numbers on bars are the patient numbers harboring the corresponding number of variant(s).
B. Numbers on bars are the patient numbers harboring variant(s) in the corresponding number of gene(s).
C. Numbers on bars are the variant numbers with the corresponding allele frequency. The allele frequency is based on gnomAD. NP: not present.
aHUS, atypical hemolytic uremic syndrome; gnomAD, Genome Aggregation Database; NP, not present.

only non-Finnish Europeans were considered: 34 were found to be overrepresented in patients with aHUS. **Figure 2** depicts the overlaps of the two analysis results: 33 variants were found to be enriched in patients regardless of ethnicity; only one variant was found to be enriched in patients when only non-Finnish Europeans were considered; seven variants were found to be enriched in patients when all ethnicities were included. However, three of the seven variants were due to the fact that they were missing in non-Finnish European populations (**Figure 2** and **Table S1**).

In Silico Pathogenic Prediction

Numerous computational methods have been developed to predict the functional impact of genetic variant at the protein level. We used four of the representative methods (SIFT, PROVEAN, FATHMM, and MutationTaster) included in the VEP tool to evaluate the pathogenicity of the genetic variants identified in patients with aHUS. Two of the methods, SIFT[21] and PROVEAN,[22] are primarily based on amino acid sequence homology and protein structure information. FATHMM[23] utilizes hidden Markov models weighted for human mutations, whereas MutationTaster uses a Bayes classifier to assess the results from a battery of *in silico* analyses and determine the combined effect on protein function.[24]

The complete prediction results are presented in **Table S2**. There was no output for variants such as insertions, deletions, frameshifts, or those affecting the splicing regions. In cases of gained stop codons, only MutationTaster could predict their impacts, but there were exceptions. In two cases where the mutations caused a frameshift before a stop codon, MutationTaster could no longer make a prediction. In addition, MutationTaster failed to predict a gained stop codon at amino acid position 160 in *CFHR1*; this mutation is right in the middle of the protein and will lead to a large truncation of the protein. Finally, only SIFT could correctly predict the deleterious effect of the loss of a start codon.

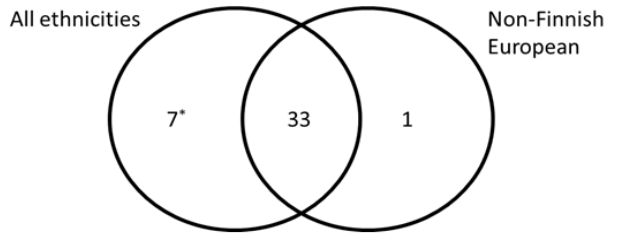

Figure 2: Comparison of enrichment analysis results using all ethnicities or non-Finnish European.
The venn diagram represents the overlap of variants exhibiting significant enrichment in aHUS patients when all ethnicities (left) or non-Finnish European (right) was considered. gnomeAD was used as reference population control.
*Three of 7 variants are not present in the non-Finnish European group in the Genome Aggregation Database.

The summary of the prediction results of 282 missense mutations is shown in **Table S3**. Sixty-six or approximately 23% of these variants were not predicted as "deleterious" by any of the methods. By contrast, 43 variants were predicted to be "deleterious" by all four methods. Interestingly, a little more than half of the variants (22 of 43) involve the substitution of a cysteine residue by another amino acid (**Table S2**). Because cysteine residue is sometimes involved in forming disulfide bonds, which play an important role in the folding and stability of proteins, its substitution can be deleterious for maintaining protein structure and function. For example, *CFH* contains 20 cysteine-rich short consensus repeats. These repeats create a beta-sandwich arrangement held together by disulfide bonds formed by cysteine residues.[30,31]

The concordance of missense variant prediction varied among the methods utilized (**Table S4**). The two homology-based methods, SIFT and PROVEAN, shared high concordance in the prediction results. FATHMM predicted the fewest number of "deleterious" variants, and its output was least consistent with those of the other methods.

Concordance Between Prediction and Enrichment Analyses

The concordance of results generated by computational prediction and enrichment analyses is shown in **Table S5**. In general, if a variant was significantly enriched in the patient population, it was more likely to have a "deleterious" prediction by at least one of the prediction methods. Conversely, if a variant was predicted to be "deleterious," it was more likely to be statistically significantly enriched in the patient population.

When using "enriched" variants (corrected $P \leq 0.05$) as benchmarks for performance, FATHMM performed very well in terms of specificity (rows "Specificity – prediction"). However, the homology-based methods SIFT and PROVEAN were more sensitive, especially for missense variants, likely because these methods utilize protein sequence alignments in their predictions (rows "Sensitivity – prediction"). Overall, SIFT and PROVEAN have the better combination of sensitivity and specificity compared with the other prediction methods.

Conversely, when using "deleterious" variants (predicted by at least one tool) as benchmarks to assess the performance of enrichment analysis, the best concordance was with MutationTaster when all variants are considered. However, when only missense variants were included, results from the enrichment analysis also had very good concordance with those generated by SIFT and PROVEAN (rows "Specificity – enrichment" and "Sensitivity – enrichment", **Table S5**).

An enrichment analysis can evaluate variants that are completely missed by prediction methods. For example, most of the variants flagged as potentially deleterious by only the enrichment analysis are variants in the splicing regions, deletions, and frameshifts (**Table S6**).

To examine the discordance between computational prediction and enrichment analyses, we used a scheme as depicted in **Figure 3** to identify variants of discordance. To minimize random sampling bias, we examined variants with at least five allele counts in the literature cohort. The scheme identified five variants that were predicted by at least one computational method to be "deleterious" but exhibited no enrichment in the patient population. One of these variants (CFH c.2850G>T, p.Q950H) is within the SCR16 repeat in the CFH protein and is highly conserved among vertebrates (**Figure 4A**).[32] As expected, SIFT and PROVEAN predicted it to be deleterious. This variant appears to predispose a person to develop aHUS[33] but has incomplete penetrance.[34,35] There was only one variant not predicted to be "deleterious" but showed enrichment in the literature cohort (**Figure 3**). CFH c.481G>T p.Ala161Ser showed enrichment regardless of whether the non-Finnish European subgroup was considered. This variant is located in SCR3 and affects the cofactor activity of CFH.[36] This position exhibits moderate conservation among vertebrates as shown in **Figure 4B**.

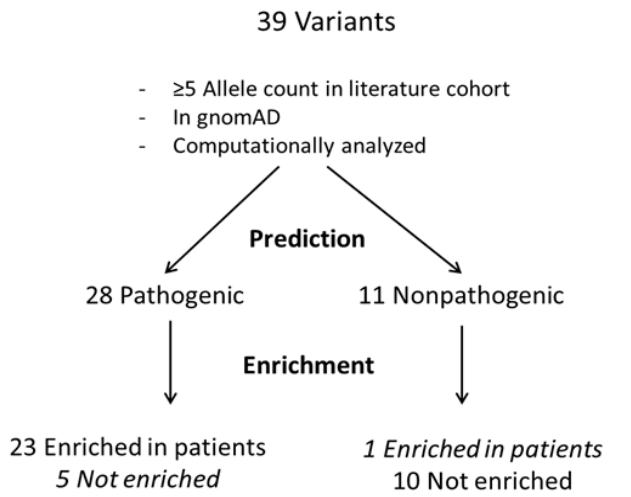

Figure 3: Concordance between prediction and enrichment analyses of variant pathogenicity.

Flowchart showing variants that passed the specified criteria.

gnomAD, Genome Aggregation Database.

Discussion

The biggest challenge in diagnosing and treating any rare disease is, arguably, a lack of information. In the past two decades, the development of new technologies, such as the next-generation sequencing methods, has greatly increased the number of rare diseases with an identified genetic cause. However, interpreting the large amount of genetic data is challenging, and many genetic variants identified in patients remain uncharacterized and their significance to disease phenotypes unknown.[14] Improved understanding of the genotype-to-phenotype correlation is important to guide long-term treatment and management decisions for these patients.

We systematically explored the case studies of aHUS in MEDLINE and created a literature cohort of more than 1600 patients with aHUS. This cohort was much larger than any published patient cohort of this disease and allowed for additional characterization of rare genetic

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A. CFH c.2850G>T, p.Q950H
NP_000177.2      931   CKSPPE-ISHGVVAHMSDSYHYGEEVTYKCFEGFGIDG   967 human
XP_001136531.1   931   CKSPPE-ISHGVVAHMSDSYQYGEEVTYKCFEGFGIDG   967 chimp
XP_001111875.1   931   CKSPPE-ISHGVVAHTSDSYQYGEEVTYKCSEGFGIDG   967 rhesus
XP_536110.2      935   CAPPAYMVTHGILIQQSDSYQYGEEVTYKCSEGFAIDG   967 wolf
NP_001029108.1   939   CGLPPY-VQNGVVSHKKDRYQYGEEVTYDCDEGFGTDG   975 cattle
NP_034018.2      954   CGPPPS-IPLGTVSLELESYQHGEEVTYHCSTGFGIDG   990 mouse
NP_569093.2      937   CGPPPS-IPLGIVSHELESYQYGEEVTYNCSEGFGIDG   973 rat

B. CFH c.481G>T, p.A161S
NP_000177.2      132   CEVVKCLPVTAPENGKIVSSSMEPDREYHFGQAVRFVC   178 human
XP_001136531.1   132   CEVVKCLPVTAPENGKIVSSAMEPDREYRFGQAVRFVC   178 chimp
XP_001111875.1   132   CEVVKCLPVKPPENGKIMSGAMEPDREYYFGQVVRFAC   178 rhesus
XP_536110.2      132   CEVVKCLPVTEPENGRLASIPLESDQEYTFGNVVRFEC   178 wolf
NP_001029108.1   132   CEVVKCLPVTEPENGKIFSDALEPDQEYTYGQVVQFEC   178 cattle
NP_034018.2      150   CEVVKCLPVTELENGRIVSGAAETDQEYYFGQVVRFEC   196 mouse
NP_569093.2      132   CEVVKCLPVTELENGRIVSGAAEPDQEYYFGQVVRFEC   178 rat
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Figure 4: Examples of variants showing discordance between in silico prediction and enrichment analysis.

Multiple sequence alignments were taken from Homologene.32 Representative variants predicted to be "deleterious" by one approach (e.g. in silico prediction) but not the other (e.g. enrichment analysis) were examined to understand possible reason(s) of discordance between the two approaches.

variants using computational approaches. Importantly, the gene and variant distributions in this virtual cohort were in good agreement with what has been reported in actual cohorts of patients with aHUS (**Table 1**).

We analyzed the pathogenicity of genetic variants identified in 10 genes associated with aHUS. A Fisher exact test was utilized to compare those variants' AFs in the literature cohort with those in a reference population, gnomAD.[17] Even though gnomAD contains sequencing data of more than 138 000 individuals, most of the identified variants (301 of 447) are not present, highlighting the challenge and importance of obtaining more sequencing data from individuals of diverse genetic ancestry to enable assessment of rare and ultra-rare variants. Based on the current ACMG guidelines, the 301 variants have moderate evidence for pathogenicity (PM2).

Enrichment analysis enabled by a large patient cohort can provide novel insight into the pathogenicity of variants. Our enrichment analysis provides strong evidence for pathogenicity (PS4) based on ACMG guidelines. In our analysis, 40 variants showed enrichment in the literature cohort as compared with the reference population. 22 of these variants have been analyzed using functional assays and all 22 were found to be either "pathogenic" or "probably pathogenic" (Table S1).[37-43]

Moreover, the enrichment method can be applied to variant types that cannot be processed by the prediction methods. For example, seven out of the ten variants enriched in the patient population but not flagged as "deleterious" by any of the prediction methods are insertion/deletion, frameshift, splice, and stop codon variants (**Table S6**). This shows the importance of enrichment analysis because at least 30% of all identified variants are not missense variants and cannot be processed by many prediction methods.

The ten variants also include three pathogenic missense variants occurring at amino acid positions not conserved evolutionarily (Table S6). The consequence of the mutations can be appreciated by inspecting the crystal structures of complement complexes. For example, CFH variants c.481G>T, p.Ala161Ser and c.2908A>G, p.Ile970Val are located in SCR3 and SCR16, which mediate the binding of CFH to C3b and C3d,[36,44] respectively. Nevertheless, neither of the prediction tools can take this information into account.

We also ran the enrichment analysis by matching genetic ancestry of the literature cohort and the reference population. Because only the non-Finnish European population had sufficient numbers, the analysis was done only for this subgroup. The concordance between the analyses (when all groups or when only non-Finnish Europeans were included) was very high: 33 variants were found to be enriched in both analyses (**Figure 2**). For the four variants found to be enriched only when all ethnicities were considered, higher allele counts in non-Finnish European patients were observed, but the difference was not statistically significant. The lack of statistical significance might be due to the lack of power because of reduced population numbers. There was only one variant, CFI c.1270A>C p.Ile424Leu, found to be enriched only when non-Finnish Europeans were considered. This variant showed clear enrichment in non-Finnish Europeans. However, it was also present at high AFs in other populations, such as Africans (285 of 24 024, or approximately 0.012), raising the doubt whether the variant is truly pathogenic.

We recognize that there are caveats in creating patient cohorts from the literature and computational analyses. First, genes tested are not likely to be uniform across all literature cases. Differences in testing panels, sequencing, and analyzing methods likely will lead to heterogeneity in data collection. For example, if a gene was not tested, it could potentially lead to false negatives (e.g., variant exists, but not identified). Second, although we adjusted the AF in patients by a factor of two, this is still an unknown factor and may be different from population to population. Third, enrichment and prediction methods may not be sensitive for variants with incomplete penetrance and variants acting in combinations. Additional information such as genetic segregation data is needed to supplement the computational methods. Lastly, many structural variants remain a challenge to be assessed by enrichment analysis because of undefined breakpoints. If possible, these variants should be categorized at the gene level or by a specific focused region (e.g., missing a particular exon), so that AF can be calculated and the analysis performed.

