Meet the Experts - Tough Genetic Cases

ESPN Research Conference
(Complement)

Florence, Italy
March 13, 2026

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Disclosures

- ML
  - Speaker and consulting: Alnylam
  - Consulting services: Novo Nordisk, Arbor Biotechnologies
  - Research grants: CIHR, NIH, CDA
- MN
  - Speaker and consulting: Sobi, Alexion, Novartis
  - Research grants: Novo Nordisk, Q32Bio, Eleva, Kedrion

Note

We assume that the audience has a good understanding of basic genetics concepts and is familiar with the major forms of kidney TMAs and complement biology

illustration by Alex Willliamson (for Experience Life)

Cases (all heterozygous)

Cases	Variants	Diagnoses	Authors
1	An old pathogenic *CFH* mutation	HUS	Toronto
2	A splice site *CFH* variant classified as a VUS	aHUS	La Porta et al.
3	A *C3* variant classified as a VUS	IC-MPGN	Coccia et al.
4	A *CFI* variant variable interpretations	aHUS	Borovitz et a.
5	Hotspot *CFH* variant	aHUS, ARMD	Bergamo

Data to assess ? genetic disease

Cases	Variants	Diagnoses	Family history	Consanguinity	Disease relapse?	Parent testing?	Disease mechanism
1	*CFH* missense	aHUS	Yes	No	No	No	LOF
2	*CFH* splice site	aHUS	?	?	Yes	No	LOF
3	*C3* missense	IC-MPGN	?	?	?	No	GOF
4	*CFI* missense	aHUS	?	?	?	Yes	LOF
5	*CFH* missense	aHUS	?	No	?	No	LOF

Case 1

Atypical HUS

heterozygous *CFH* missense variant

Toronto

Case 1 - unaffected subject, aHUS in the sister

Gene panel done + carrier testing in ~12 y earlier, patient seen in the clinic @ age 17 y

Older sister with aHUS (treated with eculizumab)

Genetic Analysis	*Genetic variant*	*Interpretation*
CFB gene sequencing	Exon 2: c.94C>T (p.Arg32Trp)	Reported polymorphism*; heterozygous
CFB gene sequencing	Exon 3: c.450A>G (p.Arg150Arg)	Reported polymorphism*; heterozygous
CFH gene sequencing	Exon 10: c.1419G>A (p.Ala473Ala)	Reported polymorphism*; homozygous
CFH gene sequencing	Exon 20: c.3148A>T (p.Asn1050Tyr)	Expected to cause disease**; heterozygous
CFH gene sequencing	Exon 7: c.921A>C (p.Ala307Ala)	Reported polymorphism*; homozygous
CFH gene sequencing	Exon 9: c.1204C>T (p.Tyr402His)	Reported polymorphism*; homozygous
CFHR5 gene sequencing	Exon 1: c.-20T>C	Reported polymorphism*; homozygous
CFI gene sequencing	Exon 7: c.898A>G (p.Thr300Ala)	Reported polymorphism*; homozygous

This patient and/or guardian should receive genetic counselling to discuss the implications of this result.

*http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene;
** Esparza-Gordillo (2005) Human Molecular Genetics 14:703

Unaffected subject (sister)

Genetic Analysis	*Genetic variant*	*Interpretation*
CFH gene sequencing	Exon 20: c.3148A>T (p.Asn1050Tyr)	Expected to cause disease*; heterozygous

Human Molecular Genetics, 2005, Vol. 14, No. 5 **703–712**
doi:10.1093/hmg/ddi066
Advance Access published on January 20, 2005

Predisposition to atypical hemolytic uremic syndrome involves the concurrence of different susceptibility alleles in the regulators of complement activation gene cluster in 1q32

Jorge Esparza-Gordillo[1], Elena Goicoechea de Jorge[1], Alfonso Buil[2], Luis Carreras Berges[3], Margarita López-Trascasa[4], Pilar Sánchez-Corral[4] and Santiago Rodríguez de Córdoba[1,*]

Table 1. Summary of mutation and protein data for aHUS patients

Mutation	Protein levels[a]
HF1	
W1183L (heterozygote)	Normal
V1197A/Δexon2	Low
V1197A (heterozygote)	Normal
L1189R (heterozygote)	Normal
T956M (heterozygote)	Normal
R1210C (heterozygote)	Normal
S1191W (heterozygote)	Normal
L1189F (heterozygote)	Normal
c.3221A>T (heterozygote) ?	Low

no match!; likely variant nomenclature mistake as per HGMD

Revisiting your patient's results

- repeat analysis even if it was "positive" -- it may now be benign!
- if negative and done >5-10 years ago, consider re-testing with current panels
- if negative, important to check there are novel disease-causing genes that were not tested at the time

Free online resources to help you

- HMGD (The Human Gene Mutation Database)
- gnomAD (Genome Aggregation Database)
- ClinVar (public archive of interpretations of genetic variants)
- OMIM (Online Catalog of Human Genes and Genetic Disorders)

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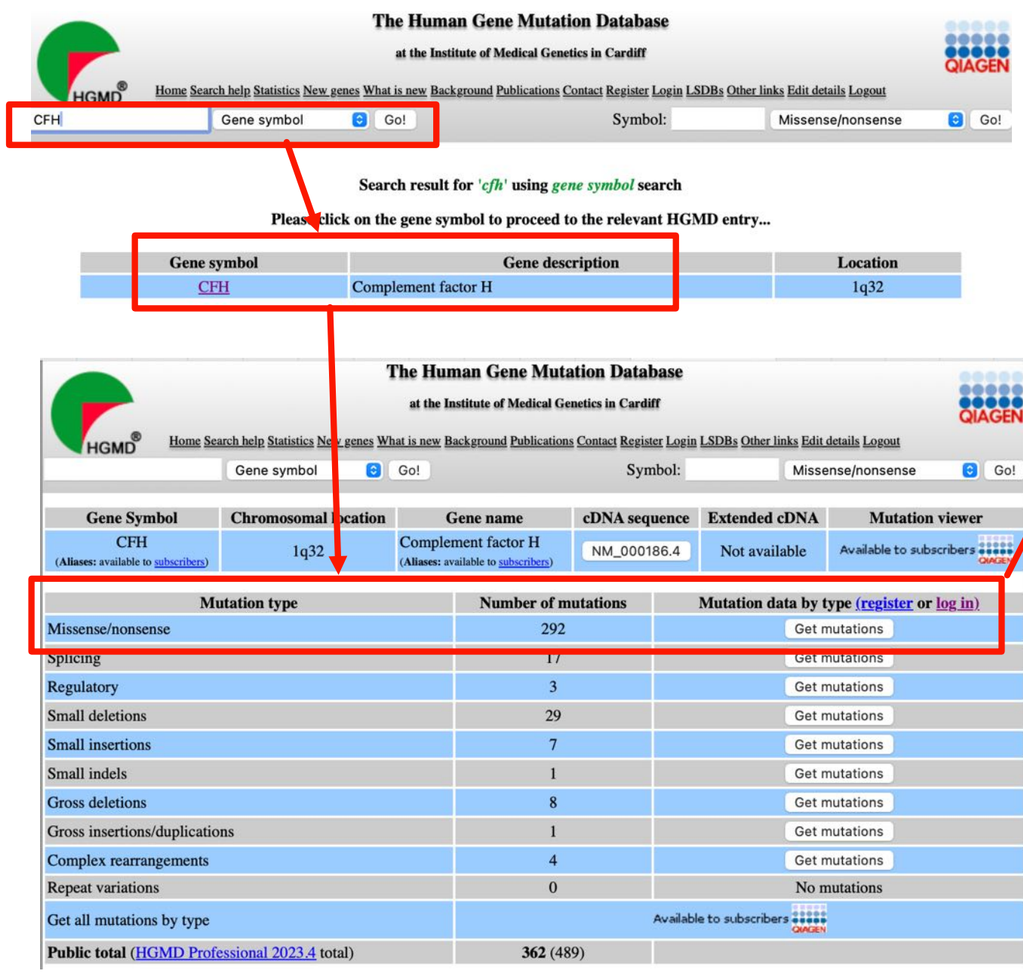
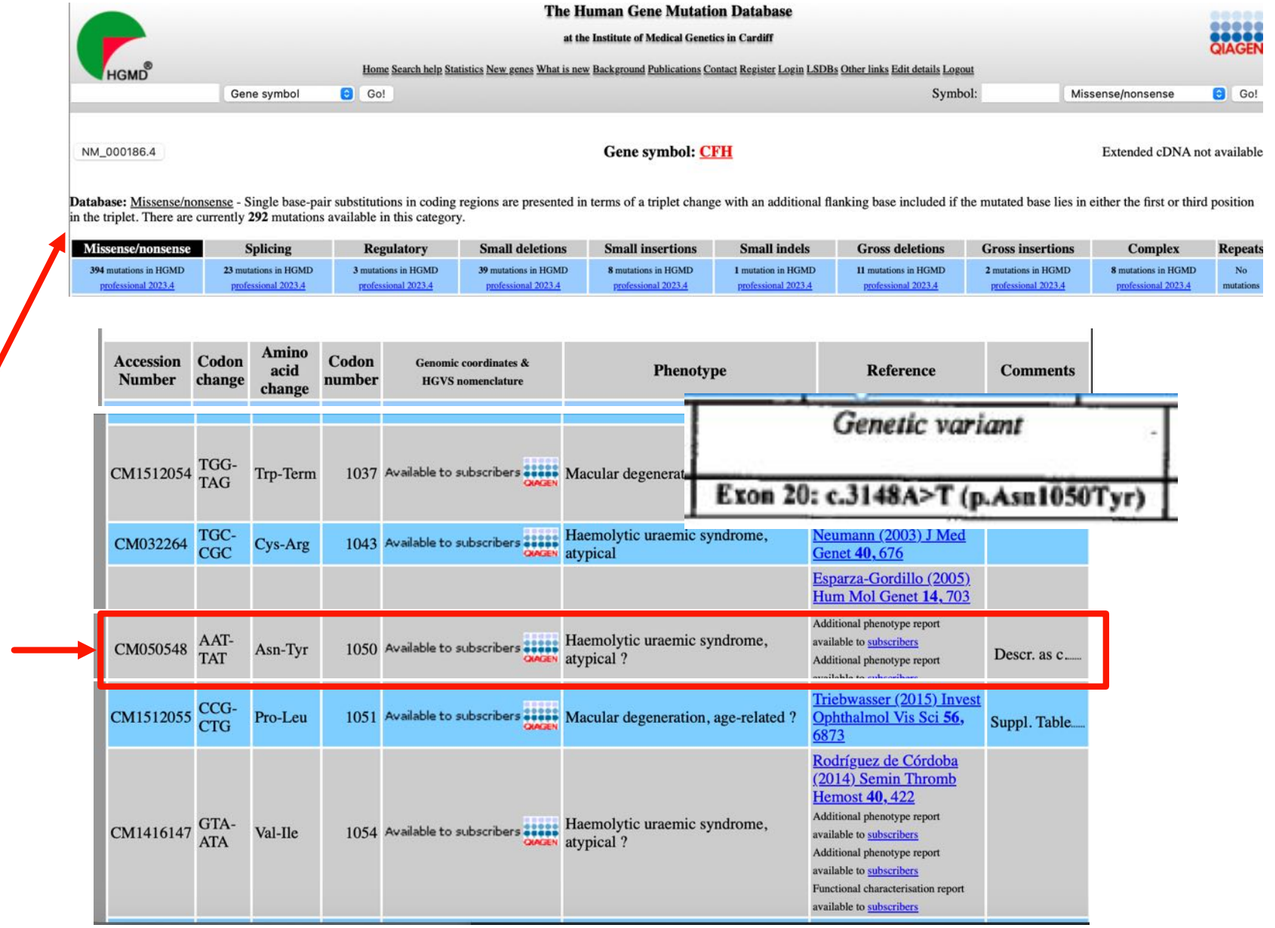
Change in *NPHS1* variant numbers since 2012 in HGMD