Conclusions

We have presented an *in silico* framework where an artificial patient cohort was created and used to assess the pathogenicity of genetic variants. This framework can be efficiently applied to rare diseases where information is sparse to shed light on genotype-phenotype associations and ultimately help diagnose and treat patients with rare diseases who are in desperate need of better health care.

Acknowledgments

The authors would like to acknowledge Guillermo del Angel and John Reynders of Alexion Pharmaceuticals, Inc., for critical review of the manuscript, and Guillermo del Angel for database querying and formatting. The authors would also like to acknowledge Peloton Advantage, LLC, which provided medical writing/editorial/layout support with funding from Alexion Pharmaceuticals, Inc.

Conflict of Interests

RRJ is an employee of Alexion Pharmaceuticals, INC. and owns the company stocks.

Funding Information

Alexion Pharmaceuticals, Inc. provided funding to this work.

Author's contributions

RRJ did the analyses and wrote the manuscript. TS and NK directed the literature mining efforts. All authors read and approved the final manuscript.

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S1 Table. Complete enrichment analysis results of 146 variants present in both the atypical hemolytic uremic syndrome literature cohort and the Genome Aggregation Database (gnomAD).

					All ethnic groups							non-Finnish European only								
Gene	Transcript	Transcript Consequence	Protein Consequence	Type	AF in gnomAD	AC in aHUS	NAC in aHUS	AC in gnomAD	NAC in gnomAD	P value	P corrected	AF in NFE	AC in aHUS	NAC in aHUS	AC in gnomAD	NAC in gnomAD	P value	P corrected	Source pubmed ID	Impact based on functional assays
C3	ENST00000245907	c.3124C>T	p.Arg1042Trp	missense	2.44E-05	2	6606	6	246202	1.72E-02	1.00E+00	0.00E+00	2	5042	0	111680	0.001867013		20595690, 23431077	
C3	ENST00000245907	c.481C>T	p.Arg161Trp	missense	4.06E-06	44	6564	1	246249	8.67E-69	1.27E-66	8.95E-06	42	5002	1	111707	1.72E-56	1.72E-54	20203157, 22246034, 22669319, 25879158, 23356914, 22410797, 23307876, 23431077, 25899302, 27177491, 28110418, 28187980, 27452363	
C3	ENST00000245907	c.1273C>T	p.Arg425Cys	missense	2.23E-04	2	6606	61	273051	4.40E-01	1.00E+00	5.62E-05	0	5044	7	124455	1		25431709, 27722136	
C3	ENST00000245907	c.1433G>T	p.Arg478Leu	missense	2.03E-05	3	6605	5	246257	9.05E-04	1.32E-01	4.48E-05	3	5041	5	111705	3.83E-03	3.83E-01	25608561, 20595690, 23431077	
C3	ENST00000245907	c.1774C>T	p.Arg592Trp	missense	4.06E-06	7	6601	1	246251	6.49E-11	9.47E-09	8.95E-06	6	5038	1	111709	4.37E-08	4.37E-06	18796626, 25879158, 21902819, 20595690, 23431077	
C3	ENST00000245907	c.2852G>A	p.Arg951His	missense	2.03E-05	1	6607	5	246261	1.47E-01	1.00E+00	3.58E-05	1	5043	4	111710	1.98E-01	1.00E+00	26826462	
C3	ENST00000245907	c.1407G>C	p.Glu469Asp	missense	4.40E-03	1	6607	1219	275959	1.00E+00	1.00E+00	2.05E-04	0	5044	26	126666	1		25608561	
C3	ENST00000245907	c.4645C>A	p.Leu1549Met	missense	1.33E-03	2	6606	367	274873	9.98E-01	1.00E+00	2.40E-05	1	5043	3	125017	1.46E-01	1.00E+00	25608561	
C3	ENST00000245907	c.3152A>T	p.Lys1051Met	missense	8.13E-06	3	6605	2	246032	1.72E-04	2.51E-02	1.79E-05	3	5041	2	111520	7.58E-04	7.58E-02	20595690, 23431077, 25037630	
C3	ENST00000245907	c.3625A>G	p.Lys1209Glu	missense	2.03E-05	1	6607	5	246209	1.47E-01	1.00E+00	4.48E-05	0	5044	5	111713	1		25608561	
C3	ENST00000245907	c.463A>C	p.Lys155Gln	missense	2.73E-03	2	6606	756	276418	1.00E+00	1.00E+00	5.39E-03	2	5042	683	125995	1.00E+00	1.00E+00	20016463, 27177491	
C3	ENST00000245907	c.1898A>G	p.Lys633Arg	missense	4.37E-04	4	6604	121	276841	3.33E-01	1.00E+00	7.90E-04	3	5041	100	126464	7.60E-01	1.00E+00	25608561, 19861685, 25037630	
C3	ENST00000245907	c.193A>C	p.Lys65Gln	missense	4.87E-05	16	6592	12	246254	1.05E-18	1.53E-16	8.95E-05	16	5028	10	111704	5.05E-16	5.05E-14	25608561, 22669319, 23307876, 25899302, 26541438, 28025630	
C3	ENST00000245907	c.3187A>C	p.Ser1063Arg	missense	8.26E-06	3	6605	2	242012	1.80E-04	2.63E-02	1.82E-05	3	5041	2	110038	7.87E-04	7.87E-02	20595690, 23431077, 25037630	

C3	ENST00000245907	c.4855A>C	p.Ser1619Arg	missense	1.16E-03	5	6603	322	276852	8.79E-01	1.00E+00	2.17E-03	3	5041	275	126403	9.99E-01	1.00E+00	25608561, 23847193, 24029428	
C3	ENST00000245907	c.4148C>A	p.Thr1383Asn	missense	1.55E-04	4	6604	43	277201	2.37E-02	1.00E+00	1.66E-04	3	5041	21	126705	6.23E-02	1.00E+00	25608561, 20595690, 23431077, 28056875	
C3	ENST00000245907	c.2284G>A	p.Val762Ile	missense	1.22E-05	2	6606	3	246267	6.48E-03	9.46E-01	0.00E+00	2	5042	0	111718	0.001865798		20595690, 23431077	
CD46	ENST00000358170	c.932C>T	p.Ala311Val	missense	5.78E-05	2	6606	16	277006	6.49E-02	1.00E+00	7.11E-05	0	5044	9	126543	1		25951460, 27399110	
CD46	ENST00000358170	c.175C>T	p.Arg59Ter	stop gained	1.22E-05	35	6573	3	246203	2.88E-52	4.20E-50	0.00E+00	23	5021	0	111668	3.97E-32		16621965, 21906045, 17599974, 16762990, 20059470, 17699195, 16882452, 20595690, 23307876, 18235085, 23431077, 24021908, 26880462, 27799617	pathogenic
CD46	ENST00000358170	c.553G>A	p.Asp185Asn	missense	1.62E-05	4	6604	4	246214	3.00E-05	4.38E-03	3.58E-05	3	5041	4	111688	2.47E-03	2.47E-01	17599974, 16762990, 20090363, 23431077	pathogenic
CD46	ENST00000358170	c.811_816delG-ACAGT	p.Asp271_ Ser272del	inframe deletion	4.06E-06	9	6599	1	246217	5.53E-14	8.07E-12	8.95E-06	9	5035	1	111679	5.02E-12	5.02E-10	20106822, 14566051, 22410797, 19446882, 28110418, 28187980	pathogenic
CD46	ENST00000358170	c.104G>A	p.Cys35Tyr	missense	1.22E-05	18	6590	3	246151	3.93E-26	5.73E-24	8.96E-06	14	5030	1	111665	1.12E-18	1.12E-16	20203157, 16621965, 21906045, 20059470, 20090363, 16882452, 20595690, 23307876, 18235085, 23431077	pathogenic
CD46	ENST00000358170	c.424G>C	p.Glu142Gln	missense	7.24E-05	3	6605	20	276160	1.59E-02	1.00E+00	1.59E-04	2	5042	20	126136	2.07E-01	1.00E+00	26826462, 21906045, 25733390	
CD46	ENST00000358170	c.535G>C	p.Glu179Gln	missense	1.14E-04	4	6604	28	246142	9.36E-03	1.00E+00	1.79E-05	2	5042	2	111664	1.06E-02	1.00E+00	16762990, 23431077, 28056875	pathogenic
CD46	ENST00000358170	c.389G>T	p.Gly130Val	missense	4.25E-06	1	6607	1	235541	5.38E-02	1.00E+00	0.00E+00	1	5043	0	105310	0.045707451		23431077	
CD46	ENST00000358170	c.404G>A	p.Gly135Asp	missense	4.10E-06	2	6606	1	243943	2.05E-03	2.99E-01	9.07E-06	2	5042	1	110269	5.57E-03	5.57E-01	21706448	pathogenic

CD46	ENST00000358170	c.417A>G	p.Leu139Leu	synonymous	6.66E-03	6	6602	1836	274036	1.00E+00	1.00E+00	9.61E-03	6	5038	1210	124680	1.00E+00	1.00E+00	15661753, 21706448, 20059470, 20595690	
CD46	ENST00000358170	c.785T>C	p.Leu262Pro	missense	8.12E-06	1	6607	2	246200	7.64E-02	1.00E+00	1.79E-05	0	5044	2	111668	1		23389237	pathogenic
CD46	ENST00000358170	c.523T>G	p.Phe175Val	missense	1.63E-05	1	6607	4	246132	1.24E-01	1.00E+00	3.58E-05	1	5043	4	111646	1.98E-01	1.00E+00	24656451	
CD46	ENST00000358170	c.493C>T	p.Pro165Ser	missense	4.08E-06	5	6603	1	245253	7.29E-08	1.06E-05	9.00E-06	4	5040	1	111119	1.71E-05	1.71E-03	26826462, 16386793, 15661753, 16882452	pathogenic
CD46	ENST00000358170	c.718T>C	p.Ser240Pro	missense	7.22E-06	11	6597	2	277012	8.14E-17	1.19E-14	7.90E-06	5	5039	1	126575	4.79E-07	4.79E-05	14566051, 20059470, 19861685, 23431077, 27177491, 27452363	pathogenic
CD46	ENST00000358170	c.800_801delCA	p.Thr267Asnf-sTer4	frameshift	4.06E-06	7	6601	1	246203	6.50E-11	9.48E-09	8.96E-06	7	5037	1	111667	2.16E-09	2.16E-07	16621965, 14615110, 20090363, 20595690, 23431077	pathogenic
CD46	ENST00000358170	c.1148C>T	p.Thr383Ile	missense	7.22E-04	4	6604	200	276838	7.02E-01	1.00E+00	9.87E-04	3	5041	125	126485	8.72E-01	1.00E+00	21706448, 23431077, 26989566, 27646857	
CD46	ENST00000358170	c.646T>G	p.Trp216Gly	missense	4.06E-06	1	6607	1	246261	5.16E-02	1.00E+00	0.00E+00	1	5043	0	111714	0.043200466		25899302	
CD46	ENST00000358170	c.565T>G	p.Tyr189Asp	missense	1.44E-05	17	6591	4	277214	9.31E-25	1.36E-22	7.89E-06	11	5033	1	126711	2.97E-15	2.97E-13	20513133, 25951460, 21906045, 17599974, 16762990, 25443527, 20059470, 20595690, 24029428, 23307876, 23431077, 26880462, 28110418	pathogenic
CD46	ENST00000358170	c.475+1G>A		splice donor	4.12E-06	1	6607	1	242777	5.23E-02	1.00E+00	9.13E-06	1	5043	1	109513	8.61E-02	1.00E+00	25381125	
CD46	ENST00000358170	c.287-2A>G		splice acceptor	2.13E-05	10	6598	5	234627	6.26E-13	9.13E-11	1.91E-05	8	5036	2	104844	8.12E-10	8.12E-08	20513133, 20203157, 16621965, 23519521, 20540647, 20595690, 23307876, 23431077, 27799617	pathogenic

CD46	ENST00000358170	c.286+1G>C		splice donor	8.17E-06	9	6599	2	244728	3.13E-13	4.57E-11	8.96E-06	9	5035	1	111563	5.06E-12	5.06E-10	15661753, 18514989, 23307876, 23431077, 24021908, 27799617	pathogenic
CD46	ENST00000358170	c.286+2T>G		splice donor	4.91E-05	35	6573	12	244628	1.76E-45	2.56E-43	9.86E-05	26	5018	11	111543	1.74E-27	1.74E-25	20513133, 26826462, 20016463, 20106822, 23731345, 21906045, 17599974, 16762990, 23356914, 20059470, 17617869, 19301397, 26307634, 24944786, 20595690, 23307876, 23431077, 24021908, 25899302, 28056875	pathogenic
CFB	ENST00000456570	c.397G>A	p.Gly133Arg	missense	4.09E-06	1	6607	1	244551	5.19E-02	1.00E+00	9.05E-06	0	5044	1	110499	1		28056875	
CFB	ENST00000456570	c.991A>G	p.Ile331Val	missense	3.97E-04	1	6607	108	271846	9.27E-01	1.00E+00	1.38E-04	0	5044	17	123227	1		25951460	
CFB	ENST00000456570	c.1298T>C	p.Met433Thr	missense	4.15E-06	3	6605	1	240875	7.46E-05	1.09E-02	9.24E-06	3	5041	1	108205	3.41E-04	3.41E-02	24009284, 24652797, 25037630	pathogenic
CFH	ENST00000367429	c.481G>T	p.Ala161Ser	missense	7.73E-05	6	6602	19	245835	3.70E-05	5.40E-03	2.69E-05	4	5040	3	111381	1.11E-04	1.11E-02	20203157, 17599974, 21902819, 23307876, 23431077, 24021908	pathogenic
CFH	ENST00000367429	c.3445C>T	p.Arg1149Ter	stop gained	3.23E-05	1	6607	1	30947	3.21E-01	1.00E+00	0.00E+00	1	5043	0	15002	0.251621271		23787556	
CFH	ENST00000367429	c.3607C>T	p.Arg1203Trp	missense	4.69E-05	2	6606	13	276905	4.66E-02	1.00E+00	1.58E-05	2	5042	2	126410	8.39E-03	8.39E-01	26826462, 20106822	

CFH	ENST00000367429	c.3628C>T	p.Arg1210Cys	missense	1.44E-04	72	6536	40	276940	3.05E-88	4.45E-86	3.08E-04	53	4991	39	126447	2.17E-50	2.17E-48	20513133, 26826462, 20016463, 20106822, 20203157, 16621965, 15661753, 21906045, 11851332, 12424708, 17517971, 19633317, 23356914, 20059470, 11158219, 12960213, 15816899, 20534299, 14583443, 20703214, 22410797, 16189652, 16882452, 20595690, 23307876, 18235085, 23431077, 24656451, 27268256, 27799617, 25037630	pathogenic
CFH	ENST00000367429	c.3643C>T	p.Arg1215Ter	stop gained	4.06E-06	1	6607	1	246081	5.16E-02	1.00E+00	0.00E+00	1	5043	0	111550	0.043261231		23307876	
CFH	ENST00000367429	c.497G>T	p.Arg166Leu	missense	7.23E-06	1	6607	2	276692	6.84E-02	1.00E+00	7.92E-06	1	5043	1	126331	7.53E-02	1.00E+00	24333077	
CFH	ENST00000367429	c.694C>T	p.Arg232Ter	stop gained	8.17E-06	1	6607	2	244648	7.68E-02	1.00E+00	9.03E-06	1	5043	1	110755	8.52E-02	1.00E+00	25899302	
CFH	ENST00000367429	c.1022G>A	p.Arg341His	missense	4.07E-05	3	6605	10	245416	4.23E-03	6.18E-01	6.30E-05	3	5041	7	111085	7.81E-03	7.81E-01	20203157, 23307876	
CFH	ENST00000367429	c.157C>T	p.Arg53Cys	missense	1.45E-05	6	6602	4	276654	3.12E-08	4.55E-06	2.38E-05	6	5038	3	126249	2.44E-07	2.44E-05	26826462, 20203157, 25006455, 23307876, 23431077	pathogenic
CFH	ENST00000367429	c.1745G>A	p.Arg582His	missense	1.63E-05	1	6607	4	245292	1.24E-01	1.00E+00	1.80E-05	1	5043	2	110950	1.25E-01	1.00E+00	23307876	
CFH	ENST00000367429	c.3148A>T	p.Asn1050Tyr	missense	1.47E-02	4	6604	4070	273086	1.00E+00	1.00E+00	1.98E-02	3	5041	2505	124147	1.00E+00	1.00E+00	15661753, 20059470, 18268093, 28056875	
CFH	ENST00000367429	c.1548T>A	p.Asn516Lys	missense	2.93E-04	3	6605	81	276335	3.13E-01	1.00E+00	3.57E-04	3	5041	45	126091	2.81E-01	1.00E+00	20595690, 23431077, 25037630	
CFH	ENST00000367429	c.3454T>A	p.Cys1152Ser	missense	4.06E-06	2	6606	1	246213	2.01E-03	2.94E-01	0.00E+00	2	5042	0	111688	0.001866758		25925370, 27495036	
CFH	ENST00000367429	c.2608T>C	p.Cys870Arg	missense	4.08E-06	1	6607	1	245081	5.18E-02	1.00E+00	0.00E+00	1	5043	0	111084	0.043434831		18268093	pathogenic

CFH	ENST00000367429	c.3226C>G	p.Gln1076Glu	missense	3.82E-04	10	6598	106	277042	4.04E-04	5.90E-02	3.08E-04	6	5038	39	126609	7.12E-03	7.12E-01	21906045, 20059470, 11170896, 12960213, 17699195, 16470555, 23431077	
CFH	ENST00000367429	c.3427C>G	p.Gln1143Glu	missense	9.67E-03	1	6607	2680	274472	1.00E+00	1.00E+00	1.74E-04	0	5044	22	126650	1		24933457	
CFH	ENST00000367429	c.1198C>A	p.Gln400Lys	missense	1.16E-04	5	6603	32	276112	1.63E-03	2.38E-01	2.38E-04	4	5040	30	126112	4.05E-02	1.00E+00	20106822, 14978182, 22410797, 23431077, 25616634	
CFH	ENST00000367429	c.2850G>T	p.Gln950His	missense	3.85E-03	22	6586	1068	276068	7.79E-01	1.00E+00	5.85E-03	18	5026	741	125903	9.90E-01	1.00E+00	20513133, 26826462, 20106822, 22250080, 25733390, 19951285, 18006700, 20059470, 14583443, 19861685, 20595690, 23431077, 24656451, 25899302, 28056875, 28187980	
CFH	ENST00000367429	c.3405G>C	p.Glu1135Asp	missense	4.06E-06	1	6607	1	246201	5.16E-02	1.00E+00	8.95E-06	1	5043	1	111681	8.46E-02	1.00E+00	21906045	
CFH	ENST00000367429	c.3514G>T	p.Glu1172Ter	stop gained	1.22E-05	13	6595	3	245837	1.39E-18	2.03E-16	8.98E-06	8	5036	1	111323	1.07E-10	1.07E-08	12697737, 17229916, 15816899, 14583443, 16192651, 20595690, 24029428, 23431077, 25037630	
CFH	ENST00000367429	c.1873G>T	p.Glu625Ter	stop gained	1.45E-05	5	6603	4	276644	8.04E-07	1.17E-04	3.17E-05	3	5041	4	126272	1.76E-03	1.76E-01	20513133, 23195022, 23847193, 24029428	
CFH	ENST00000367429	c.2548G>A	p.Glu850Lys	missense	4.08E-06	2	6606	1	245393	2.03E-03	2.96E-01	8.99E-06	2	5042	1	111257	5.48E-03	5.48E-01	21906045, 12960213	
CFH	ENST00000367429	c.3581G>A	p.Gly1194Asp	missense	1.63E-05	13	6595	4	245946	5.74E-18	8.39E-16	3.59E-05	6	5038	4	111404	1.19E-06	1.19E-04	20513133, 11851332, 12960213, 17699195, 14583443, 20304497, 16882452, 20595690, 23431077	
CFH	ENST00000367429	c.2940C>T	p.His980His	synonymous	1.14E-04	1	6607	28	246090	5.36E-01	1.00E+00	0.00E+00	0	5044	0	111602	1		21868097	

CFH	ENST00000367429	c.3176T>C	p.Ile1059Thr	missense	6.67E-03	1	6607	1848	275326	1.00E+00	1.00E+00	2.45E-04	0	5044	31	126641	1		24933457	
CFH	ENST00000367429	c.647T>C	p.Ile216Thr	missense	1.13E-04	1	6607	31	275241	5.32E-01	1.00E+00	0.00E+00	1	5043	0	125644	0.038595739		22669321	
CFH	ENST00000367429	c.2908A>G	p.Ile970Val	missense	4.06E-06	3	6605	1	246185	7.00E-05	1.02E-02	8.96E-06	3	5041	1	111649	3.12E-04	3.12E-02	16621965, 20595690, 23431077	pathogenic
CFH	ENST00000367429	c.3557A>C	p.Lys1186Thr	missense	4.07E-06	4	6604	1	245939	2.29E-06	3.35E-04	8.98E-06	4	5040	1	111397	1.70E-05	1.70E-03	24021908, 26019860, 27799617	
CFH	ENST00000367429	c.245A>G	p.Lys82Arg	missense	1.81E-05	1	6607	5	276295	1.32E-01	1.00E+00	0.00E+00	1	5043	0	126252	0.038417012		27799617	
CFH	ENST00000367429	c.484A>G	p.Met162Val	missense	2.89E-05	2	6606	8	276754	2.16E-02	1.00E+00	7.91E-06	2	5042	1	126349	4.31E-03	4.31E-01	23356914, 23307876	
CFH	ENST00000367429	c.773C>T	p.Pro258Leu	missense	4.08E-06	1	6607	1	245169	5.18E-02	1.00E+00	9.00E-06	1	5043	1	111083	8.50E-02	1.00E+00	27799617	
CFH	ENST00000367429	c.2944C>T	p.Pro982Ser	missense	7.31E-05	1	6607	18	246092	3.96E-01	1.00E+00	0.00E+00	0	5044	0	111588	1		25443527	
CFH	ENST00000367429	c.2669G>T	p.Ser890Ile	missense	2.09E-02	10	6598	5783	270983	1.00E+00	1.00E+00	1.31E-03	7	5037	166	126282	4.97E-01	1.00E+00	16621965, 21881555, 20595690, 23431077, 26163426	
CFH	ENST00000367429	c.3649_3651del-ACA	p.Thr1217del	inframe deletion	4.06E-06	2	6606	1	246083	2.02E-03	2.94E-01	0.00E+00	2	5042	0	111554	0.001871051		26826462, 21906045	
CFH	ENST00000367429	c.272C>G	p.Thr91Ser	missense	8.13E-06	1	6607	2	246050	7.64E-02	1.00E+00	1.79E-05	1	5043	2	111514	1.24E-01	1.00E+00	24029428	
CFH	ENST00000367429	c.2867C>T	p.Thr956Met	missense	1.29E-03	8	6600	358	276754	6.20E-01	1.00E+00	1.67E-03	8	5036	212	126438	6.09E-01	1.00E+00	20513133, 26826462, 15661753, 21717289, 11170895, 23431077, 25899302	benign
CFH	ENST00000367429	c.213G>A	p.Trp71Ter	stop gained	4.09E-06	1	6607	1	244519	5.19E-02	1.00E+00	9.07E-06	1	5043	1	110283	8.56E-02	1.00E+00	25899302	
CFH	ENST00000367429	c.3048C>A	p.Tyr1016Ter	stop gained	4.06E-06	4	6604	1	246175	2.28E-06	3.33E-04	0.00E+00	4	5040	0	111650	3.49E-06		24021908, 27799617	
CFH	ENST00000367429	c.3172T>C	p.Tyr1058His	missense	6.24E-04	3	6605	173	276905	7.80E-01	1.00E+00	3.95E-05	0	5044	5	126669	1		25135378	
CFH	ENST00000367429	c.2127_2129delT-TA	p.Tyr711del	inframe deletion	4.06E-06	1	6607	1	246005	5.16E-02	1.00E+00	0.00E+00	0	5044	0	111512	1		28056875	
CFH	ENST00000367429	c.2851T>C	p.Tyr951His	missense	1.22E-05	1	6607	3	246183	1.01E-01	1.00E+00	1.79E-05	0	5044	2	111652	1		14583443	
CFH	ENST00000367429	c.3019G>T	p.Val1007Leu	missense	2.75E-02	12	6596	7630	269504	1.00E+00	1.00E+00	1.41E-03	9	5035	179	126473	2.95E-01	1.00E+00	20513133, 21881555, 26163426	
CFH	ENST00000367429	c.3178G>C	p.Val1060Leu	missense	5.74E-04	3	6605	159	276881	7.30E-01	1.00E+00	6.32E-05	0	5044	8	126658	1		25135378	
CFH	ENST00000367429	c.332T>A	p.Val111Glu	missense	9.76E-05	2	6606	24	246000	1.47E-01	1.00E+00	0.00E+00	1	5043	0	111516	0.04327385		21717289, 23431077	
CFH	ENST00000367429	c.1825G>A	p.Val609Ile	missense	2.75E-04	6	6602	76	276664	1.25E-02	1.00E+00	5.15E-04	5	5039	65	126247	1.31E-01	1.00E+00	20513133, 23847193, 24029428, 25899302	
CFH	ENST00000367429	c.2509G>A	p.Val837Ile	missense	1.34E-03	3	6605	370	275826	9.93E-01	1.00E+00	0.00E+00	0	5044	0	126270	1		25135378, 27064621, 27150874	