	Yearly data for *NPHS1* in HGMD database						
Mutation types	**2012**	**2014**	**2016**	**2018**	**2020**	**2022**	**2024**
Missense/nonsense	87	113	145	152	180	202	239
Splicing	14	20	25	28	39	43	48
Regulatory	0	0	0	0	1	1	1
Small deletions	20	25	33	36	40	42	50
Small insertions	10	10	13	14	16	19	23
Small indels	2	2	3	3	4	4	4
Gross deletions	0	1	3	3	3	5	7
Gross insertions/duplications	0	0	0	0	0	0	0
Complex rearrangements	0	0	0	0	0	0	0
Repeat variations	0	0	0	0	0	0	0
Get all mutations by type	133	171	222	236	283	316	372
Available in HGMD PRO	215	236	280	315	358	398	471
% freely available	62	72	79	75	79	79	79


The Human Gene Mutation Database
at the Institute of Medical Genetics in Cardiff
HGMD
QIAGEN
Home Search help Statistics New genes What is new Background Publications Contact Register Login LSDBs Other links Edit details Logout
CFH
Gene symbol
Go!
Symbol:
Missense/nonsense
Go!
Search result for 'cfh' using gene symbol search
Please click on the gene symbol to proceed to the relevant HGMD entry...
Gene symbol
Gene description
Location
CFH
Complement factor H
1q32
The Human Gene Mutation Database
at the Institute of Medical Genetics in Cardiff
HGMD
QIAGEN
Home Search help Statistics New genes What is new Background Publications Contact Register Login LSDBs Other links Edit details Logout
Gene symbol
Go!
Symbol:
Missense/nonsense
Go!
Gene Symbol
Chromosomal location
Gene name
cDNA sequence
Extended cDNA
Mutation viewer
CFH
(Aliases: available to subscribers)
1q32
Complement factor H
(Aliases: available to subscribers)
NM_000186.4
Not available
Available to subscribers
Mutation type
Number of mutations
Mutation data by type (register or log in)
Missense/nonsense
292
Get mutations
Splicing
17
Get mutations
Regulatory
3
Get mutations
Small deletions
29
Get mutations
Small insertions
7
Get mutations
Small indels
1
Get mutations
Gross deletions
8
Get mutations
Gross insertions/duplications
1
Get mutations
Complex rearrangements
4
Get mutations
Repeat variations
0
No mutations
Get all mutations by type
Available to subscribers
Public total (HGMD Professional 2023.4 total)
362 (489)


The Human Gene Mutation Database
at the Institute of Medical Genetics in Cardiff
HGMD
QIAGEN
Home Search help Statistics New genes What is new Background Publications Contact Register Login LSDBs Other links Edit details Logout
Gene symbol
Go!
Symbol:
Missense/nonsense
Go!
NM_000186.4
Gene symbol: CFH
Extended cDNA not available
Database: Missense/nonsense - Single base-pair substitutions in coding regions are presented in terms of a triplet change with an additional flanking base included if the mutated base lies in either the first or third position in the triplet. There are currently 292 mutations available in this category.
Missense/nonsense
Splicing
Regulatory
Small deletions
Small insertions
Small indels
Gross deletions
Gross insertions
Complex
Repeats
394 mutations in HGMD professional 2023.4
23 mutations in HGMD professional 2023.4
3 mutations in HGMD professional 2023.4
39 mutations in HGMD professional 2023.4
8 mutations in HGMD professional 2023.4
1 mutation in HGMD professional 2023.4
11 mutations in HGMD professional 2023.4
2 mutations in HGMD professional 2023.4
8 mutations in HGMD professional 2023.4
No mutations
Accession Number
Codon change
Amino acid change
Codon number
Genomic coordinates & HGVS nomenclature
Phenotype
Reference
Comments
CM1512054
TGG-TAG
Trp-Term
1037
Available to subscribers
Macular degenerat
Genetic variant
Exon 20: c.3148A>T (p.Asn1050Tyr)
CM032264
TGC-CGC
Cys-Arg
1043
Available to subscribers
Haemolytic uraemic syndrome, atypical
Neumann (2003) J Med Genet 40, 676
Esparza-Gordillo (2005) Hum Mol Genet 14, 703
CM050548
AAT-TAT
Asn-Tyr
1050
Available to subscribers
Haemolytic uraemic syndrome, atypical ?
Additional phenotype report available to subscribers
Additional phenotype report
Descr. as c.....
CM1512055
CCG-CTG
Pro-Leu
1051
Available to subscribers
Macular degeneration, age-related ?
Triebwasser (2015) Invest Ophthalmol Vis Sci 56, 6873
Suppl. Table.....
CM1416147
GTA-ATA
Val-Ile
1054
Available to subscribers
Haemolytic uraemic syndrome, atypical ?
Rodríguez de Córdoba (2014) Semin Thromb Hemost 40, 422
Additional phenotype report available to subscribers
Additional phenotype report available to subscribers
Functional characterisation report available to subscribers

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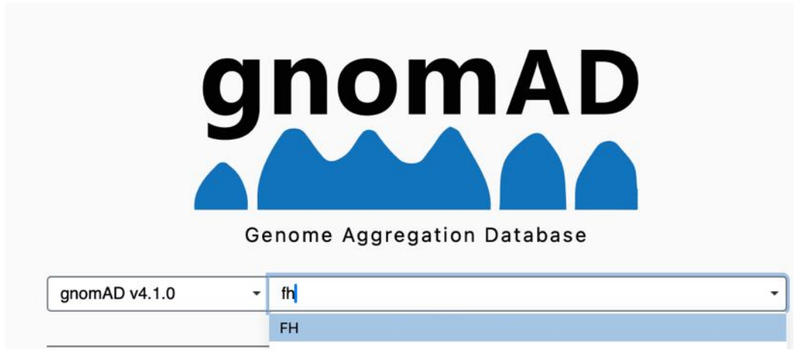

"730,947 exome sequences and 76,215 whole-genome sequences from unrelated individuals, of diverse ancestries,"

CFH complement factor H

Dataset: gnomAD v4.1.0 | gnomAD SVs v4.1.0

Genome build GRCh38 / hg38
Ensembl gene ID ENSG00000000971.16
MANE Select transcript ENST00000367429.9 / NM_000186.4
Ensembl canonical transcript ENST00000367429.9
Other transcripts ENST00000470918.1, ENST00000359637.2, and 3 more
Region 1:196652043-196747504
External resources Ensembl, UCSC Browser, and more

Constraint | Variant co-occurrence

Category	Expected SNVs	Observed SNVs	Constraint metrics
Synonymous	452.5	475	Z = -0.58 o/e = 1.05 (0.97 - 1.13)
Missense	1372.2	1223	Z = 1.47 o/e = 0.89 (0.85 - 0.93)
pLoF	121.1	40	pLI = 1 o/e = 0.33 (0.26 - 0.43)

Constraint metrics based on MANE Select transcript (ENST00000367429.9).

196,652,043 196,673,949 196,679,601 196,689,464 196,701,401 196,725,095 196,726,828 196,736,945 196,740,782 196,743,675 196,747,385

pLoF only | Missense / Inframe indel only | Synonymous only | Other only | all

Exomes Genomes | SNVs Indels | Filtered variants Display neighboring variants

1050

Export variants to CSV | Configure table

Note Only variants located in or within 75 base pairs of a coding exon are shown here. To see variants in UTRs or introns, use the region view.

The table below shows the HGVS consequence and VEP annotation for each variant's most severe consequence across all transcripts in this gene. Cases where the most severe consequence occurs in a non-MANE Select transcript (or non-canonical transcript if no MANE Select transcript exists) are denoted with †. To see consequences in a specific transcript, use the transcript view.

Variant ID	Source	HGVS Consequence	VEP Annotation	LoF Curation	Clinical Significance	Flags	Allele Count
1-196743457-T-A	E	p.Ser1047Thr	missense				2
1-196743458-C-T	E	p.Ser1047Phe	missense				1
1-196743458-C-G	E	p.Ser1047Cys	missense				1
1-196743461-G-A	G	p.Cys1048Tyr	missense				1
1-196743466-A-T	E G	p.Asn1050Tyr	missense		Benign/Likely beni...		29027
1-196743467-A-T	E G	p.Asn1050Ile	missense				11
1-196743469-C-T	E	p.Pro1051Ser	missense				1

SNV: 1-196743466-A-T(GRCh38)

	Exomes	Genomes	Total
Filters	Pass	Pass	
Allele Count	26099	2928	29027
Allele Number	1461426	152318	1613744
Allele Frequency	0.01786	0.01922	0.01799
Grpmax Filtering AF (95% confidence)	0.02556	0.02609	0.02625
Number of homozygotes	281	30	311

External Resources

- dbSNP (rs35274867)
- UCSC
- ClinVar (294520)
- ClinGen Allele Registry (CA1305856)
- All of Us

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (non-Finnish)	23690	1179660	239	0.02008
African/African American	2044	75048	32	0.02724
South Asian	724	91080	15	0.007949
Remaining	1058	62492	14	0.01693
Admixed American	581	60032	5	0.009678
European (Finnish)	577	64030	4	0.009011
Middle Eastern	68	6058	2	0.01122
Ashkenazi Jewish	266	29598	0	0.008987
East Asian	1	44834	0	0.00002230
Amish	18	912	0	0.01974
XX	15071	812258	154	0.01855
XY	13956	801486	157	0.01741
Total	**29027**	**1613744**	**311**	**0.01799**

In Silico Predictors

- CADD: 12.7
- REVEL: 0.0910
- SpliceAI: 0.0400
- Pangolin: -0.0600
- phyloP: -0.401
- PolyPhen (max): 0.843

https://gnomad.broadinstitute.org/variant/1-196743466-A-T?dataset=gnomad_r4

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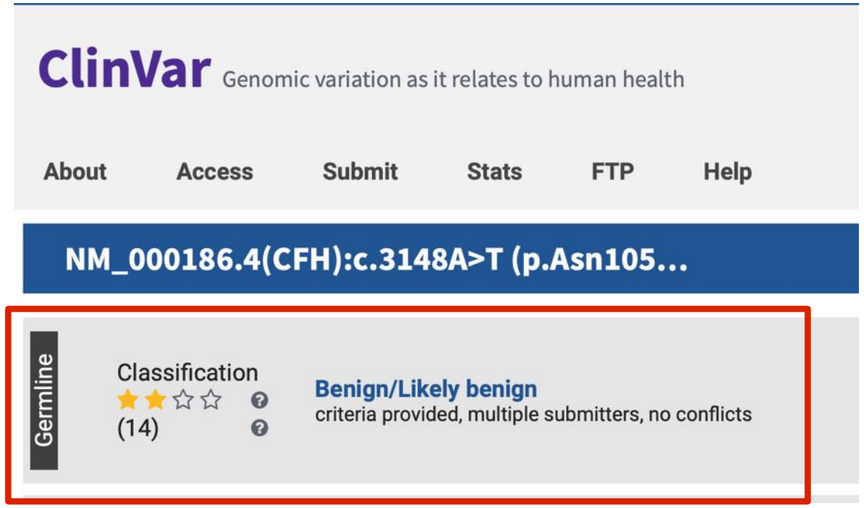


Global minor allele frequency (GMAF) : 0.01418 (T)

Allele frequency :
1000 Genomes Project 0.01418
The Genome Aggregation Database (gnomAD), exomes 0.01432
Exome Aggregation Consortium (ExAC) 0.01512
1000 Genomes Project 30x 0.01593
The Genome Aggregation Database (gnomAD) 0.01982
Trans-Omics for Precision Medicine (TOPMed) 0.02004
NHLBI Exome Sequencing Project (ESP) Exome Variant Server 0.02407

Links :
ClinGen: CA1305856
dbSNP: rs35274867
VarSome

Conditions - Germline

Condition	Classification (# of submissions)	Review status	Last evaluated	Variation/condition record
CFH-Related Dense Deposit Disease / Membranoproliferative Glomerulonephritis Type II	Likely benign (1)	★☆☆☆	Apr 27, 2017	RCV000298640.5
Basal laminar drusen	Likely benign (2)	★★☆☆	Apr 11, 2023	RCV000302390.6
Hemolytic uremic syndrome, atypical, susceptibility to, 1	Likely benign (2)	★★☆☆	Apr 11, 2023	RCV000355977.6
Age related macular degeneration 4	Likely benign (2)	★★☆☆	Apr 11, 2023	RCV000403627.6
Thrombotic microangiopathy	Likely benign (1)	★☆☆☆	Jun 20, 2015	RCV001849180.1
Atypical hemolytic-uremic syndrome	Likely benign (1)	★☆☆☆	Dec 6, 2021	RCV002294240.2
Factor H deficiency	Likely benign (1)	★☆☆☆	Apr 11, 2023	RCV003454853.1
not specified	Benign (1)	☆☆☆☆	-	RCV001701992.1
not provided	Benign/Likely benign (3)	★★☆☆	Aug 1, 2024	RCV001723878.13

https://www.ncbi.nlm.nih.gov/clinvar/variation/294520/

Case 1 - Conclusion

VUS or likely benign!

- Evidence against variant being pathogenic is overwhelming
  - far too high MAF (2.8% in AA)
  - all prediction softwares = benigns
  - also most ClinVar entries = benign

Case 2

Atypical HUS

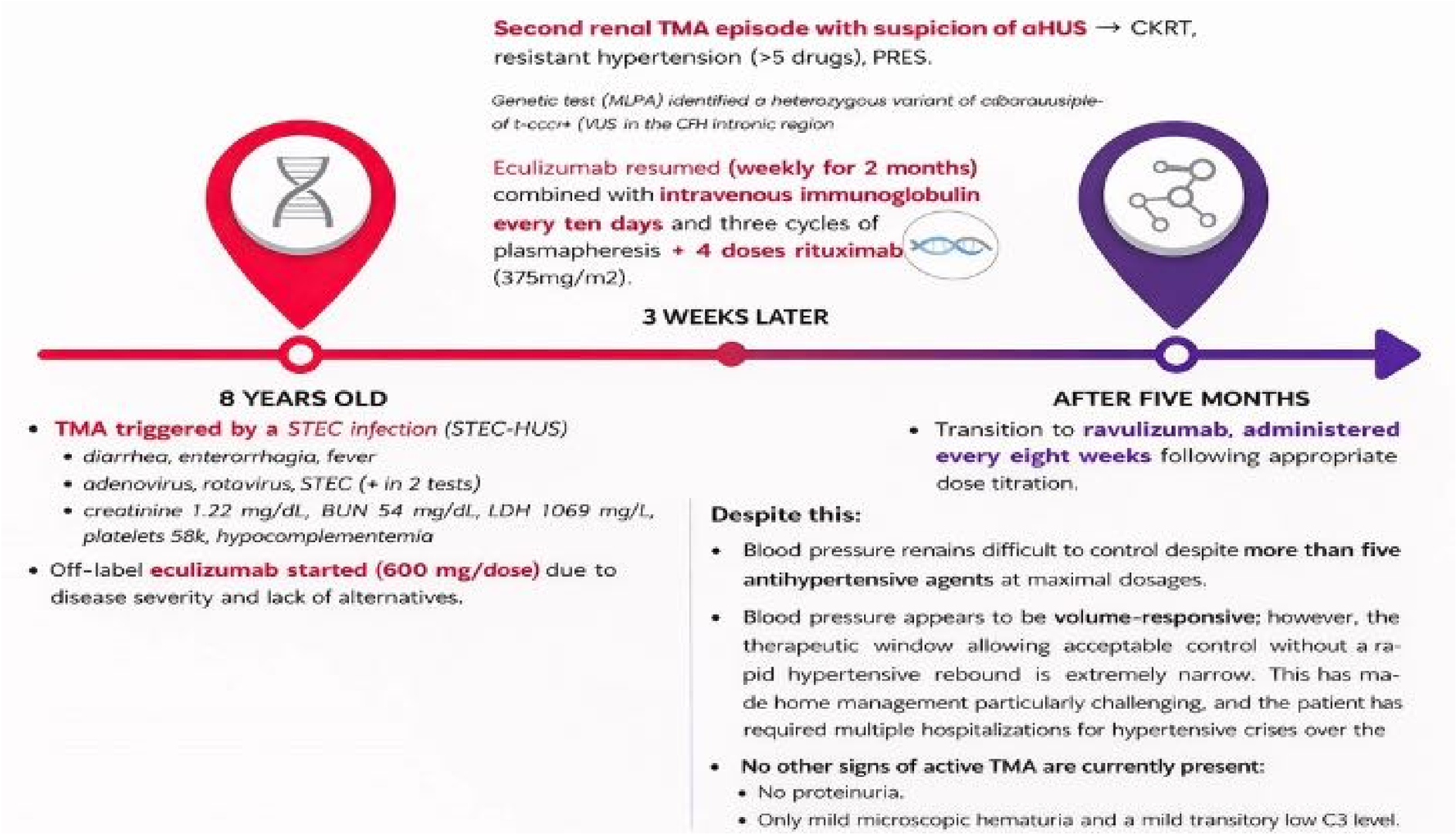
heterozygous *CFH* splice variant

La Porta et al.

Case 2

- Chronic multisystem inflammatory disease from 5 mo through age 8, with fever/arthritis/rash plus immune dysregulation and broad organ involvement
  - partially responsive to immunomodulation
- Age 8: STEC HUS, CVVHDF for 3 weeks
  - Rx: eculizumab plus IVIG/plasmapheresis
- 3 weeks later: another episode of HUS (fall, neuro lesion, ?relapse)
  - Complement blockade + IVIG + rituximab
- Genetics/functional testing: ?complement-mediated susceptibility
  - no pathogenic variant

Case 2


Second renal TMA episode with suspicion of aHUS → CKRT, resistant hypertension (>5 drugs), PRES.
Genetic test (MLPA) identified a heterozygous variant of cáborauusiple- of t-cccr+ (VUS in the CFH intronic region
Eculizumab resumed (weekly for 2 months) combined with intravenous immunoglobulin every ten days and three cycles of plasmapheresis + 4 doses rituximab (375mg/m2).
3 WEEKS LATER
8 YEARS OLD
TMA triggered by a STEC infection (STEC-HUS)
diarrhea, enterorrhagia, fever
adenovirus, rotavirus, STEC (+ in 2 tests)
creatinine 1.22 mg/dL, BUN 54 mg/dL, LDH 1069 mg/L, platelets 58k, hypocomplementemia
Off-label eculizumab started (600 mg/dose) due to disease severity and lack of alternatives.
AFTER FIVE MONTHS
Transition to ravulizumab, administered every eight weeks following appropriate dose titration.
Despite this:
Blood pressure renains difficult to control despite more than five antihypertensive agents at maximal dosages.
Blood pressure appears to be volume-responsive; however, the therapeutic window allowing acceptable control without a rapid hypertensive rebound is extremely narrow. This has made home management particularly challenging, and the patient has required multiple hospitalizations for hypertensive crises over the
No other signs of active TMA are currently present:
No proteinuria.
Only mild microscopic hematuria and a mild transitory low C3 level.