CFH	ENST00000367429	c.3493+1G>A		splice donor	4.06E-06	4	6604	1	246209	2.28E-06	3.33E-04	0.00E+00	4	5040	0	111682	3.48E-06		21906045, 23356914, 12960213, 23307876	pathogenic
CFH	ENST00000367429	c.2596+1G>C		splice donor	4.09E-06	1	6607	1	244601	5.19E-02	1.00E+00	9.04E-06	1	5043	1	110667	8.53E-02	1.00E+00	27268256	
CFHR3	ENST00000367425	c.839_840delTA	p.Ile280LysfsTer7	frameshift	1.07E-03	1	6607	280	260316	9.99E-01	1.00E+00	1.83E-03	1	5043	221	120329	1.00E+00	1.00E+00	19745068	
CFHR5	ENST00000367414	c.508G>A	p.Glu170Lys	missense	4.08E-06	2	6606	1	245187	2.03E-03	2.96E-01	0.00E+00	0	5044	0	110862	1		25443527, 27064621	
CFHR5	ENST00000367414	c.832G>A	p.Gly278Arg	missense	2.85E-05	3	6605	7	245691	1.88E-03	2.74E-01	5.39E-05	3	5041	6	111350	5.61E-03	5.61E-01	24029428	
CFI	ENST00000394635	c.719C>G	p.Ala240Gly	missense	2.38E-04	1	6607	66	277072	7.94E-01	1.00E+00	5.53E-05	1	5043	7	126633	2.68E-01	1.00E+00	16621965	probably pathogenic
CFI	ENST00000394635	c.772G>A	p.Ala258Thr	missense	1.12E-04	4	6604	31	277111	8.65E-03	1.00E+00	2.29E-04	3	5041	29	126643	1.23E-01	1.00E+00	26826462, 21906045, 20059470, 21902819	possibly pathogenic
CFI	ENST00000394635	c.1292C>A	p.Ala431Glu	missense	2.17E-05	1	6607	6	277064	1.52E-01	1.00E+00	0.00E+00	1	5043	0	126624	0.038308473		27268256	
CFI	ENST00000394635	c.1315G>A	p.Ala439Thr	missense	2.84E-05	5	6603	7	246127	8.28E-06	1.21E-03	3.58E-05	5	5039	4	111620	1.64E-05	1.64E-03	20016463, 23307876, 27268256	
CFI	ENST00000394635	c.560G>A	p.Arg187Gln	missense	7.94E-05	2	6606	22	277110	1.07E-01	1.00E+00	7.89E-05	2	5042	10	126656	7.50E-02	1.00E+00	27268256, 25037630	
CFI	ENST00000394635	c.973C>T	p.Arg325Trp	missense	8.67E-05	4	6604	24	276904	3.86E-03	5.63E-01	1.11E-04	4	5040	14	126540	4.28E-03	4.28E-01	16621965, 20595690, 23431077	
CFI	ENST00000394635	c.1240C>T	p.Arg414Cys	missense	9.75E-05	4	6604	27	276967	5.61E-03	8.19E-01	2.37E-05	3	5041	3	126609	1.03E-03	1.03E-01	19861685, 25899302, 27268256, 27452363	
CFI	ENST00000394635	c.1445G>A	p.Arg482Gln	missense	4.88E-05	1	6607	12	246064	2.91E-01	1.00E+00	2.69E-05	1	5043	3	111597	1.62E-01	1.00E+00	26826462	
CFI	ENST00000394635	c.1444C>T	p.Arg482Ter	stop gained	3.25E-05	5	6603	8	246104	1.32E-05	1.92E-03	6.27E-05	5	5039	7	111625	9.24E-05	9.24E-03	20016463, 20106822, 20203157, 15173250, 23307876	
CFI	ENST00000394635	c.452A>G	p.Asn151Ser	missense	3.25E-05	8	6600	8	246212	2.31E-09	3.38E-07	1.79E-05	8	5036	2	111694	5.03E-10	5.03E-08	20016463, 17914026, 23307876, 23431077, 26541438, 28187980	
CFI	ENST00000394635	c.530A>T	p.Asn177Ile	missense	5.41E-05	1	6607	15	277097	3.14E-01	1.00E+00	8.68E-05	1	5043	11	126655	3.74E-01	1.00E+00	23431077	benign
CFI	ENST00000394635	c.1231G>A	p.Asp411Asn	missense	8.13E-06	2	6606	2	246072	3.96E-03	5.78E-01	8.96E-06	2	5042	1	111637	5.44E-03	5.44E-01	20016463, 23307876	
CFI	ENST00000394635	c.1579G>A	p.Asp527Asn	missense	8.13E-06	7	6601	2	245896	2.88E-10	4.21E-08	1.79E-05	7	5037	2	111436	9.48E-09	9.48E-07	16621965, 20595690, 23431077, 24656451, 27268256	
CFI	ENST00000394635	c.1685A>T	p.Glu562Val	missense	1.08E-05	2	6606	3	277009	5.18E-03	7.56E-01	1.58E-05	1	5043	2	126536	1.11E-01	1.00E+00	20595690, 23431077	

CFI	ENST00000394635	c.355G>A	p.Gly119Arg	missense	4.22E-04	18	6590	117	276963	3.15E-09	4.60E-07	8.45E-04	17	5027	107	126563	5.57E-06	5.57E-04	20513133, 20016463, 20203157, 23847193, 24029428, 23307876, 23431077, 27177491, 27268256, 27357251, 27587606, 27799617	probably pathogenic
CFI	ENST00000394635	c.485G>A	p.Gly162Asp	missense	1.22E-05	3	6605	3	245503	3.39E-04	4.95E-02	8.97E-06	3	5041	1	111497	3.14E-04	3.14E-02	21906045, 23356914, 20059470	probably pathogenic
CFI	ENST00000394635	c.782G>A	p.Gly261Asp	missense	1.35E-03	19	6589	373	276809	2.47E-03	3.61E-01	1.93E-03	16	5028	244	126418	4.38E-02	1.00E+00	24009284, 20513133, 20016463, 17084897, 17599974, 23356914, 20059470, 20595690, 23307876, 23431077, 27268256, 25037630	benign
CFI	ENST00000394635	c.786delA	p.Gly263Alaf-sTer45	frameshift	2.03E-05	4	6604	5	246175	5.29E-05	7.72E-03	4.48E-05	4	5040	5	111631	3.69E-04	3.69E-02	20016463, 23307876, 23431077	pathogenic
CFI	ENST00000394635	c.805G>A	p.Gly269Ser	missense	1.33E-04	2	6606	37	277147	2.30E-01	1.00E+00	7.89E-06	1	5043	1	126663	7.51E-02	1.00E+00	24656451, 26880462	
CFI	ENST00000394635	c.859G>A	p.Gly287Arg	missense	4.69E-05	7	6601	13	277157	2.20E-07	3.21E-05	8.69E-05	6	5038	11	126639	2.70E-05	2.70E-03	20513133, 23847193, 24029428, 25899302, 27268256	probably pathogenic
CFI	ENST00000394635	c.548A>G	p.His183Arg	missense	6.50E-04	9	6599	180	276948	3.40E-02	1.00E+00	0.00E+00	7	5037	0	126666	1.20E-10		20513133, 20016463, 17599974, 18371543, 23307876, 23431077, 27268256	
CFI	ENST00000394635	c.419T>C	p.Ile140Thr	missense	4.06E-06	1	6607	1	246227	5.16E-02	1.00E+00	0.00E+00	1	5043	0	111696	0.043207127		24656451	
CFI	ENST00000394635	c.1043T>C	p.Ile348Thr	missense	7.31E-05	10	6598	18	246116	1.26E-09	1.84E-07	8.06E-05	9	5035	9	111587	1.79E-08	1.79E-06	20106822, 22410797, 23431077, 24021908, 26019860, 26880462, 27268256, 27799617, 25037630	

CFI	ENST00000394635	c.1095T>G	p.Ile365Met	missense	3.25E-05	7	6601	8	246208	4.44E-08	6.49E-06	5.37E-05	5	5039	6	111662	5.58E-05	5.58E-03	20106822, 22410797, 20595690, 23307876, 23431077, 27452363, 25037630	
CFI	ENST00000394635	c.1270A>C	p.Ile424Leu	missense	1.19E-03	11	6597	329	276803	1.74E-01	1.00E+00	3.16E-05	10	5034	4	126670	5.84E-12	5.84E-10	20513133, 20016463, 17599974, 23307876, 23431077, 27268256	
CFI	ENST00000394635	c.1346A>G	p.Lys449Arg	missense	3.57E-03	2	6606	990	276190	1.00E+00	1.00E+00	2.41E-03	1	5043	305	126399	1.00E+00	1.00E+00	22903728, 23431077	
CFI	ENST00000394635	c.414G>T	p.Met138Ile	missense	8.12E-06	2	6606	2	246224	3.96E-03	5.78E-01	1.79E-05	1	5043	2	111690	1.24E-01	1.00E+00	17597211, 27268256	
CFI	ENST00000394635	c.612G>A	p.Met204Ile	missense	1.08E-05	1	6607	3	277189	8.99E-02	1.00E+00	0.00E+00	1	5043	0	126706	0.03828463		27268256	
CFI	ENST00000394635	c.667A>G	p.Met223Val	missense	4.07E-06	1	6607	1	245951	5.16E-02	1.00E+00	8.97E-06	1	5043	1	111445	8.47E-02	1.00E+00	27268256	
CFI	ENST00000394635	c.148C>G	p.Pro50Ala	missense	9.75E-05	10	6598	27	276955	9.18E-09	1.34E-06	1.03E-04	9	5035	13	126471	5.62E-08	5.62E-06	20016463, 24034049, 23307876, 23431077, 23787556, 27268256, 25037630	probably pathogenic
CFI	ENST00000394635	c.1681C>T	p.Pro561Ser	missense	1.36E-03	10	6598	378	276552	4.18E-01	1.00E+00	2.70E-03	10	5034	341	126125	8.68E-01	1.00E+00	20016463, 22223611, 23356914, 23307876, 23431077, 27268256	
CFI	ENST00000394635	c.191C>T	p.Pro64Leu	missense	2.27E-04	1	6607	63	276909	7.79E-01	1.00E+00	2.37E-05	1	5043	3	126477	1.45E-01	1.00E+00	20513133	probably pathogenic
CFI	ENST00000394635	c.436A>C	p.Ser146Arg	missense	1.22E-05	1	6607	3	246231	1.01E-01	1.00E+00	8.95E-06	1	5043	1	111699	8.45E-02	1.00E+00	27268256	
CFI	ENST00000394635	c.608C>T	p.Thr203Ile	missense	4.58E-04	1	6607	127	277049	9.51E-01	1.00E+00	3.47E-04	0	5044	44	126644	1		28056875	
CFI	ENST00000394635	c.215C>G	p.Thr72Ser	missense	2.44E-05	2	6606	6	245976	1.73E-02	1.00E+00	5.38E-05	2	5042	6	111450	4.41E-02	1.00E+00	20595690, 23431077	
CFI	ENST00000394635	c.1219T>C	p.Trp407Arg	missense	1.80E-05	2	6606	5	277009	1.05E-02	1.00E+00	3.95E-05	2	5042	5	126617	2.71E-02	1.00E+00	20595690, 23431077	
CFI	ENST00000394635	c.1130A>C	p.Tyr377Ser	missense	4.06E-06	3	6605	1	246175	7.00E-05	1.02E-02	8.96E-06	3	5041	1	111625	3.13E-04	3.13E-02	20513133, 18805611	
CFI	ENST00000394635	c.454G>A	p.Val152Met	missense	3.97E-05	3	6605	11	277167	3.79E-03	5.53E-01	7.89E-05	3	5041	10	126680	1.20E-02	1.00E+00	20106822, 27268256	probably pathogenic
CFI	ENST00000394635	c.1258G>A	p.Val420Met	missense	9.02E-05	1	6607	25	277047	4.58E-01	1.00E+00	3.95E-05	0	5044	5	126637	1		23731345	
CFI	ENST00000394635	c.482+6C>T		splice region	1.34E-02	3	6605	3705	273399	1.00E+00	1.00E+00	3.70E-03	3	5041	469	126225	1.00E+00	1.00E+00	27268256	
DGKE	ENST00000284061	c.1009C>T	p.Arg337Ter	stop gained	1.22E-05	2	6606	3	246197	6.48E-03	9.46E-01	0.00E+00	0	5044	0	111658	1		28056875	
DGKE	ENST00000284061	c.585T>G	p.Ile195Met	missense	1.95E-05	1	6607	4	205638	1.46E-01	1.00E+00	0.00E+00	0	5044	0	100266	1		26018111	
DGKE	ENST00000284061	c.1133C>G	p.Pro378Arg	missense	4.07E-06	1	6607	1	245661	5.17E-02	1.00E+00	8.96E-06	0	5044	1	111569	1		28056875	

DGKE	ENST00000284061	c.966G>A	p.Trp322Ter	stop gained	9.02E-05	18	6590	25	277177	1.38E-18	2.01E-16	1.82E-04	12	5032	23	126663	3.59E-09	3.59E-07	23542698, 25135762, 25854283, 27177491	
THBD	ENST00000377103	c.707C>G	p.Ala236Gly	missense	1.37E-04	1	6607	22	160800	6.04E-01	1.00E+00	0.00E+00	1	5043	0	64336	0.072701067		20513133	
THBD	ENST00000377103	c.127G>A	p.Ala43Thr	missense	2.04E-03	7	6601	497	242863	9.80E-01	1.00E+00	3.65E-03	4	5040	393	107209	1.00E+00	1.00E+00	19625716, 20595690, 23307876, 24656451	pathogenic
THBD	ENST00000377103	c.1456G>T	p.Asp486Tyr	missense	7.62E-03	13	6595	2070	269548	1.00E+00	1.00E+00	2.27E-04	4	5040	28	123494	3.55E-02	1.00E+00	19625716, 25135762, 20513133, 25951460, 23847193, 20595690	possibly pathogenic
THBD	ENST00000377103	c.1504G>C	p.Gly502Arg	missense	1.94E-03	1	6607	505	259493	1.00E+00	1.00E+00	5.10E-05	0	5044	6	117584	1		24933457	
THBD	ENST00000377103	c.1483C>T	p.Pro495Ser	missense	5.26E-04	2	6606	139	264095	8.61E-01	1.00E+00	1.09E-03	0	5044	131	119663	1		19625716, 20595690	pathogenic
THBD	ENST00000377103	c.1502C>T	p.Pro501Leu	missense	1.80E-03	10	6598	472	261118	7.50E-01	1.00E+00	2.95E-03	6	5038	349	118063	9.97E-01	1.00E+00	19625716, 24118826, 20513133, 23847193, 24652797, 20595690, 24029428, 23307876, 27904864	pathogenic
THBD	ENST00000377103	c.131C>T	p.Thr44Ile	missense	4.85E-05	1	6607	12	247212	2.90E-01	1.00E+00	4.55E-05	1	5043	5	109779	2.36E-01	1.00E+00	23787556	
THBD	ENST00000377103	c.1499C>T	p.Thr500Met	missense	1.91E-05	1	6607	5	262167	1.39E-01	1.00E+00	8.43E-06	0	5044	1	118655	1		25951460	
THBD	ENST00000377103	c.241G>C	p.Val81Leu	missense	7.33E-06	1	6607	1	136483	9.02E-02	1.00E+00	1.92E-05	0	5044	1	52069	1		20595690	pathogenic

AC: allele count
NAC: no-allele count
AF: allele frequency
NFE: non-Finnish European

S2 Table. Complete prediction results of 412 genetic variants identified in aHUS literature cohort.