Case 2 - Genetic testing

Gene (Transcript)	DNA Change	Protein Change	Zygosity	Classification	Associated disease	OMIM	Disease Inheritance
CFH (NM_000186.4)	c.3133+4 C>G	NA	Heterozygous	Uncertain Significance	Susceptibility to atypical hemolytic uremic syndrome 1	235400	Autosomal dominant, Autosomal recessive
PAX6 (NM_001368894.2)	c.-115_ -112del	NA	Heterozygous	Uncertain Significance	*PAX6*-related aniridia	106210	Autosomal dominant
HBB (NM_000518.5)	c.-151C>T	NA	Heterozygous	Pathogenic	Beta thalassemia	613985	Autosomal recessive
MPO (NM_000250.2)	c.2031-2A>C	NA	Heterozygous	Pathogenic	Myeloperoxidase deficiency	254600	Autosomal recessive
PEPD (NM_000285.4)	c.1342G>A	p.Gly448Arg	Heterozygous	Pathogenic	Prolidase deficiency	170100	Autosomal recessive
PTPRC (NM_002838.5)	c.2847+383T>A	NA	Heterozygous	Uncertain Significance	Severe combined immunodeficiency 105	619924	Autosomal recessive

CFH variant previously reported in association with pathogenic *CFI* genotype

- classified as pathogenic by Zuber et al. JASN 2019
- reported as variant of unknown significance (VUS) in ClinVar

CLINICAL RESEARCH www.jasn.org JASN 30: 2449–2463, 2019

Use of Highly Individualized Complement Blockade Has Revolutionized Clinical Outcomes after Kidney Transplantation and Renal Epidemiology of Atypical Hemolytic Uremic Syndrome

Julien Zuber,[1,2] Marie Frimat,[2,3] Sophie Caillard,[2,4] Nassim Kamar,[2,5] Philippe Gatault,[2,6] Florent Petitprez,[7] Lionel Couzi,[2,8] Noemie Jourde-Chiche,[2,9] Valérie Chatelet,[2,10] Raphael Gaisne,[11] Dominique Bertrand,[2,12] Jamal Bamoulid,[2,13] Magali Louis,[2,14] Rebecca Sberro Soussan,[1,2] David Navarro,[1,15] Pierre-Francois Westeel,[2,16] Luc Frimat,[2,17] Charlotte Colosio,[2,18] Antoine Thierry,[2,19] Joseph Rivalan,[2,20] Laetitia Albano,[2,21] Nadia Arzouk,[2,22] Emilie Cornec-Le Gall,[2,23] Guillaume Claisse,[2,24] Michelle Elias,[2,25] Khalil El Karoui,[2,26] Sophie Chauvet,[2,27] Jean-Philippe Coindre,[2,28] Jean-Philippe Rerolle,[2,29] Leila Tricot,[2,30] Johnny Sayegh,[2,31] Cyril Garrouste,[2,32] Christophe Charasse,[2,33] Yahsou Delmas,[2,8] Ziad Massy,[2,34] Maryvonne Hourmant,[2,11] Aude Servais,[1,2] Chantal Loirat,[2,35] Fadi Fakhouri,[2,11] Claire Pouteil-Noble,[2,36] Marie-Noelle Peraldi,[2,37] Christophe Legendre,[1,2] Eric Rondeau,[2,38] Moglie Le Quintrec,[2,39] and Véronique Frémeaux-Bacchi[2,7]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

TABLE S1

Pt#	Age at onset (years)	KTx rank	Previous recur.	Anti-CFH Ab	CFHR1/ 3 copies	Positive Genetic screening	Result 1	Variant 1	AA change	MAF (%)	Class.	Funct. Conseq.
56	36	1			2	Yes	CFI	c. 1071T>G	p.Ile357Met	0.0033	P	Reduced FI plasma level

Result 2	Variant 2	AA change	MAF (%)	Class.	CFH-H3 (homoz.)
CFH	c.3133+4C >G		0.0274	P	No

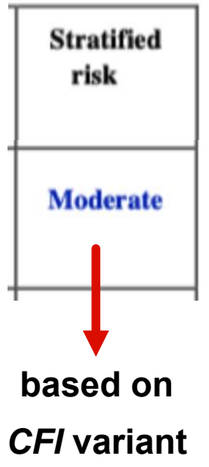
How variants assigned degrees of pathogenicity is not described

"risk stratification (high/moderate/low) for aHUS recurrence [post-Tx] was based on a classification described in previous reports.

- “high risk”: patients who had experienced a recurrence with a previous allograft and/or were harboring a pathogenic variant in *CFH*, *C3* or *CFB*

- "moderate risk": patients who had either a negative complement screening result or a pathogenic variant in the *CFI* gene or detectable circulating anti-CFH antibody

- “low-risk”: isolated mutations in MCP or DGKE, or anti-CFH antibodies no longer detected



based on *CFI* variant

History of genetic variant analysis

Year	Milestone	Details
2000	First ACMG Recommendations	ACMG Laboratory Practice Committee publishes initial guidance for interpreting sequence variations in clinical testing
2007 Richards *Genet Med*	Revised ACMG Guidelines	6 categories introduced improved but still lacked weighted, combinable evidence criteria
2013	ACMG/AMP/CAP Workgroup Convened	Multidisciplinary workgroup of clinical lab directors and clinicians develop a systematic, criteria-based framework
2015 Richards *Genet Med*	**ACMG/AMP 2015 Guidelines Published**	Landmark publication 28 weighted evidence criteria Classification system (P, LP, VUS, LB, B) Combining rules
2016 Amendola *AJHG*	International Adoption Begins	9-lab concordance study UK ACGS formally recommends adoption for germline variant classification

Year	Milestone	Details
2017 Rehm *Genet Med*	Wide Adoption & First Refinements	Guidelines described as "widely adopted nationally and internationally"
2018 Tavtigian *Genet Med*	Bayesian Quantitative Framework	ACMG criteria mocelled as a Bayesian classification framework, enabling quantitative point-based scoring
2019 Niehaus *Genet Med*	~97% Laboratory Adoption	Survey of 65 labs from 15 countries
2019-	Gene-Specific Specifications	ClinGen VCEPs publish adapted ACMG/AMP criteria for >50 gene-disease pairs
2024-	Ongoing Evolution	ACMG/AMP/CAP/ClinGen SVC v4.0; European ABC system proposed as alternative

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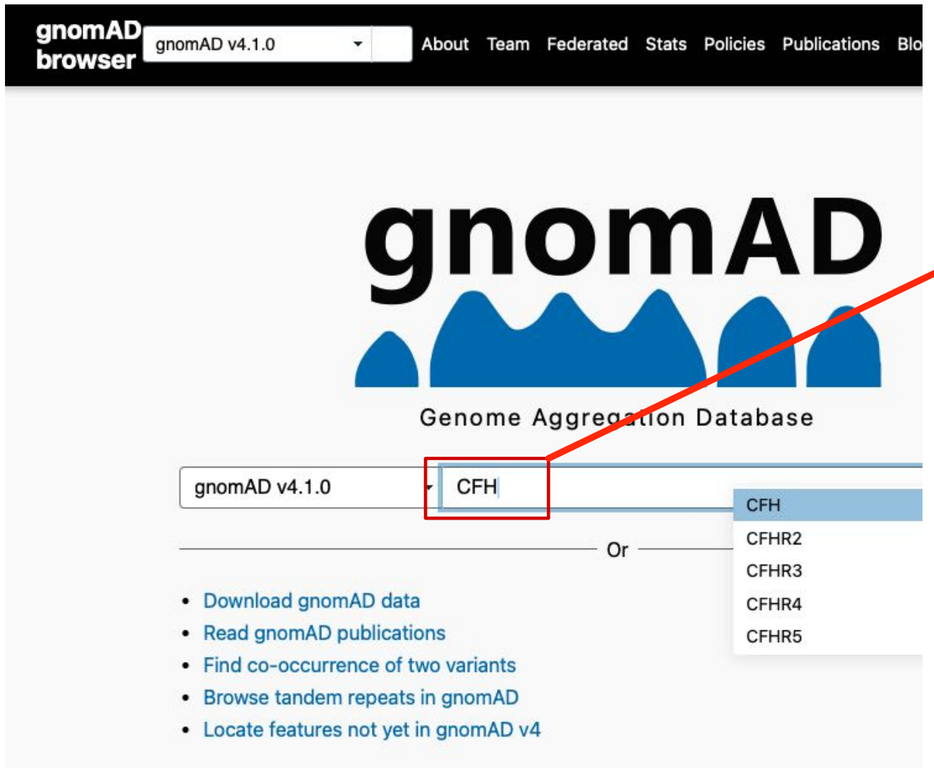
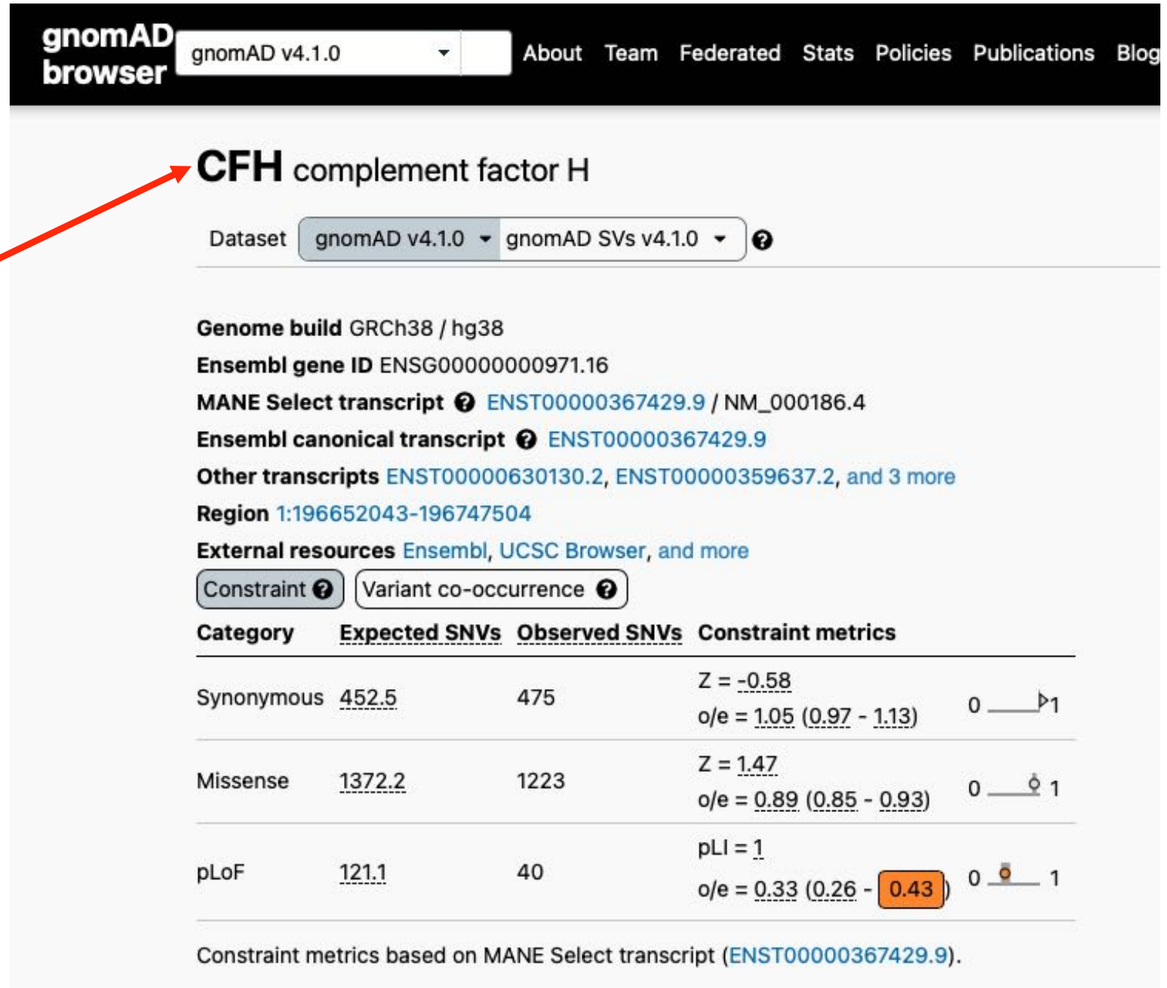
- **gnomAD (Genome Aggregation Database)**
- HMGD (The Human Gene Mutation Database)
- ClinVar (public archive of interpretations of genetic variants)
- OMIM (Online Catalog of Human Genes and Genetic Disorders)