Gene	Transcript	Transcript consequence	Protein consequence	Type	"deleterious" count	SIFT	FATHMM	MutationTaster	PROVEAN	Source pubmed ID
CFH	ENST00000367429	c.351-4dupT	NA	splice_region_variant,intron_variant	0					27268256
CFH	ENST00000367429	c.1160-2A>G	NA	splice_acceptor_variant	0					20513133, 24933457, 24029428
CFH	ENST00000367429	c.2596+1G>C	NA	splice_donor_variant	0					27268256
CFH	ENST00000367429	c.2782+2T>G	NA	splice_donor_variant	0					23307876
CFH	ENST00000367429	c.2956+1G>A	NA	splice_donor_variant	0					20106822
CFH	ENST00000367429	c.3133+1G>A	NA	splice_donor_variant	0					27646857, 28056875
CFH	ENST00000367429	c.3493+1G>A	NA	splice_donor_variant	0					21906045, 23356914, 12960213, 23307876
CD46	ENST00000358170	c.98-1G>C	NA	splice_acceptor_variant	0					16621965
CD46	ENST00000358170	c.286+1G>C	NA	splice_donor_variant	0					15661753, 18514989, 23307876, 23431077, 24021908, 27799617
CD46	ENST00000358170	c.286+2T>G	NA	splice_donor_variant	0					20513133, 26826462, 20016463, 20106822, 23731345, 21906045, 17599974, 16762990, 23356914, 20059470, 17617869, 19301397, 26307634, 24944786, 20595690, 23307876, 23431077, 24021908, 25899302, 28056875
CD46	ENST00000358170	c.287-2A>G	NA	splice_acceptor_variant	0					20513133, 20203157, 16621965, 23519521, 20540647, 20595690, 23307876, 23431077, 27799617
CD46	ENST00000358170	c.390-2A>G	NA	splice_acceptor_variant	0					26880462, 27268256
CD46	ENST00000358170	c.390-1G>C	NA	splice_acceptor_variant	0					23431077, 27974740
CD46	ENST00000358170	c.475+1G>A	NA	splice_donor_variant	0					25381125
CD46	ENST00000358170	c.476-2A>G	NA	splice_acceptor_variant	0					28056875
CD46	ENST00000358170	c.852_856delTAAAG	NA	frameshift_variant,splice_region_variant	0					15661753
CD46	ENST00000358170	c.902-2A>G	NA	splice_acceptor_variant	0					17599974, 16762990, 23431077
CD46	ENST00000358170	c.1027+2T>C	NA	splice_donor_variant	0					17599974, 17261436, 23307876, 23431077
CD46	ENST00000358170	c.1027+5G>T	NA	splice_region_variant,intron_variant	0					24422172, 28056875
DGKE	ENST00000284061	c.888+40A>G	NA	intron_variant	0					25854283
DGKE	ENST00000284061	c.889-1G>A	NA	splice_acceptor_variant	0					23542698

DGKE	ENST00000284061	c.1213-2A>G	NA	splice_acceptor_variant	0					26018111
C3	ENST00000245907	c.1976-6C>T	NA	splice_region_variant,intron_variant	0					28056875
C3	ENST00000245907	c.-3_-2dup	NA	5_prime_UTR_variant	0					19861685
CFI	ENST00000394635	c.786delA	NA	frameshift_variant	0					20016463, 23307876, 23431077
CFI	ENST00000394635	c.482+6C>T	NA	splice_region_variant,intron_variant	0					27268256
CFH	ENST00000367429	c.3695_*2del	p.*1232Fext*37	stop_lost,3_prime_UTR_variant	0					21906045, 17599974, 12960213, 23307876
CFH	ENST00000367429	c.3694_*1del	p.*1232Iext*37	stop_lost,3_prime_UTR_variant	0					19568827, 27177491, 21396679, 24088957
C3	ENST00000245907	c.3281C>A	p.A1094D	missense_variant	0					25608561
C3	ENST00000245907	c.3280G>T	p.A1094S	missense_variant	0					23307876
C3	ENST00000245907	c.3281C>T	p.A1094V	missense_variant	0					18796626, 23431077
CFH	ENST00000367429	c.481G>T	p.A161S	missense_variant	0					20203157, 17599974, 21902819, 23307876, 23431077, 24021908
CFI	ENST00000394635	c.651delG	p.A219Qfs*12	frameshift_variant	0					27268256
THBD	ENST00000377103	c.707C>G	p.A236G	missense_variant	0					20513133
CFI	ENST00000394635	c.719C>G	p.A240G	missense_variant	4	1	1	1	1	16621965
CFI	ENST00000394635	c.772G>A	p.A258T	missense_variant,splice_region_variant	2		1	1		26826462, 21906045, 20059470, 21902819
CD46	ENST00000358170	c.932C>T	p.A311V	missense_variant	0					25951460, 27399110
CD46	ENST00000358170	c.100G>A	p.A34T	missense_variant,splice_region_variant	0					27268256
CFI	ENST00000394635	c.1292C>A	p.A431E	missense_variant	1		1			27268256
CFI	ENST00000394635	c.1315G>A	p.A439T	missense_variant	4	1	1	1	1	20016463, 23307876, 27268256
THBD	ENST00000377103	c.127G>A	p.A43T	missense_variant	0					19625716, 20595690, 23307876, 24656451
CFH	ENST00000367429	c.2827_2831delGCTCA	p.A943Hfs*17	frameshift_variant	0					25752761
CFH	ENST00000367429	c.3127T>C	p.C1043R	missense_variant	4	1	1	1	1	21906045, 12960213
CFH	ENST00000367429	c.3231T>G	p.C1077W	missense_variant	4	1	1	1	1	17295030, 21396679
CFH	ENST00000367429	c.3454T>A	p.C1152S	missense_variant	3	1	1		1	25925370, 27495036
C3	ENST00000245907	c.3474C>G	p.C1158W	missense_variant	3	1		1	1	18796626, 23431077
CFH	ENST00000367429	c.3489C>G	p.C1163W	missense_variant	4	1	1	1	1	14583443, 20595690, 23431077
CFH	ENST00000367429	c.3652T>C	p.C1218R	missense_variant	4	1	1	1	1	20703214, 23431077
CFH	ENST00000367429	c.3653G>A	p.C1218Y	missense_variant	3	1	1		1	26880823
CD46	ENST00000358170	c.381T>A	p.C127*	stop_gained	1			1		25443527
DGKE	ENST00000284061	c.413G>A	p.C138Y	missense_variant	4	1	1	1	1	28185420

CD46	ENST00000358170	c.469T>C	p.C157R	missense_variant	4	1	1	1	1	27268256
DGKE	ENST00000284061	c.501C>G	p.C167W	missense_variant	4	1	1	1	1	25443527
CD46	ENST00000358170	c.629G>T	p.C210F	missense_variant	4	1	1	1	1	19459807
CFH	ENST00000367429	c.974G>A	p.C325Y	missense_variant	4	1	1	1	1	20513133
CD46	ENST00000358170	c.105T>A	p.C35*	stop_gained	1			1		20595690, 23431077, 26111906
CD46	ENST00000358170	c.104G>A	p.C35Y	missense_variant	4	1	1	1	1	20203157, 16621965, 21906045, 20059470, 20090363, 16882452, 20595690, 23307876, 18235085, 23431077
CFH	ENST00000367429	c.1292G>A	p.C431Y	missense_variant	4	1	1	1	1	20203157, 23307876, 23431077
CFH	ENST00000367429	c.1343G>A	p.C448Y	missense_variant	3	1		1	1	26826462
CFH	ENST00000367429	c.1690_1691delinsCC	p.C564P	missense_variant	1	1				23356914, 23307876
CFH	ENST00000367429	c.1707C>A	p.C569*	stop_gained	1			1		23431077
CFH	ENST00000367429	c.1789T>C	p.C597R	missense_variant	4	1	1	1	1	27799617
CFH	ENST00000367429	c.1832G>A	p.C611Y	missense_variant	4	1	1	1	1	21877169
CFH	ENST00000367429	c.1868G>C	p.C623S	missense_variant	4	1	1	1	1	20305136, 23431077, 27799617
CFH	ENST00000367429	c.1890T>G	p.C630W	missense_variant	4	1	1	1	1	21906045, 12960213
CD46	ENST00000358170	c.192T>C	p.C64C	synonymous_variant	0					16621965
CD46	ENST00000358170	c.191G>T	p.C64F	missense_variant	3	1	1		1	19376828, 24005975
CFH	ENST00000367429	c.2018G>A	p.C673Y	missense_variant	4	1	1	1	1	22223611, 14978182, 23307876, 23431077
CFH	ENST00000367429	c.2198G>A	p.C733Y	missense_variant	3	1	1		1	23307876
CFH	ENST00000367429	c.2557T>C	p.C853R	missense_variant	4	1	1	1	1	20703214, 23307876, 28187980
CFH	ENST00000367429	c.2557_2558delinsAC	p.C853T	missense_variant	1	1				23431077
CFH	ENST00000367429	c.2591G>C	p.C864S	missense_variant	4	1	1	1	1	20203157, 23307876, 23431077
CFH	ENST00000367429	c.2608T>C	p.C870R	missense_variant	4	1	1	1	1	18268093
CFH	ENST00000367429	c.2745C>A	p.C915*	stop_gained	1			1		20513133, 23847193, 24029428
CFH	ENST00000367429	c.2743T>A	p.C915S	missense_variant	4	1	1	1	1	17599974, 14978182, 23307876, 23431077
CFH	ENST00000367429	c.2777G>T	p.C926F	missense_variant	4	1	1	1	1	14986080
CFH	ENST00000367429	c.2918G>A	p.C973Y	missense_variant	3	1	1		1	16889549
CD46	ENST00000358170	c.295T>C	p.C99R	missense_variant	4	1	1	1	1	16621965, 20090363, 20595690, 23431077
C3	ENST00000245907	c.3085G>A	p.D1029N	missense_variant	3	1		1	1	24029428

C3	ENST00000245907	c.3343G>A	p.D1115N	missense_variant	3	1		1	1	25608561, 18796626, 20595690, 23431077, 25899302
CFH	ENST00000367429	c.3356A>G	p.D1119G	missense_variant	3	1		1	1	11170896, 23307876, 23431077
CFH	ENST00000367429	c.3355G>A	p.D1119N	missense_variant	3	1		1	1	23431077
C3	ENST00000245907	c.3466G>A	p.D1156N	missense_variant	1	1				25608561
CFB	ENST00000456570	c.397G>A	p.D133N	missense_variant	1			1		28056875
CD46	ENST00000358170	c.553G>A	p.D185N	missense_variant	1	1				17599974, 16762990, 20090363, 23431077
CD46	ENST00000358170	c.770delA	p.D257Vfs*41	frameshift_variant	0					21906045
CD46	ENST00000358170	c.811_816delGACAGT	p.D271_S272delDS	inframe_deletion	0					20106822, 14566051, 22410797, 19446882, 28110418, 28187980
THBD	ENST00000377103	c.102C>A	p.D34E	missense_variant	0					20513133
CFI	ENST00000394635	c.1231G>A	p.D411N	missense_variant	1		1			20016463, 23307876
THBD	ENST00000377103	c.1456G>T	p.D486Y	missense_variant	0					19625716, 25135762, 20513133, 25951460, 23847193, 20595690
CFI	ENST00000394635	c.1579G>A	p.D527N	missense_variant	4	1	1	1	1	16621965, 20595690, 23431077, 24656451, 27268256
THBD	ENST00000377103	c.158A>G	p.D53G	missense_variant	1	1				19625716, 20595690
CFH	ENST00000367429	c.2242_2245delGATA	p.D748Nfs*10	frameshift_variant	0					23307876
DGKE	ENST00000284061	c.263_264insGGGCGCCA	p.D88Efs*84	frameshift_variant	0					28056875
CFH	ENST00000367429	c.3210delT	p.E1071Rfs*19	frameshift_variant	0					23847193
CFH	ENST00000367429	c.3405G>C	p.E1135D	missense_variant	2	1		1		21906045
C3	ENST00000245907	c.3478G>A	p.E1160K	missense_variant	0					25608561
CFH	ENST00000367429	c.3514G>T	p.E1172*	stop_gained	1			1		12697737, 17229916, 15816899, 14583443, 16192651, 20595690, 24029428, 23431077, 25037630
CFH	ENST00000367429	c.3514_3515delinsAG	p.E1172R	missense_variant	1	1				21215749
CFH	ENST00000367429	c.3583G>T	p.E1195*	stop_gained	1			1		20513133, 23847193, 24029428
CFH	ENST00000367429	c.3592G>T	p.E1198*	stop_gained	1			1		18268093, 21556717
CFH	ENST00000367429	c.3593A>C	p.E1198A	missense_variant	2	1			1	14583443, 20595690, 23431077
CFH	ENST00000367429	c.3592G>A	p.E1198K	missense_variant	2	1			1	20513133, 16528247, 24029428
CFH	ENST00000367429	c.3593A>T	p.E1198V	missense_variant	2	1			1	25443527

C3	ENST00000245907	c.3968A>C	p.E1323A	missense_variant,splice_region_variant	2	1			1	25608561
CD46	ENST00000358170	c.424G>C	p.E142Q	missense_variant	0					26826462, 21906045, 25733390
CD46	ENST00000358170	c.535G>C	p.E179Q	missense_variant	0					16762990, 23431077, 28056875
CFHR5	ENST00000367414	c.53dupG	p.E19Rfs*6	frameshift_variant	0					28056875
CD46	ENST00000358170	c.106G>T	p.E36*	stop_gained	1			1		23307876
C3	ENST00000245907	c.1407G>C	p.E469D	missense_variant	0					25608561
CFI	ENST00000394635	c.1642G>C	p.E548Q	missense_variant	1		1			27268256
CFI	ENST00000394635	c.1685A>T	p.E562V	missense_variant	3	1	1		1	20595690, 23431077
CFH	ENST00000367429	c.1873G>T	p.E625*	stop_gained,splice_region_variant	1			1		20513133, 23195022, 23847193, 24029428
CFH	ENST00000367429	c.1905A>T	p.E635D	missense_variant	0					17599974, 23307876
CFH	ENST00000367429	c.2284G>T	p.E762*	stop_gained	1			1		23431077
CFH	ENST00000367429	c.2540A>T	p.E847V	missense_variant	1	1				23431077
CFH	ENST00000367429	c.2548G>A	p.E850K	missense_variant	3	1		1	1	21906045, 12960213
CFH	ENST00000367429	c.3595T>C	p.F1199L	missense_variant	4	1	1	1	1	27587606
CFH	ENST00000367429	c.3596T>C	p.F1199S	missense_variant	4	1	1	1	1	14978182, 23307876, 23431077
CD46	ENST00000358170	c.523T>G	p.F175V	missense_variant	0					24656451
CD46	ENST00000358170	c.725T>G	p.F242C	missense_variant	2	1			1	20513133, 16621965, 20595690, 23431077
C3	ENST00000245907	c.1807T>G	p.F603V	missense_variant	3	1		1	1	20513133
CFH	ENST00000367429	c.2169delT	p.F723Lfs*3	frameshift_variant	0					23307876
CFH	ENST00000367429	c.2880delT	p.F960Lfs*15	frameshift_variant	0					23870792
CFH	ENST00000367429	c.3032delG	p.G1011Vfs*4	frameshift_variant	0					16621965, 20595690, 23431077, 25037630
C3	ENST00000245907	c.3346G>A	p.G1116R	missense_variant	4	1	1	1	1	25608561, 23431077
CFH	ENST00000367429	c.3581G>A	p.G1194D	missense_variant	1				1	20513133, 11851332, 12960213, 17699195, 14583443, 20304497, 16882452, 20595690, 23431077
CFI	ENST00000394635	c.355G>A	p.G119R	missense_variant	1				1	20513133, 20016463, 20203157, 23847193, 24029428, 23307876, 23431077, 27177491, 27268256, 27357251, 27587606, 27799617
CD46	ENST00000358170	c.389G>T	p.G130V	missense_variant,splice_region_variant	3	1		1	1	23431077
CD46	ENST00000358170	c.404G>A	p.G135D	missense_variant	2	1			1	21706448

CD46	ENST00000358170	c.404delG	p.G135Vfs*13	frameshift_variant	0					21906045, 20059470
CFI	ENST00000394635	c.485G>A	p.G162D	missense_variant,splice_region_variant	3	1		1	1	21906045, 23356914, 20059470
CD46	ENST00000358170	c.586G>A	p.G196R	missense_variant	2	1			1	16762990, 23431077
CD46	ENST00000358170	c.610G>A	p.G204R	missense_variant	3	1		1	1	23431077
CFH	ENST00000367429	c.653G>A	p.G218E	missense_variant	3	1		1	1	20203157, 23307876, 23431077
CD46	ENST00000358170	c.776G>T	p.G259V	missense_variant	2	1			1	26826462, 25733390
CFI	ENST00000394635	c.782G>A	p.G261D	missense_variant	1		1			24009284, 20513133, 20016463, 17084897, 17599974, 23356914, 20059470, 20595690, 23307876, 23431077, 27268256, 25037630
C3	ENST00000245907	c.784G>T	p.G262W	missense_variant	3	1		1	1	25135762
CFI	ENST00000394635	c.805G>A	p.G269S	missense_variant	4	1	1	1	1	24656451, 26880462
CFHR5	ENST00000367414	c.832G>A	p.G278S	missense_variant	2	1			1	24029428
CFI	ENST00000394635	c.859G>A	p.G287R	missense_variant	4	1	1	1	1	20513133, 23847193, 24029428, 25899302, 27268256
CFH	ENST00000367429	c.1189G>A	p.G397R	missense_variant	3	1		1	1	20203157, 23307876, 23431077
CFI	ENST00000394635	c.1295G>A	p.G432D	missense_variant	1		1			20016463, 20203157, 23431077, 26880462, 25037630
THBD	ENST00000377103	c.1504G>C	p.G502R	missense_variant	0					24933457
CD46	ENST00000358170	c.198delA	p.G67Dfs*40	frameshift_variant	0					16621965, 20090363
C3	ENST00000245907	c.4390C>G	p.H1464D	missense_variant	3	1		1	1	18796626, 23307876, 23431077
CFI	ENST00000394635	c.548A>G	p.H183R	missense_variant	0					20513133, 20016463, 17599974, 18371543, 23307876, 23431077, 27268256
CFI	ENST00000394635	c.1253A>T	p.H418L	missense_variant	1		1			27268256
DGKE	ENST00000284061	c.1608_1609delCA	p.H536Qfs*16	frameshift_variant	0					25135762
CFH	ENST00000367429	c.2678A>G	p.H893R	missense_variant	2	1			1	14978182, 23307876, 23431077
CFH	ENST00000367429	c.2940C>T	p.H980H	synonymous_variant	0					21868097
CFH	ENST00000367429	c.3176T>C	p.I1059T	missense_variant	2	1			1	24933457
C3	ENST00000245907	c.3284T>G	p.I1095S	missense_variant	3	1		1	1	20203157, 23356914, 23307876, 23431077

C3	ENST00000245907	c.3470T>C	p.I1157T	missense_variant	1				1	20513133, 26826462, 25608561, 25951460, 25135378, 25879158, 20595690, 23431077, 26572892, 27139899, 27150874
CFH	ENST00000367429	c.3505A>C	p.I1169L	missense_variant	1		1			20513133
CFH	ENST00000367429	c.372_396del25	p.I124Mfs*13	frameshift_variant	0					17599974, 14978182, 23307876
CFI	ENST00000394635	c.419T>C	p.I140T	missense_variant	3	1		1	1	24656451
DGKE	ENST00000284061	c.585T>G	p.I195M	missense_variant	0					26018111
CD46	ENST00000358170	c.608T>C	p.I203T	missense_variant	3	1		1	1	27799617
CD46	ENST00000358170	c.622_623delinsTA	p.I208Y	missense_variant	1	1				23431077
CFH	ENST00000367429	c.647T>C	p.I216T	missense_variant	0					22669321
CFB	ENST00000456570	c.724A>C	p.I242L	missense_variant	1		1			20513133, 26826462, 24652797, 27268256
CFHR3	ENST00000367425	c.839_840delTA	p.I280Kfs*7	frameshift_variant	0					19745068
CFI	ENST00000394635	c.1043T>C	p.I348T	missense_variant	3	1	1		1	20106822, 22410797, 23431077, 24021908, 26019860, 26880462, 27268256, 27799617, 25037630
CFI	ENST00000394635	c.1095T>G	p.I365M	missense_variant	3	1	1	1		20106822, 22410797, 20595690, 23307876, 23431077, 27452363, 25037630
CFI	ENST00000394635	c.1270A>C	p.I424L	missense_variant	2		1	1		20513133, 20016463, 17599974, 23307876, 23431077, 27268256
CFH	ENST00000367429	c.2908A>G	p.I970V	missense_variant	0					16621965, 20595690, 23431077
DGKE	ENST00000284061	c.301A>T	p.K101*	stop_gained	1			1		24511134
C3	ENST00000245907	c.310A>G	p.K104E	missense_variant	0					26826462
C3	ENST00000245907	c.3152A>T	p.K1051M	missense_variant,splice_region_variant	3	1		1	1	20595690, 23431077, 25037630
CFH	ENST00000367429	c.3196A>T	p.K1066*	stop_gained	1			1		23356914
C3	ENST00000245907	c.3313A>C	p.K1105Q	missense_variant	3	1		1	1	25951460
CFH	ENST00000367429	c.3486delA	p.K1162Nfs*7	frameshift_variant	0					11170896, 17699195
CFH	ENST00000367429	c.3557A>C	p.K1186T	missense_variant	1		1			24021908, 26019860, 27799617
CFH	ENST00000367429	c.3562_3564delAAG	p.K1188delK	inframe_deletion	0					18295065, 23431077
C3	ENST00000245907	c.3625A>G	p.K1209E	missense_variant	1			1		25608561

C3	ENST00000245907	c.463A>C	p.K155Q	missense_variant	0					20016463, 27177491
DGKE	ENST00000284061	c.607_610delAAAA	p.K203Qfs*6	frameshift_variant	0					28056875
CD46	ENST00000358170	c.747_751delAGCAA	p.K249Nfs*5	frameshift_variant	0					23431077
CFB	ENST00000456570	c.1048_1050delinsGAC	p.K350D	missense_variant	1	1				20530807, 23307876
CFB	ENST00000456570	c.1050G>C	p.K350N	synonymous_variant	0					19584399, 24906628, 26911616
CFB	ENST00000456570	c.1050G>T	p.K350N	synonymous_variant	0					28056875
CFI	ENST00000394635	c.1346A>G	p.K449R	missense_variant	1		1			22903728, 23431077
CFH	ENST00000367429	c.1422delA	p.K474Nfs*6	frameshift_variant	0					11158219, 14583443, 20595690, 23431077
CFH	ENST00000367429	c.1750A>T	p.K584*	stop_gained	1			1		20203157, 23307876, 23431077
C3	ENST00000245907	c.1898A>G	p.K633R	missense_variant	0					25608561, 19861685, 25037630
CFH	ENST00000367429	c.1934_1935insA	p.K646Efs*8	frameshift_variant	0					20513133
CD46	ENST00000358170	c.192_198delinsC	p.K65_K66delKK	protein_altering_variant	0					20595690
C3	ENST00000245907	c.193A>C	p.K65Q	missense_variant	3	1		1	1	25608561, 22669319, 23307876, 25899302, 26541438, 28025630
C3	ENST00000245907	c.219G>C	p.K73N	missense_variant	0					25608561
CFH	ENST00000367429	c.245A>G	p.K82R	missense_variant,splice_region_variant	0					27799617
CFH	ENST00000367429	c.2686_2700del	p.K896_T900delKLSYT	inframe_deletion	0					16621965, 20595690, 23431077
C3	ENST00000245907	c.3325C>G	p.L1109V	missense_variant	2	1		1		25608561
CFH	ENST00000367429	c.3565C>T	p.L1189F	missense_variant	1				1	15661753, 17517971, 24933457, 15140578, 23431077, 27064621
CFH	ENST00000367429	c.3566T>A	p.L1189H	missense_variant	2	1			1	24671321
CFH	ENST00000367429	c.3566T>C	p.L1189P	missense_variant	2	1			1	20513133
CFH	ENST00000367429	c.3566T>G	p.L1189R	missense_variant	2	1			1	15661753, 17517971, 15140578, 23431077
CD46	ENST00000358170	c.417A>G	p.L139L	synonymous_variant	0					15661753, 21706448, 20059470, 20595690
C3	ENST00000245907	c.4645C>A	p.L1549M	missense_variant	1	1				25608561
C3	ENST00000245907	c.537_539delCTT	p.L180delL	inframe_deletion	0					28056875
DGKE	ENST00000284061	c.71delT	p.L24Cfs*145	frameshift_variant	0					26018111
CD46	ENST00000358170	c.785T>C	p.L262P	missense_variant	2	1			1	23389237
CD46	ENST00000358170	c.858_872del15	p.L287_S291delLPPSS	inframe_deletion,splice_region_variant	0					20090363
CFB	ENST00000456570	c.1298T>C	p.L433S	missense_variant	0					24009284, 24652797, 25037630

CFH	ENST00000367429	c.1733T>A	p.L578*	stop_gained	1			1		23356914, 23307876
CFH	ENST00000367429	c.1778T>A	p.L593*	stop_gained	1			1		25616634
CFH	ENST00000367429	c.3269delT	p.M1090Sfs*3	frameshift_variant	0					23307876
CFI	ENST00000394635	c.414G>T	p.M138I	missense_variant	0					17597211, 27268256
CFH	ENST00000367429	c.484A>G	p.M162V	missense_variant	0					23356914, 23307876
CD46	ENST00000358170	c.2T>A	p.M1K	start_lost	1	1				21706448
CFI	ENST00000394635	c.612G>A	p.M204I	missense_variant	0					27268256
CFI	ENST00000394635	c.667A>G	p.M223V	missense_variant	1		1			27268256
CFB	ENST00000456570	c.1374G>T	p.M458I	missense_variant	1		1			20513133, 24652797
CFH	ENST00000367429	c.3148A>T	p.N1050Y	missense_variant	1				1	15661753, 20059470, 18268093, 28056875
CFI	ENST00000394635	c.452A>G	p.N151S	missense_variant	3	1		1	1	20016463, 17914026, 23307876, 23431077, 26541438, 28187980
CFI	ENST00000394635	c.530A>T	p.N177I	missense_variant	2	1			1	23431077
CFB	ENST00000456570	c.991A>G	p.N331D	missense_variant	2	1	1			25951460
CFH	ENST00000367429	c.1548T>A	p.N516K	missense_variant	1				1	20595690, 23431077, 25037630
CFH	ENST00000367429	c.2300_2300dupA	p.N767Kfs*8	frameshift_variant	0					20016463, 17599974, 14978182, 18371543, 23307876, 23431077
C3	ENST00000245907	c.3341C>T	p.P1114L	missense_variant	2			1	1	20016463, 23307876
CFH	ENST00000367429	c.3389C>T	p.P1130L	missense_variant	2	1			1	23307876
CFH	ENST00000367429	c.3481C>A	p.P1161T	missense_variant	3	1		1	1	26826462
CFH	ENST00000367429	c.3497C>T	p.P1166L	missense_variant	1		1			23431077
CFH	ENST00000367429	c.3676C>T	p.P1226S	missense_variant	4	1	1	1	1	21906045, 12960213
CD46	ENST00000358170	c.493C>T	p.P165S	missense_variant	4	1	1	1	1	26826462, 16386793, 15661753, 16882452
C3	ENST00000245907	c.4985C>T	p.P1662L	missense_variant	3	1		1	1	24352218
CD46	ENST00000358170	c.692C>G	p.P231R	missense_variant	3	1		1	1	20513133, 24029428
CFH	ENST00000367429	c.772_773delinsAA	p.P258K	missense_variant	0					24021908
CFH	ENST00000367429	c.773C>T	p.P258L	missense_variant	2	1			1	27799617
CD46	ENST00000358170	c.832C>T	p.P278S	missense_variant	2	1			1	16621965
CD46	ENST00000358170	c.841C>T	p.P281S	missense_variant	3	1		1	1	28056875
DGKE	ENST00000284061	c.1133C>G	p.P378R	missense_variant	1			1		28056875
THBD	ENST00000377103	c.1483C>T	p.P495S	missense_variant	1				1	19625716, 20595690
DGKE	ENST00000284061	c.1493C>G	p.P498R	missense_variant	3	1		1	1	25135762