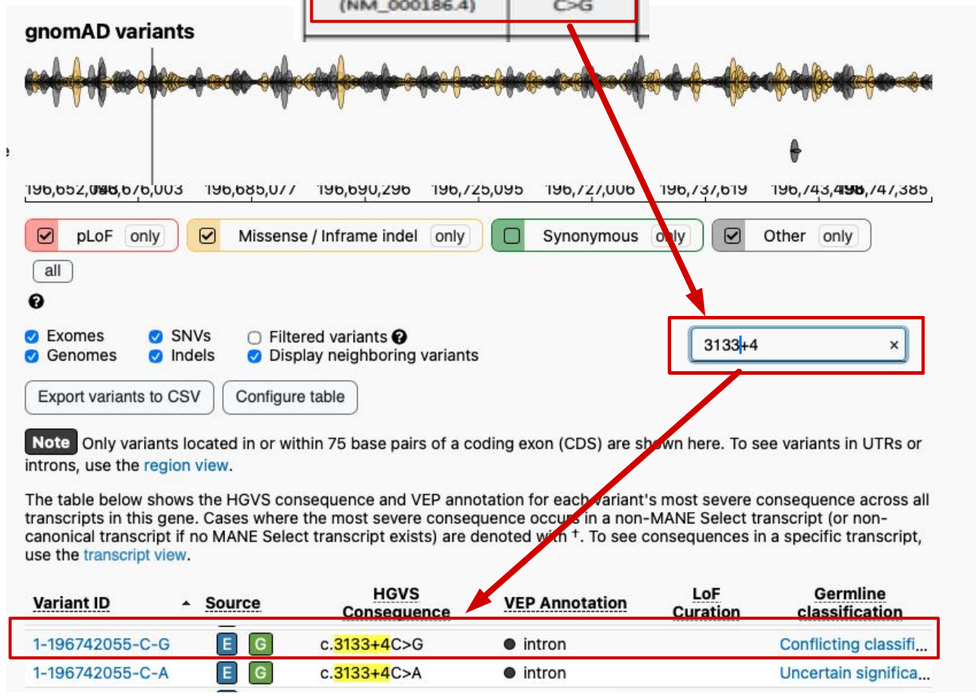


https://gnomad.broadinstitute.org/gene/ENSG00000000971?dataset=gnomad_r4



scroll down!

Gene (Transcript)	DNA Change
CFH (NM_000186.4)	c.3133+4 C>G



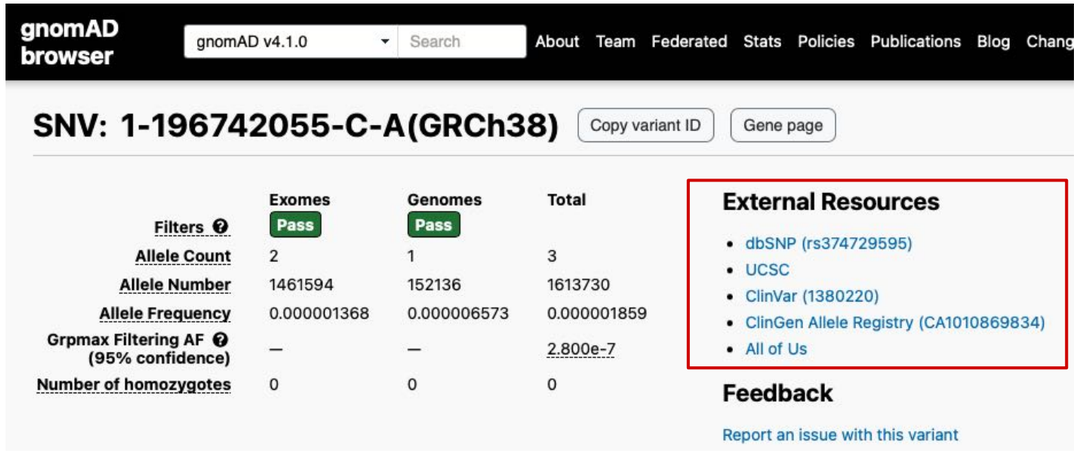
scroll down!

Genetic Ancestry Group Frequencies

gnomAD | HGDP | 1KG | Local Ancestry

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Remaining	1	62476	0	0.00001601
European (non-Finnish)	2	1179832	0	0.000001695
African/African American	0	74888	0	0.000
Admixed American	0	59992	0	0.000
Ashkenazi Jewish	0	29604	0	0.000
East Asian	0	44858	0	0.000
European (Finnish)	0	64016	0	0.000
Middle Eastern	0	6080	0	0.000
Amish	0	908	0	0.000
South Asian	0	91076	0	0.000
XX	2	812288	0	0.000002462
XY	1	801442	0	0.000001248
Total	**3**	**1613730**	**0**	**0.000001859**

Include: Exomes Genomes



ClinVar

ClinVar Variation ID 1380220
Conditions not provided
Germline classification Uncertain significance
Review status criteria provided, single submitter (1 star)
Last evaluated October 24, 2024

ClinVar

NM_000186.4(CFH):c.3133+4C>G

Germline

Classification ★☆☆☆

Conflicting classifications of pathogenicity
Uncertain significance(7); Likely benign(2)
9 out of 11 submissions contributed to this classification

Conditions - Germline

Condition	Classification (# of submissions)	Review status	Last evaluated
not provided	Conflicting classifications of pathogenicity (3)	★☆☆☆	Jan 7, 2026
Age related macular degeneration 4	Uncertain significance (1)	★☆☆☆	Jan 13, 2018
Hemolytic uremic syndrome, atypical, susceptibility to, 1	Likely benign (1)	★☆☆☆	Jan 13, 2018
CFH-Related Dense Deposit Disease / Membranoproliferative Glomerulonephritis Type II	Uncertain significance (1)	★☆☆☆	Jan 13, 2018
Basal laminar drusen	Uncertain significance (1)	★☆☆☆	Jan 13, 2018
not specified	Uncertain significance (1)	★☆☆☆	Mar 21, 2024
Age related macular degeneration 4 Basal laminar drusen Factor H deficiency Hemolytic uremic syndrome, atypical, susceptibility to, 1	Uncertain significance (1)	★☆☆☆	Jun 5, 2024
CFH-related disorder	Likely benign (1)	★☆☆☆	Jul 24, 2019
Optic atrophy	Uncertain significance (1)	★☆☆☆	Jan 1, 2022

Uncertain significance
(Jan 07, 2026)

C Contributing to aggregate classification

★☆☆☆
(Invitae Variant Classification Sherloc (09022015))

not provided

Labcorp Genetics (formerly Invitae), Labcorp
Accession: SCV002171397.5
First in ClinVar: Mar 28, 2022
Last updated: Feb 15, 2026

Comment:
This sequence change falls in intron 19 of the CFH gene. It does not directly change the encoded amino acid sequence of the CFH protein. It affects a nucleotide within the consensus splice site. This variant is present in population databases (rs374729595, gnomAD 0.05%). This variant has not been reported in the literature in individuals affected with CFH-related conditions. ClinVar contains an entry for this variant (Variation ID: 598661). Variants that disrupt the consensus splice site are a relatively common cause of aberrant splicing (PMID: 17576681, 9536098). Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site. In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance. (less)