THBD	ENST00000377103	c.1502C>T	p.P501L	missense_variant	2	1			1	19625716, 24118826, 20513133, 23847193, 24652797, 20595690, 24029428, 23307876, 27904864
CFI	ENST00000394635	c.148C>G	p.P50A	missense_variant	3	1		1	1	20016463, 24034049, 23307876, 23431077, 23787556, 27268256, 25037630
CD46	ENST00000358170	c.148C>A	p.P50T	missense_variant	0					20595690
CFI	ENST00000394635	c.1681C>T	p.P561S	missense_variant	2		1		1	20016463, 22223611, 23356914, 23307876, 23431077, 27268256
CFH	ENST00000367429	c.1861C>A	p.P621T	missense_variant	3	1		1	1	16528247
C3	ENST00000245907	c.188C>T	p.P63L	missense_variant	4	1	1	1	1	25608561, 23847193, 24029428
CFI	ENST00000394635	c.191C>T	p.P64L	missense_variant	3	1		1	1	20513133
CFH	ENST00000367429	c.2120C>T	p.P707L	missense_variant	3	1		1	1	25616634
CFH	ENST00000367429	c.2901delG	p.P968Lfs*7	frameshift_variant	0					23431077
CFH	ENST00000367429	c.2944C>T	p.P982S	missense_variant	4	1	1	1	1	25443527
CFH	ENST00000367429	c.3226C>G	p.Q1076E	missense_variant	0					21906045, 20059470, 11170896, 12960213, 17699195, 16470555, 23431077
CFH	ENST00000367429	c.3409C>T	p.Q1137*	stop_gained	1			1		23307876
CFH	ENST00000367429	c.3410A>T	p.Q1137L	missense_variant	2	1			1	20595690, 23431077
CFH	ENST00000367429	c.3415C>T	p.Q1139*	stop_gained	1			1		17295030, 21396679
CFH	ENST00000367429	c.3415_3416delinsGC	p.Q1139A	missense_variant	1	1				21215749
CFH	ENST00000367429	c.3427C>G	p.Q1143E	missense_variant	0					24933457
C3	ENST00000245907	c.3481C>A	p.Q1161K	missense_variant	0					18796626, 23431077
DGKE	ENST00000284061	c.427C>T	p.Q143*	stop_gained	1			1		28056875
C3	ENST00000245907	c.553C>G	p.Q185E	missense_variant	0					25608561, 20595690, 23431077
C3	ENST00000245907	c.555G>C	p.Q185H	missense_variant	0					25608561
DGKE	ENST00000284061	c.744G>C	p.Q248H	missense_variant,splice_region_variant	3	1		1	1	25135762
DGKE	ENST00000284061	c.1000C>T	p.Q334*	stop_gained	1			1		23542698
CFH	ENST00000367429	c.118C>T	p.Q40*	stop_gained	1			1		23356914
CFH	ENST00000367429	c.1198C>A	p.Q400K	missense_variant	0					20106822, 14978182, 22410797, 23431077, 25616634

CFH	ENST00000367429	c.242A>C	p.Q81P	missense_variant,splice_region_variant	2	1			1	20203157, 23307876, 23431077
CFH	ENST00000367429	c.2773C>T	p.Q925*	stop_gained	1			1		17599974, 14978182, 23307876, 23431077
CFH	ENST00000367429	c.2850G>T	p.Q950H	missense_variant	2	1			1	20513133, 26826462, 20106822, 22250080, 25733390, 19951285, 18006700, 20059470, 14583443, 19861685, 20595690, 23431077, 24656451, 25899302, 28056875, 28187980
CD46	ENST00000358170	c.308G>A	p.R103Q	missense_variant	0					23431077
CD46	ENST00000358170	c.307C>T	p.R103W	missense_variant	1	1				20016463, 15661753, 17914026, 23307876, 23431077, 27177491
C3	ENST00000245907	c.3124C>G	p.R1042G	missense_variant	3	1		1	1	25608561, 25899302
C3	ENST00000245907	c.3125G>T	p.R1042L	missense_variant	3	1		1	1	20513133, 25608561, 28056875
C3	ENST00000245907	c.3124C>T	p.R1042W	missense_variant	3	1		1	1	20595690, 23431077
CFH	ENST00000367429	c.3445C>T	p.R1149*	stop_gained	1			1		23787556
CFH	ENST00000367429	c.3546G>T	p.R1182S	missense_variant	3	1	1		1	21906045, 21717289, 20059470, 23431077
CFH	ENST00000367429	c.3607C>T	p.R1203W	missense_variant	0					26826462, 20106822
CFH	ENST00000367429	c.3616C>T	p.R1206C	missense_variant	1				1	20106822, 22622361, 27268256
CFH	ENST00000367429	c.3628C>T	p.R1210C	missense_variant	1			1		20513133, 26826462, 20016463, 20106822, 20203157, 16621965, 15661753, 21906045, 11851332, 12424708, 17517971, 19633317, 23356914, 20059470, 11158219, 12960213, 15816899, 20534299, 14583443, 20703214, 22410797, 16189652, 16882452, 20595690, 23307876, 18235085, 23431077, 24656451, 27268256, 27799617, 25037630
CFH	ENST00000367429	c.3643C>T	p.R1215*	stop_gained	1			1		23307876

CFH	ENST00000367429	c.3643C>G	p.R1215G	missense_variant	3	1	1		1	25951460, 9551389, 11170896, 20595690, 24029428, 23431077, 25261570, 25899302, 27064621, 27616760, 25037630
CFH	ENST00000367429	c.3644G>A	p.R1215Q	missense_variant	3	1	1		1	20513133, 26826462, 25951460, 23314101, 25443527, 11851332, 17973958, 20738267, 21868097, 11158219, 15816899, 24221349, 17699195, 14583443, 16189652, 20595690, 24029428, 23431077, 26865178, 28056875
C3	ENST00000245907	c.481C>T	p.R161W	missense_variant	2	1			1	20203157, 22246034, 22669319, 25879158, 23356914, 22410797, 23307876, 23431077, 25899302, 27177491, 28110418, 28187980, 27452363
CFH	ENST00000367429	c.497G>T	p.R166L	missense_variant	2	1			1	24333077
CFI	ENST00000394635	c.560G>A	p.R187Q	missense_variant	0					27268256, 25037630
CD46	ENST00000358170	c.685C>T	p.R229*	stop_gained	1			1		25443527
CFH	ENST00000367429	c.694C>T	p.R232*	stop_gained	1			1		25899302
DGKE	ENST00000284061	c.818G>C	p.R273P	missense_variant	3	1		1	1	23542698
CFH	ENST00000367429	c.83_86delGAAA	p.R28Ifs*5	frameshift_variant	0					9551389
CFI	ENST00000394635	c.973C>T	p.R325W	missense_variant	2		1		1	16621965, 20595690, 23431077
DGKE	ENST00000284061	c.1009C>T	p.R337*	stop_gained	1			1		28056875
CFH	ENST00000367429	c.1022G>A	p.R341H	missense_variant	0					20203157, 23307876
CFI	ENST00000394635	c.1166G>A	p.R389H	missense_variant	4	1	1	1	1	27268256
CFI	ENST00000394635	c.1240C>T	p.R414C	missense_variant	2	1	1			19861685, 25899302, 27268256, 27452363
C3	ENST00000245907	c.1273C>T	p.R425C	missense_variant	3	1		1	1	25431709, 27722136
C3	ENST00000245907	c.1433G>T	p.R478L	missense_variant	2	1			1	25608561, 20595690, 23431077
CFI	ENST00000394635	c.1444C>T	p.R482*	stop_gained	1			1		20016463, 20106822, 20203157, 15173250, 23307876
CFI	ENST00000394635	c.1445G>A	p.R482Q	missense_variant	2		1	1		26826462

CFH	ENST00000367429	c.157C>T	p.R53C	missense_variant	3	1		1	1	26826462, 20203157, 25006455, 23307876, 23431077
CFH	ENST00000367429	c.1745G>A	p.R582H	missense_variant	1	1				23307876
CD46	ENST00000358170	c.175C>T	p.R59*	stop_gained	1			1		16621965, 21906045, 17599974, 16762990, 20059470, 17699195, 16882452, 20595690, 23307876, 18235085, 23431077, 24021908, 26880462, 27799617
C3	ENST00000245907	c.1775G>A	p.R592Q	missense_variant	0					18796626, 19590060, 23356914, 19775316, 23307876, 23431077, 24021908, 27177491
C3	ENST00000245907	c.1774C>T	p.R592W	missense_variant	2	1			1	18796626, 25879158, 21902819, 20595690, 23431077
DGKE	ENST00000284061	c.188G>C	p.R63P	missense_variant	2		1	1		23542698
CFH	ENST00000367429	c.232A>G	p.R78G	missense_variant	2	1			1	14583443, 20595690, 23431077, 25037630
CFH	ENST00000367429	c.2655delG	p.R885Sfs*13	frameshift_variant	0					28025630
C3	ENST00000245907	c.2852G>A	p.R951H	missense_variant	0					26826462
CFH	ENST00000367429	c.3181T>C	p.S1061P	missense_variant	0					15754282
C3	ENST00000245907	c.3187A>C	p.S1063R	missense_variant	1	1				20595690, 23431077, 25037630
DGKE	ENST00000284061	c.32C>A	p.S11*	stop_gained	1			1		23542698
CFH	ENST00000367429	c.3398C>G	p.S1133*	stop_gained	1			1		27268256
CFH	ENST00000367429	c.3572C>T	p.S1191L	missense_variant	2	1			1	20513133, 26826462, 21906045, 17599974, 25733390, 25443527, 18425537, 19005013, 19854549, 21868097, 21881555, 24933457, 20059470, 11170896, 19856002, 15300478, 15696434, 16470555, 17076561, 22410797, 10577907, 23847193, 21161283, 19625720, 20595690, 23307876, 23431077, 24656451, 24021908, 25899302, 26604087, 26880462, 27799617, 25037630

CFH	ENST00000367429	c.3572C>G	p.S1191W	missense_variant	2	1			1	15661753, 17517971, 24931815, 15140578, 24558625, 23431077, 27799617
CFI	ENST00000394635	c.436A>C	p.S146R	missense_variant	2	1			1	27268256
CFHR1	ENST00000320493	c.479C>A	p.S160*	stop_gained	0					19745068
C3	ENST00000245907	c.4856_4857delinsTG	p.S1619M	missense_variant	1	1				25608561
C3	ENST00000245907	c.4855A>C	p.S1619R	missense_variant	0					25608561, 23847193, 24029428
CFHR5	ENST00000367414	c.583T>A	p.S195T	missense_variant	1	1				22622361
CFH	ENST00000367429	c.595A>G	p.S199G	missense_variant	3	1		1	1	24029428
CD46	ENST00000358170	c.718T>C	p.S240P	missense_variant	2	1			1	14566051, 20059470, 19861685, 23431077, 27177491, 27452363
CD46	ENST00000358170	c.815_829del15	p.S272_D277delinsN	inframe_deletion	0					16621965
CD46	ENST00000358170	c.815_833delinsACAG	p.S272_P278delinsNS	protein_altering_variant	0					20595690, 23431077
CFH	ENST00000367429	c.1231T>A	p.S411T	missense_variant	0					23307876, 23431077
DGKE	ENST00000284061	c.118_121dupTGTA	p.S41Mfs*2	stop_gained,frameshift_variant	0					28056875
DGKE	ENST00000284061	c.1452delG	p.S485Lfs*9	frameshift_variant	0					25135762
CFH	ENST00000367429	c.1466C>A	p.S489*	stop_gained	1			1		15816899
CFH	ENST00000367429	c.2141C>G	p.S714*	stop_gained	1			1		21906045, 20059470, 12960213
CFH	ENST00000367429	c.2165C>A	p.S722*	stop_gained	1			1		26826462, 25496981
CFH	ENST00000367429	c.2669G>T	p.S890I	missense_variant	0					16621965, 21881555, 20595690, 23431077, 26163426
CFH	ENST00000367429	c.3550A>G	p.T1184A	missense_variant	1		1			21601332, 23431077
CFH	ENST00000367429	c.3551C>G	p.T1184R	missense_variant	1		1			11170896, 23431077
CFH	ENST00000367429	c.3649_3651delACA	p.T1217delT	inframe_deletion	0					26826462, 21906045
C3	ENST00000245907	c.4148C>A	p.T1383N	missense_variant	1	1				25608561, 20595690, 23431077, 28056875
C3	ENST00000245907	c.419_420delinsGG	p.T140R	missense_variant	1	1				25037630
C3	ENST00000245907	c.485C>A	p.T162K	missense_variant	1				1	25608561, 20595690, 23431077
C3	ENST00000245907	c.485C>G	p.T162R	missense_variant	1				1	25608561, 20595690, 23431077, 25899302, 27064621, 27268256
CFI	ENST00000394635	c.608C>T	p.T203I	missense_variant	0					28056875
DGKE	ENST00000284061	c.610_610dupA	p.T204Nfs*4	frameshift_variant	0					25443527
DGKE	ENST00000284061	c.793A>C	p.T265P	missense_variant	1			1		28056875