Observation 1

Collection method: clinical testing
Allele origin: germline
Affected status: unknown

Likely benign
(Jan 13, 2018)

C Contributing to aggregate classification

★☆☆☆
(ICSL Variant Classification Criteria 13 December 2019)

Hemolytic uremic syndrome, atypical, susceptibility to, 1

Illumina Laboratory Services, Illumina
Accession: SCV001253622.1
First in ClinVar: May 31, 2020
Last updated: May 31, 2020

Comment:
This variant was observed in the ICSL laboratory as part of a predisposition screen in an ostensibly healthy population. It had not been previously curated by ICSL or reported in the Human Gene Mutation Database (HGMD: prior to June 1st, 2018), and was therefore a candidate for classification through an automated scoring system. Utilizing variant allele frequency, disease prevalence and penetrance estimates, and inheritance mode, an automated score was calculated to assess if this variant is too frequent to cause the disease. Based on the score and internal cut-off values, a variant classified as likely benign is not then subjected to further curation. The score for this variant resulted in a classification of likely benign for this disease. (less)

Observation 1

Collection method: clinical testing
Allele origin: germline
Affected status: unknown

Case 2 - More investigations

1) ?aberrant CFH mRNA splicing in leukocytes ➡ None

2) Measure serum CFH level ➡ 143 mg/L (141-411 mg/L)

2) Functional testing using subject's plasma applied to human microvascular endothelial cells (HMEC)

- look for ⬆deposition of C5b-9 vs. control

HMEC	Deposition C5b-9	Normal values
Resting (ADP)	119%	< 150%
Activate	160%	

? ⬆risk of TMA

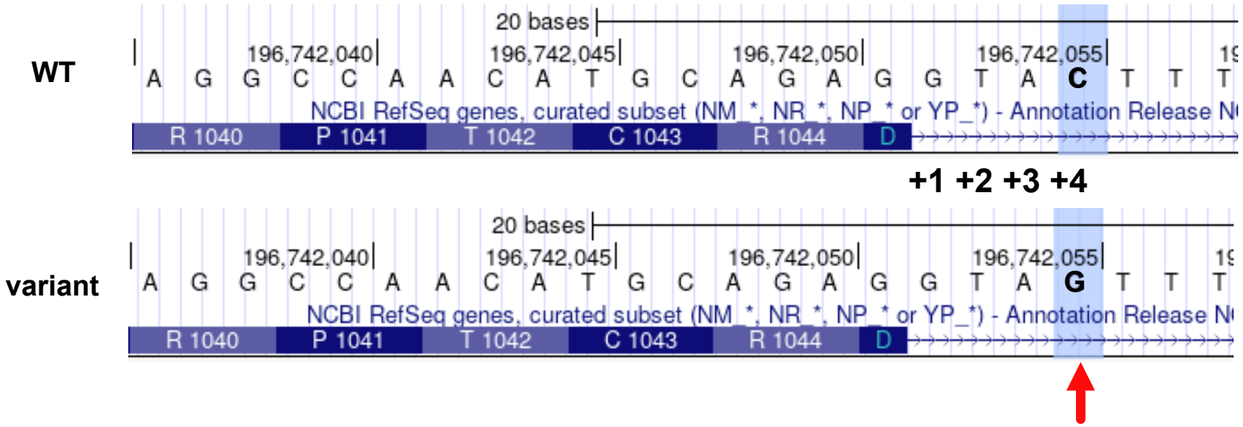
Relevant references

- Noris et al. (2014) Dynamics of complement activation in aHUS and how to monitor eculizumab therapy. Blood

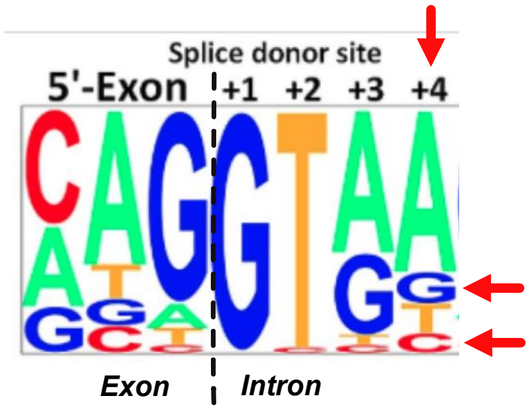
- Galbusera et al. (2019) An Ex Vivo Test of Complement Activation on Endothelium for Individualized Eculizumab Therapy in Hemolytic Uremic Syndrome. AJKD

- Martin et al. (2024) Ex vivo C5b-9 Deposition Test to Monitor Complement Activity in Clinical and Subclinical aHUS and in TA-TMA Kidney Int Rep

Evaluating the potential impact of a splice site variant



Canonical donor splice site

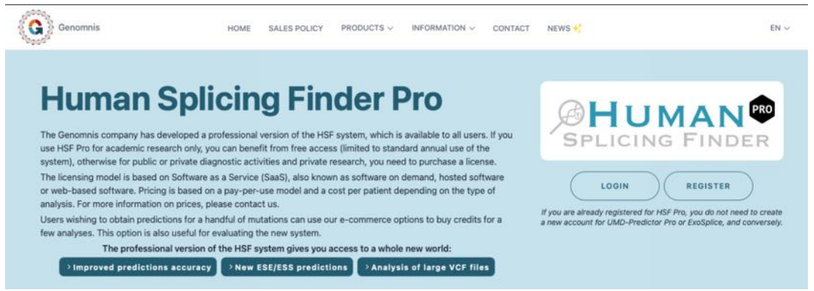


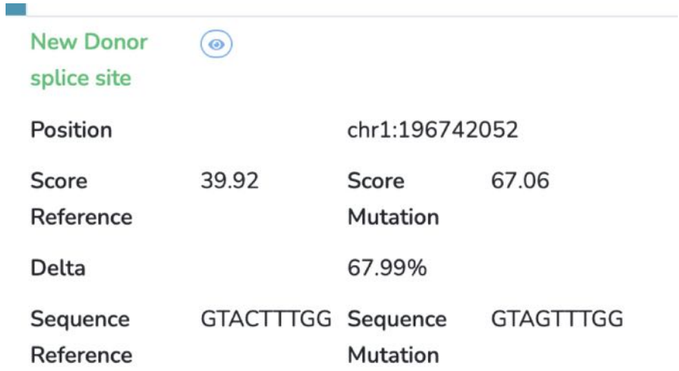
In Silico Predictors **From gnomAD**

- CADD: 0.407
- SpliceAI: 0.00
- Pangolin: 0.0100
- phyloP: -0.640

Splicing predictors

Note The SpliceAI and Pangolin predictions displayed here were precomputed by Illumina and Invitae. For more detailed and up to date SpliceAI and Pangolin predictions, please visit our SpliceAI Lookup browser.





The WT sequence motif at that position looks like a weak donor site

After the change, it looks more donor-like

But not necessarily functional

Case 2 - Conclusions

- c.3133+4C>G is at most a VUS
- probably a benign variant

Case 3

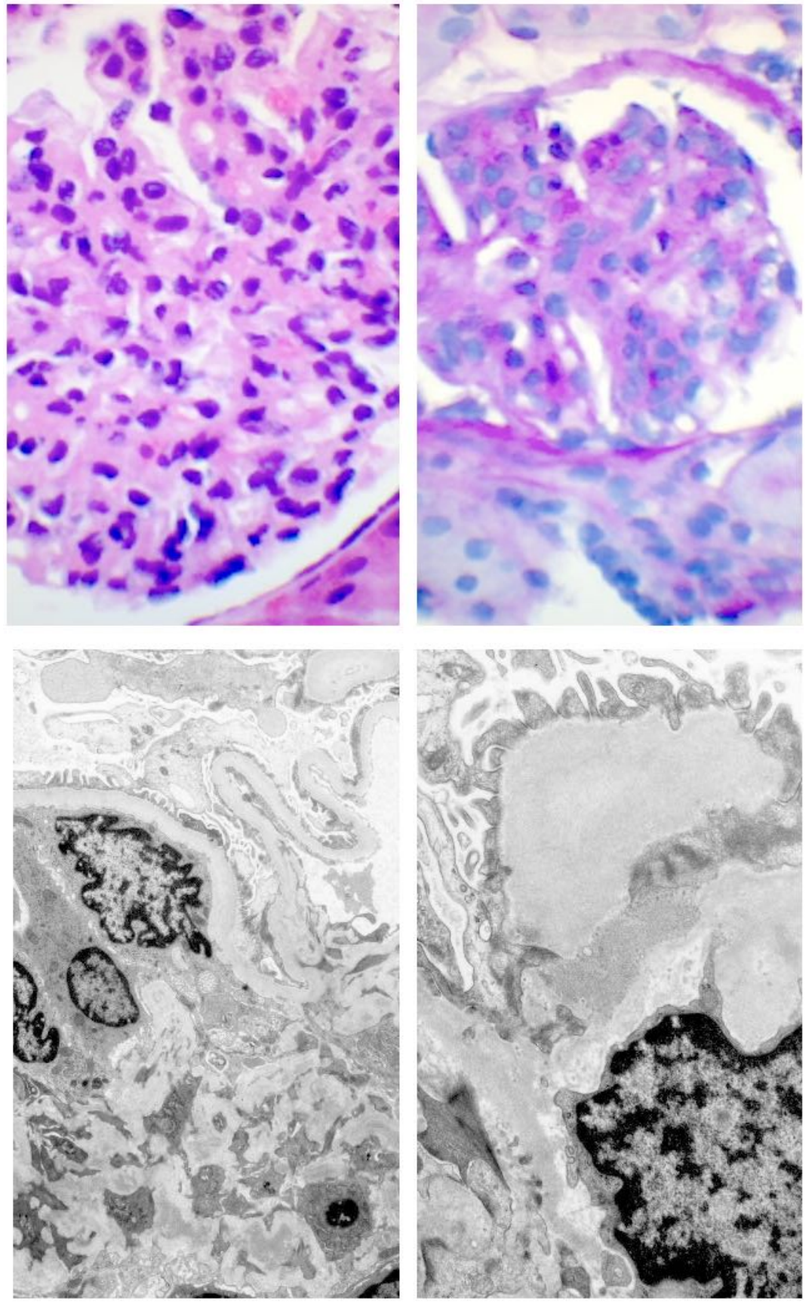
IC-MPGN

heterozygous *C3* missense variant

by Coccia et al.