CD46	ENST00000358170	c.800_820del21	p.T267_N273delTIVCDSN	inframe_deletion	0					23431077
CD46	ENST00000358170	c.800_801delCA	p.T267Nfs*4	frameshift_variant	0					16621965, 14615110, 20090363, 20595690, 23431077
DGKE	ENST00000284061	c.76delA	p.T26Rfs*143	frameshift_variant	0					28056875
CD46	ENST00000358170	c.906_926del21	p.T303_S309delTSSTTKS	inframe_deletion	0					17914026
CFH	ENST00000367429	c.88_88dupA	p.T30Nfs*10	frameshift_variant	0					23431077
CD46	ENST00000358170	c.1148C>T	p.T383I	missense_variant	2	1		1		21706448, 23431077, 26989566, 27646857
THBD	ENST00000377103	c.131C>T	p.T44I	missense_variant	1				1	23787556
THBD	ENST00000377103	c.1499C>T	p.T500M	missense_variant	0					25951460
CFH	ENST00000367429	c.1933delA	p.T645Rfs*20	frameshift_variant	0					25899302
CFI	ENST00000394635	c.215C>G	p.T72S	missense_variant	0					20595690, 23431077
CFH	ENST00000367429	c.272C>G	p.T91S	missense_variant	1	1				24029428
CFH	ENST00000367429	c.2867C>T	p.T956M	missense_variant	0					20513133, 26826462, 15661753, 21717289, 11170895, 23431077, 25899302
CFH	ENST00000367429	c.3019G>T	p.V1007L	missense_variant	0					20513133, 21881555, 26163426
CFH	ENST00000367429	c.3178G>C	p.V1060L	missense_variant	0					25135378
CFH	ENST00000367429	c.332T>A	p.V111E	missense_variant	3	1		1	1	21717289, 23431077
CFH	ENST00000367429	c.3401T>G	p.V1134G	missense_variant	3	1		1	1	21906045, 12960213
CFH	ENST00000367429	c.3503T>A	p.V1168E	missense_variant	2	1			1	18268093
CFH	ENST00000367429	c.3590T>C	p.V1197A	missense_variant	3	1		1	1	26826462, 20203157, 16621965, 15661753, 25733390, 17517971, 18425537, 21717289, 21881555, 24933457, 11158219, 11170895, 11170896, 12960213, 16889549, 14583443, 16470555, 17076561, 21161283, 20595690, 23307876, 23431077, 26880462, 24088957
CFH	ENST00000367429	c.3598G>T	p.V1200L	missense_variant	0					20595690, 23431077
CFI	ENST00000394635	c.454G>A	p.V152M	missense_variant	3	1		1	1	20106822, 27268256
DGKE	ENST00000284061	c.486_486dupA	p.V163Sfs*3	frameshift_variant	0					23542698
C3	ENST00000245907	c.4973T>C	p.V1658A	missense_variant	0					22250080, 23431077, 27177491
C3	ENST00000245907	c.493G>T	p.V165F	missense_variant	2	1			1	25899302

CFHR5	ENST00000367414	c.508G>A	p.V170M	missense_variant	2	1			1	25443527, 27064621
CFI	ENST00000394635	c.1258G>A	p.V420M	missense_variant	2	1	1			23731345
CFH	ENST00000367429	c.1826T>A	p.V609D	missense_variant	3	1		1	1	26826462
CFH	ENST00000367429	c.1825G>A	p.V609I	missense_variant	0					20513133, 23847193, 24029428, 25899302
CFH	ENST00000367429	c.2056G>A	p.V686M	missense_variant,splice_region_variant	1	1				24021908
C3	ENST00000245907	c.2284G>A	p.V762I	missense_variant	0					20595690, 23431077
THBD	ENST00000377103	c.241G>A	p.V81I	missense_variant	0					19625716
THBD	ENST00000377103	c.241G>C	p.V81L	missense_variant	0					20595690
CFH	ENST00000367429	c.2503G>T	p.V835L	missense_variant	0					20059470
CFH	ENST00000367429	c.2509G>A	p.V837I	missense_variant	0					25135378, 27064621, 27150874
C3	ENST00000245907	c.3100T>A	p.W1034R	missense_variant	3	1		1	1	25608561, 24021908, 27799617
CFH	ENST00000367429	c.3468_3468dupA	p.W1157Mfs*22	frameshift_variant	0					22223611, 27268256
CFH	ENST00000367429	c.3469T>C	p.W1157R	missense_variant	4	1	1	1	1	21906045, 12960213
CFH	ENST00000367429	c.3549G>A	p.W1183*	stop_gained	1			1		20595690, 23431077
CFH	ENST00000367429	c.3546_3581dup	p.W1183_ G1194dupWTAKQKLYSRTG	inframe_insertion	0					16621965, 15206027, 20595690, 23431077, 25037630
CFH	ENST00000367429	c.3549G>T	p.W1183C	missense_variant	3	1	1		1	20513133, 21902819
CFH	ENST00000367429	c.3548_3549delinsTT	p.W1183F	missense_variant	0					23307876
CFH	ENST00000367429	c.3548G>T	p.W1183L	missense_variant	3	1	1		1	15661753, 17599974, 12424708, 17517971, 14978182, 23307876, 23431077
CFH	ENST00000367429	c.3547T>A	p.W1183R	missense_variant	3	1	1		1	12020532, 14583443, 16189652, 21902819, 20595690, 23307876, 23431077
CFH	ENST00000367429	c.3547T>C	p.W1183R	missense_variant	3	1	1		1	21906045, 20059470, 12960213
CFH	ENST00000367429	c.400T>C	p.W134R	missense_variant	4	1	1	1	1	21717289, 23431077
DGKE	ENST00000284061	c.472_472dupT	p.W158Lfs*8	frameshift_variant	0					23542698
CFH	ENST00000367429	c.592T>C	p.W198R	missense_variant	3	1		1	1	26826462
CD46	ENST00000358170	c.648G>C	p.W216C	missense_variant	4	1	1	1	1	20513133, 24933457, 24029428
CD46	ENST00000358170	c.646T>G	p.W216G	missense_variant	4	1	1	1	1	25899302
CFH	ENST00000367429	c.942G>A	p.W314*	stop_gained	1			1		25899302
DGKE	ENST00000284061	c.966G>A	p.W322*	stop_gained	1			1		23542698, 25135762, 25854283, 27177491

CFI	ENST00000394635	c.1219T>C	p.W407R	missense_variant	2		1		1	20595690, 23431077
CFH	ENST00000367429	c.213G>A	p.W71*	stop_gained	1			1		25899302
CFH	ENST00000367429	c.2572T>A	p.W858R	missense_variant	4	1	1	1	1	25616634
CFH	ENST00000367429	c.2758T>C	p.W920R	missense_variant	4	1	1	1	1	20595690, 23431077
CFH	ENST00000367429	c.2934G>T	p.W978C	missense_variant	4	1	1	1	1	21906045, 12960213
CFH	ENST00000367429	c.3048C>A	p.Y1016*	stop_gained	1			1		24021908, 27799617
CFH	ENST00000367429	c.3062A>T	p.Y1021F	missense_variant	0					21906045, 12960213
CFH	ENST00000367429	c.3172T>C	p.Y1058H	missense_variant	0					25135378
CFH	ENST00000367429	c.3425A>G	p.Y1142C	missense_variant	2	1			1	17517971, 18423815, 23431077
CFH	ENST00000367429	c.3424T>G	p.Y1142D	missense_variant	2	1			1	21906045, 12960213
CD46	ENST00000358170	c.350_350dupA	p.Y117*fs*1	stop_gained,frameshift_variant	0					21706448
CFH	ENST00000367429	c.3530A>G	p.Y1177C	missense_variant	3	1	1		1	23356914, 22956028, 23307876, 28056875
CD46	ENST00000358170	c.350delA	p.Y117Sfs*17	frameshift_variant	0					27799617
CFH	ENST00000367429	c.351delG	p.Y118Ifs*4	frameshift_variant,splice_region_variant	0					23431077
CFH	ENST00000367429	c.3674A>T	p.Y1225F	missense_variant	3	1	1		1	11158219, 15816899
C3	ENST00000245907	c.4294T>C	p.Y1432H	missense_variant	3	1		1	1	25608561
CD46	ENST00000358170	c.565T>G	p.Y189D	missense_variant	2	1			1	20513133, 25951460, 21906045, 17599974, 16762990, 25443527, 20059470, 20595690, 24029428, 23307876, 23431077, 26880462, 28110418
CD46	ENST00000358170	c.744C>A	p.Y248*	stop_gained	1			1		17599974, 16762990, 23307876, 23431077
CD46	ENST00000358170	c.743A>G	p.Y248C	missense_variant	2	1			1	26054645
CD46	ENST00000358170	c.87C>G	p.Y29*	stop_gained	1			1		20016463, 23356914, 23307876, 23431077
CD46	ENST00000358170	c.983_984delAT	p.Y328Sfs*5	frameshift_variant	0					20513133
CFH	ENST00000367429	c.1064A>C	p.Y355S	missense_variant	2	1			1	21322001
CFI	ENST00000394635	c.1130A>C	p.Y377S	missense_variant	4	1	1	1	1	20513133, 18805611
CFH	ENST00000367429	c.1424A>C	p.Y475S	missense_variant	2	1			1	19179328
C3	ENST00000245907	c.1601A>T	p.Y534F	missense_variant	3	1		1	1	23431077
CD46	ENST00000358170	c.161A>G	p.Y54C	missense_variant	2	1			1	21906045, 24247905
CFH	ENST00000367429	c.2127_2129delTTA	p.Y711delY	inframe_deletion	0					28056875
C3	ENST00000245907	c.2562C>G	p.Y854*	stop_gained	1			1		18796626, 23307876, 23431077

CFH	ENST00000367429	c.2697T>A	p.Y899*	stop_gained	1			1		16621965, 21906045, 17599974, 19704120, 20059470, 14978182, 15685522, 19856002, 16909242, 18371543, 20595690, 20865645, 23307876, 23431077, 27744619, 21396679
CFH	ENST00000367429	c.2695T>G	p.Y899D	missense_variant	2	1			1	17699195, 20304497, 23431077
CFH	ENST00000367429	c.2851T>C	p.Y951H	missense_variant	0					14583443
NA: not applicable										

S3 Table. Summary of computational predictions of 282 missense variants.

"deleterious" predictions	0	1	2	3	4
Variant counts	66	51	57	65	43

S4 Table. Concordance among computational prediction tools.

	SIFT	FATHMM	MutationTaster	PROVEAN
SIFT	177			
FATHMM	63	85		
MutationTaster	95	48	105	
PROVEAN	150	62	92	165

Numbers are predicted "deleterious" variants in corresponding categories.

S5 Table. Concordance between computational predictions and enrichment analysis.

	Total	SIFT*	FATHMM*	MutationTaster*	PROVEAN*
All varinats					
Enriched	40	20	9	20	19
Not enriched	106	36	21	26	34
Specificity - prediction		66%	80%	75%	68%
Sensitivity - prediction		50%	23%	50%	48%
Specificity - enrichment		78%	73%	80%	77%
Sensitivity - enrichment		36%	30%	43%	36%
Missense variants only					
Enriched	27	20	9	14	19
Not enriched	93	36	21	21	34
Specificity - prediction		61%	77%	77%	63%
Sensitivity - prediction		74%	33%	52%	70%
Specificity - enrichment		89%	80%	85%	88%
Sensitivity - enrichment		36%	30%	40%	36%
*Integers are counts of predicted "deleterious" variants in the corresponding categories.					

S6 Table. Ten potentially deleterious variants identified only by the enrichment analysis.

					All ethnic groups							non-Finnish European only							
Gene	Transcript	Transcript Consequence	Protein Consequence	Type	AF in gnomAD	AC in aHUS	NAC in aHUS	AC in gnomAD	NAC in gnomAD	P value	P corrected	AF in NFE	AC in aHUS	NAC in aHUS	AC in gnomAD	NAC in gnomAD	P value	P corrected	Impact based on functional assays
CD46	ENST00000358170	c.286+1G>C		splice donor	8.17E-06	9	6599	2	244728	3.13E-13	4.57E-11	8.96E-06	9	5035	1	111563	5.06E-12	5.06E-10	pathogenic
CD46	ENST00000358170	c.286+2T>G		splice donor	4.91E-05	35	6573	12	244628	1.76E-45	2.56E-43	9.86E-05	26	5018	11	111543	1.74E-27	1.74E-25	pathogenic
CD46	ENST00000358170	c.287-2A>G		splice acceptor	2.13E-05	10	6598	5	234627	6.26E-13	9.13E-11	1.91E-05	8	5036	2	104844	8.12E-10	8.12E-08	pathogenic
CD46	ENST00000358170	c.800_801delCA	p.Thr267AsnfsTer4	frameshift	4.06E-06	7	6601	1	246203	6.50E-11	9.48E-09	8.96E-06	7	5037	1	111667	2.16E-09	2.16E-07	pathogenic
CD46	ENST00000358170	c.811_816delGACAGT	p.Asp271_ Ser272del	inframe deletion	4.06E-06	9	6599	1	246217	5.53E-14	8.07E-12	8.95E-06	9	5035	1	111679	5.02E-12	5.02E-10	pathogenic
CFH	ENST00000367429	c.2908A>G	p.Ile970Val	missense	4.06E-06	3	6605	1	246185	7.00E-05	1.02E-02	8.96E-06	3	5041	1	111649	3.12E-04	3.12E-02	pathogenic
CFH	ENST00000367429	c.3493+1G>A		splice donor	4.06E-06	4	6604	1	246209	2.28E-06	3.33E-04	0.00E+00	4	5040	0	111682	3.48E-06		pathogenic
CFH	ENST00000367429	c.481G>T	p.Ala161Ser	missense	7.73E-05	6	6602	19	245835	3.70E-05	5.40E-03	2.69E-05	4	5040	3	111381	1.11E-04	1.11E-02	pathogenic
CFI	ENST00000394635	c.786delA	p.Gly263AlafsTer45	frameshift	2.03E-05	4	6604	5	246175	5.29E-05	7.72E-03	4.48E-05	4	5040	5	111631	3.69E-04	3.69E-02	pathogenic
CFB	ENST00000456570	c.1298T>C	p.Met433Thr	missense	4.15E-06	3	6605	1	240875	7.46E-05	1.09E-02	9.24E-06	3	5041	1	108205	3.41E-04	3.41E-02	pathogenic

AC: allele count
NAC: no-allele count