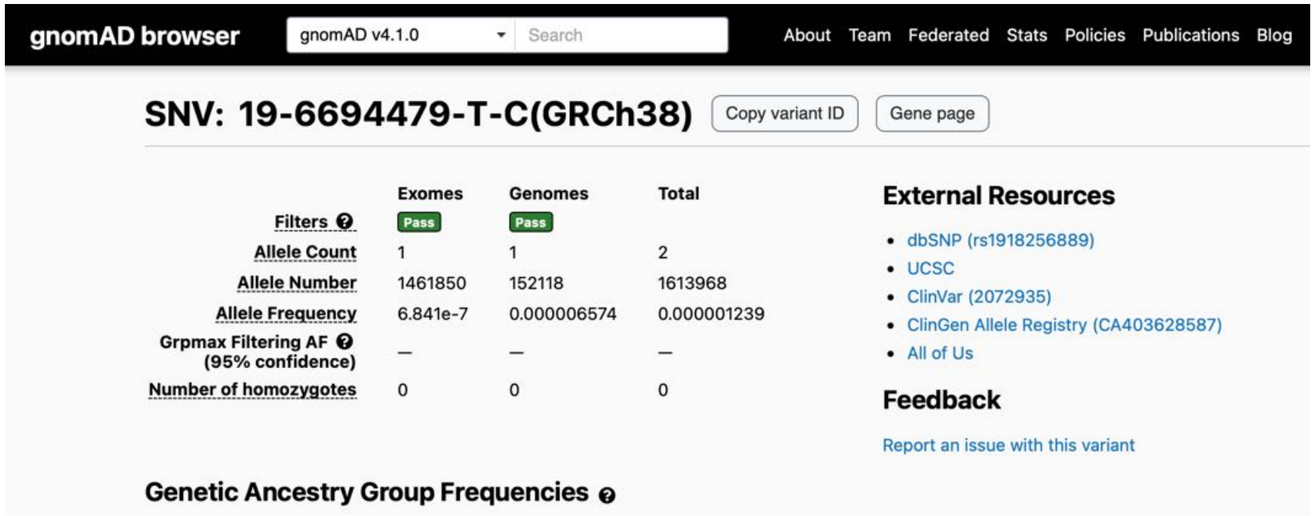
Case 3

- 2 y: SSNS, no relapses, normal complement
- 9 y: proteinuria (2 g/day) + hematuria
  - ⬇C3, normal C4, C3Nef: negative
  - ANA low-titer +ve, anti-dsDNA neg; viral serologies neg
- Kidney biopsy: MPGN pattern
  - IF: deposits in mesangium and capillary walls, IgA (2+/4), IgG, IgM, and C1q (1+/4), with dominant C3 deposition (4+/4)
  - EM: mesangial, subepithelial, subendothelial deposits; 30% FPE
- Diagnosis: primary IC-MPGN



Case 3

- Treatment: steroids 12 mo + MMF 3 y + enalapril
- Response: normalization of C3 and proteinuria at 6 months
- Current status: no proteinuria, on no treatment
- Genetics: heterozygous *C3* variant c.3106A>G; p.Lys1036Glu
  - Report: VUS



Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Admixed American	1	60000	0	0.00001667
European (non-Finnish)	1	1180000	0	8.475e-7
African/African American	0	74890	0	0.000
Ashkenazi Jewish	0	29604	0	0.000
East Asian	0	44898	0	0.000
European (Finnish)	0	64012	0	0.000
Middle Eastern	0	6082	0	0.000
Amish	0	908	0	0.000
South Asian	0	91088	0	0.000
Remaining	0	62486	0	0.000
XX	1	812440	0	0.000001231
XY	1	801528	0	0.000001248
Total	**2**	**1613968**	**0**	**0.000001239**

In Silico Predictors

- CADD: 23.5 — supports potential impact
- REVEL: 0.152 — benign
- SpliceAI: 0.00 — no effect
- Pangolin: -0.0100 — no effect
- phyloP: 6.26 — strong conservation
- PolyPhen (max): 0.481 — possibly damaging

Key point

Since C3G and aHUS are caused by a gain-of-function *C3* variant, prediction algorithms are not helpful at all

They are optimize to predict loss-of-function phenotypes!

Frequency: Rare

Prediction: not helpful!

https://gnomad.broadinstitute.org/variant/19-6694479-T-C?dataset=gnomad_r4

ClinVar Home | About | Understand the Data | Access the Data | Submit Data | Search

NM_000064.4(C3):c.3106A>G (p.Lys1036Glu) Cite Follow Print

Germline

Classification ★★★★ ?

Uncertain significance

This classification is based on the single submission received ?

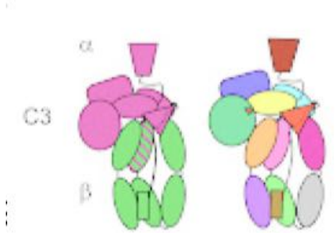
Submissions - Germline

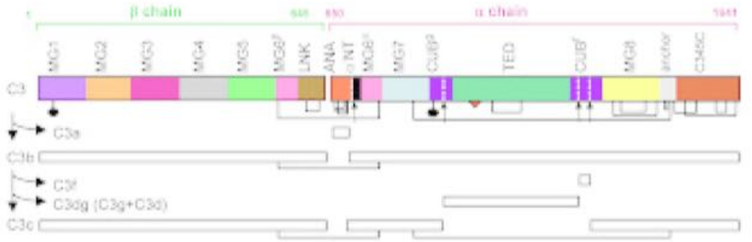
Classification (Last evaluated)	Review status (Assertion criteria)	Condition	Submitter
Uncertain significance (Sep 17, 2022) C Contributing to aggregate classification	★★★★ (Invitae Variant Classification Sherloc (09022015))	not provided	Labcorp Genetics (formerly Invitae), Labcorp Accession: SCV003285710.3 First in ClinVar: Feb 07, 2023 Last updated: Feb 25, 2025

https://www.ncbi.nlm.nih.gov/clinvar/variation/2072935/

Comment:

- Replaces lysine, which is basic and polar, with glutamic acid, which is acidic and polar
- Present in population databases (gnomAD no frequency)
- Not reported in the literature in individuals affected with C3-related conditions.
- Advanced modeling of protein sequence and biophysical properties: expected to disrupt C3 protein function
- Available evidence is insufficient to determine the role of this variant in disease
- **Classified as a VUS**





Case 4

Atypical HUS

heterozygous *CFI* missense variant

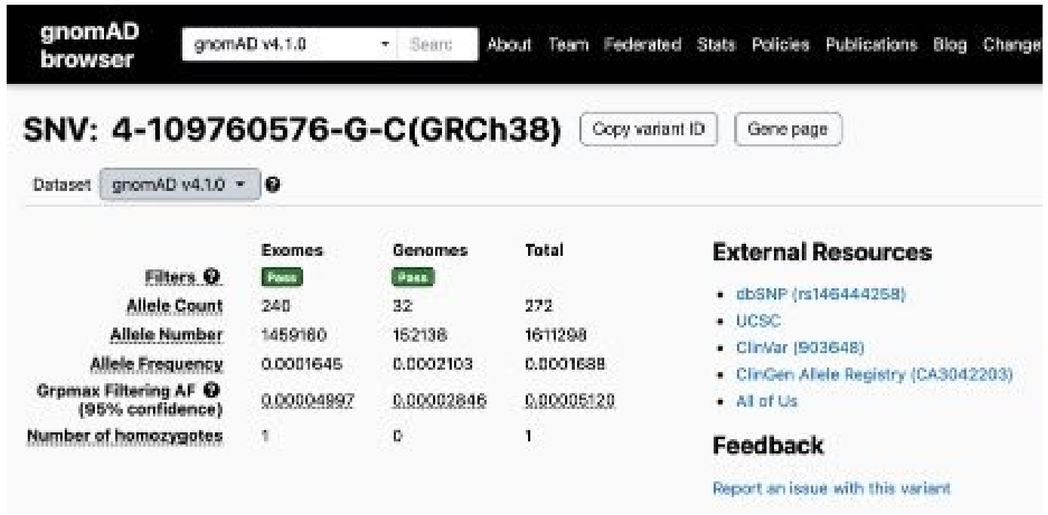
by Borovitz et al.

Case 4

- **Clinical presentation**
  - Previously healthy 17-y F with many days of malaise and extreme weakness, no diarrhea
  - Received IVF infusions x2 before labs done
- **Investigations**
  - severe anemia (Hb 6.1 g/dL)
  - thrombocytopenia (31,000/µL)
  - AKI (Cr 7.5 mg/dL; urea 150 mg/dL).
  - ADAMTS13 normal; other serologies unremarkable
  - no anti–E. coli or anti–CFH antibodies
- **Working diagnosis**
  - atypical HUS
- **Treatments**
  - blood transfusion.
  - eculizumab, later ravulizumab
- **Outcomes**
  - hematologic improvement within days
  - gradual renal recovery
  - no dialysis required.

Case 4

- **Genetics:** heterozygous *CFI* variant, c.719C>G; p.Ala240Gly
  - Rare in population databases (gnomAD)*
  - Predicted to be damaging by REVEL (0.73)*
  - ClinVar: benign, likely benign, VUS (no clinical context)
- **Carrier testing:** healthy mother is heterozygous
- **Conclusion:** VUS, leaning toward likely benign



Key point #1

The allele frequency must "make sense" vs. expected disease frequency

- Not rare at all: ~1% of Ashkenazi Jews are carriers (172/15000 subjects)

- One homozygous subject

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Ashkenazi Jewish	172	29576	1	0.005816
Remaining	26	62382	0	0.0004168
European (non-Finnish)	74	1177640	0	0.00006284
African/African American	0	74830	0	0.000
Admixed American	0	59994	0	0.000
East Asian	0	44848	0	0.000
European (Finnish)	0	64016	0	0.000
Middle Eastern	0	6082	0	0.000
Amish	0	912	0	0.000
South Asian	0	91018	0	0.000
XX	146	810918	1	0.0001800
XY	126	800380	0	0.0001574
Total	**272**	**1611298**	**1**	**0.0001688**

Key point #2

Don't be fooled by a low overall minor allele frequency

If it is too high in one ancestry group, then it is no bueno

https://gnomad.broadinstitute.org/variant/4-109760576-G-C?dataset=gnomad_r4

Framework to determine if a variant is too common for a given disease[1]

- **Main factors to take into account**
  - disease prevalence
  - genetic and allelic heterogeneity
  - inheritance mode
  - penetrance and expressivity
- Key point: Allele rarity is a necessary, but not sufficient, criterion for pathogenicity

- **For *CFI* p.Ala240Gly**
  - Estimated prevalence for all forms of aHUS is ~2-10 per million pop'n
    - Thus lower than that for *CFI*-aHUS
  - Having 1% of Ahkenazi Jews being carrier is far too high to be pathogenic

[1] Whiffin, N. et al. (2017) Genet Med.

ClinVar

NM_000204.5(CFI):c.719C>G (p.Ala240Gly) Cite Follow

Germline

Classification ★★★★

Conflicting classifications of pathogenicity
Likely pathogenic(1); Uncertain significance(2); Benign(1); Likely benign(1)
5 out of 5 submissions contributed to this classification

Conditions - Germline

Condition	Classification (# of submissions)	Review status	Last evaluated
Atypical hemolytic-uremic syndrome with I factor anomaly	Benign (1)	★★★★	Apr 27, 2017
not provided	Conflicting classifications of pathogenicity (2)	★★★★	Jul 30, 2025
Age related macular degeneration 13 Atypical hemolytic-uremic syndrome with I factor anomaly Factor I deficiency	Uncertain significance (1)	★★★★	Jun 3, 2024
CFI-related disorder	Likely pathogenic (1)	★★★★	Sep 26, 2025

Submissions - Germline

Classification (Last evaluated)	Review status (Assertion criteria)	Condition	Submitter
Benign (Apr 27, 2017) C Contributing to aggregate classification	★★★★ (ICSL Variant Classification Criteria 13 December 2019)	Atypical hemolytic-uremic syndrome with I factor anomaly	Illumina Laboratory Services, Illumina Accession: SCV001312204.1 First in ClinVar: May 31, 2020 Last updated: May 31, 2020

Comments:
- This variant was observed as part of a predisposition screen in an ostensibly healthy population.
- A literature search was performed for the gene, cDNA change, and amino acid change (where applicable).
- No publications were found based on this search.
- Allele frequency data from public databases was too high to be consistent with this variant causing disease.
- Therefore, this variant is classified as benign.

Likely pathogenic (Sep 26, 2025) C Contributing to aggregate classification	★★★★ (Genomenon Sequence Variant Interpretation Standards - Updated)	CFI-related disorder	Genomenon, Inc, Genomenon, Inc Accession: SCV006558144.1 First in ClinVar: Oct 18, 2025 Last updated: Oct 18, 2025

No data about allele frequency in 2025!

Comments:
- *CFI* p.Ala240Gly (c.719C>G) is a missense variant that changes the amino acid at residue 240 from Alanine to Glycine.
- This variant has been observed in at least one proband affected with a *CFI*-related disorder (PMID:35619721;17018561;22456601;29370420;28596415).
- At least one functional study has demonstrated a substantial alteration in protein function relative to the wild-type (PMID:37363824;19877009;32510551).
- The variant is located in a mutational hotspot.
- In silico models agree that this variant is possibly or probably damaging

Key point:

Not because the interpretation appears to come from a "professional" source that it is of good quality.

BLOOD, 15 AUGUST 2006 • VOLUME 108, NUMBER 4

Genetics of HUS: the impact of *MCP*, *CFH*, and *IF* mutations on clinical presentation, response to treatment, and outcome

Jessica Caprioli, Marina Noris, Simona Brioschi, Gaia Pianetti, Federica Castelletti, Paola Bettinaglio, Caterina Mele, Elena Bresin, Linda Cassis, Sara Gamba, Francesca Porrati, Sara Bucchioni, Giuseppe Monteferrante, Celia J. Fang, M. K. Liszewski, David Kavanagh, John P. Atkinson, and Giuseppe Remuzzi, for the International Registry of Recurrent and Familial HUS/TTP

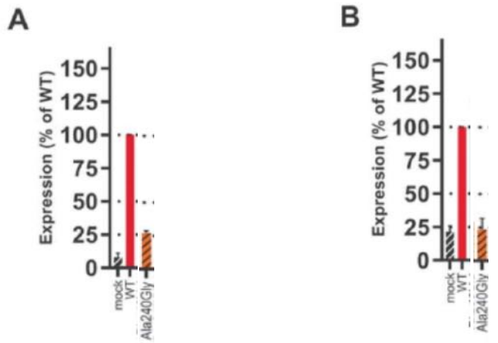
Table 4. *IF* gene mutations in non-Stx–HUS patients from our registry

Exon/intron, subject/family code	Mutation	Effect	Subgroups	Inheritance	IF serum levels, %*
Ex V					
S211 117	719C > G	A240G	Sporadic	Heterozygote	98

No discussion… assumed to be pathogenic back then

FI levels in supernatant (secreted)

FI levels in lysates (whole cell)



Conclusion: p.Ala240Gly results in reduced expression of FI in vitro

Human Molecular Genetics, 2020, Vol. 29, No. 14 2313–2324

GENERAL ARTICLE

Effect of rare coding variants in the *CFI* gene on Factor I expression levels

Sarah de Jong[1], Elena B. Volokhina[2,3,4], Anita de Breuk[1], Sara C. Nilsson[5], Eiko K. de Jong[1], Nicole C.A.J. van der Kar[2,3], Bjorn Bakker[1], Carel B. Hoyng[1], Lambert P. van den Heuvel[2,4], Anna M. Blom[5,†] and Anneke I. den Hollander[1,*]

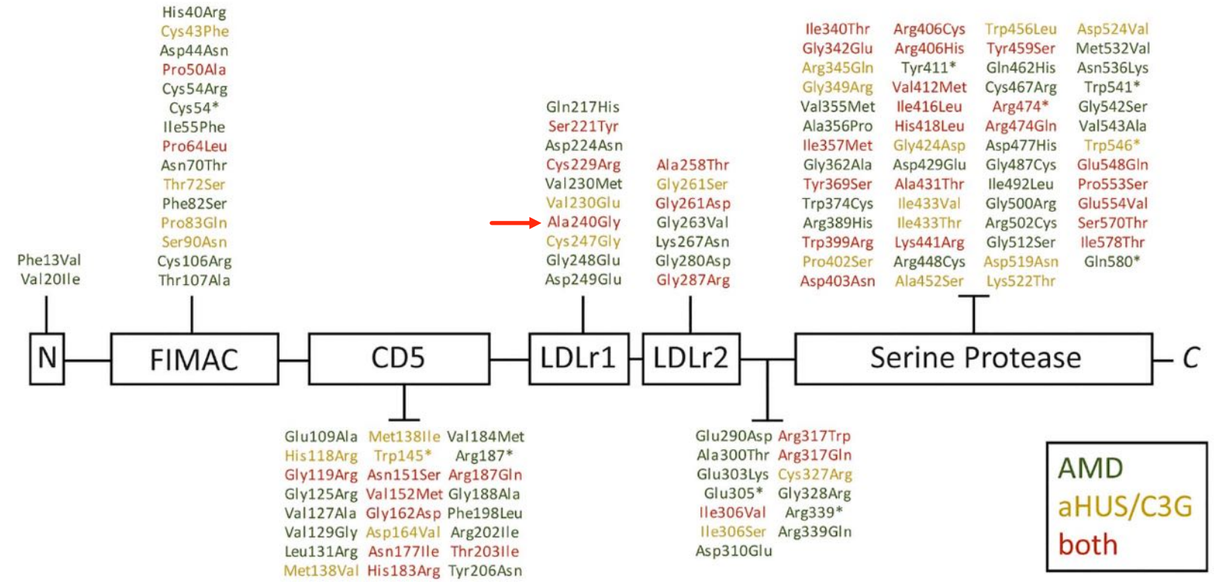


Figure 1. Distribution of rare missense or truncating variants in CFI included in this study. The listed variants were found in AMD (green), aHUS/C3G (yellow) or both in AMD and aHUS/C3G (red). Variant selection was based on (14, 16). Details of the shown variants are summarized in Supplementary Material, Table S1.

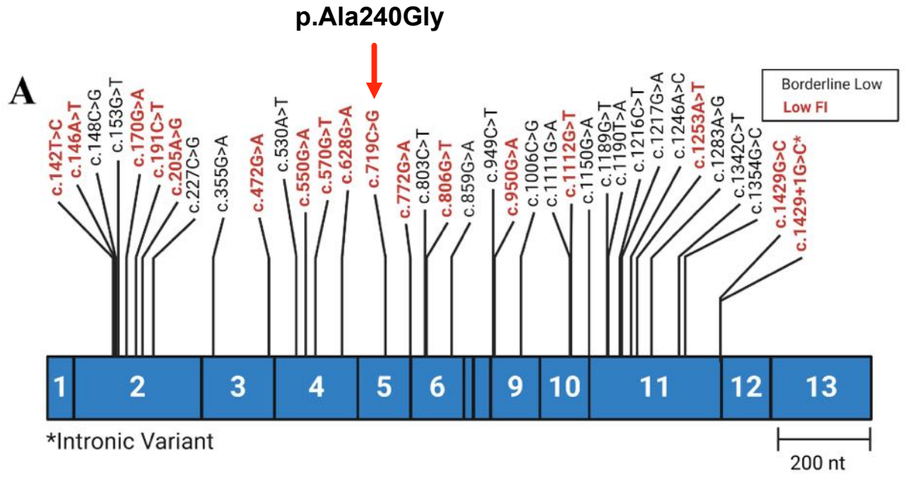
Frontiers in Immunology

TYPE Original Research
PUBLISHED 22 August 2024
DOI 10.3389/fimmu.2024.1446081

Functional evaluation of rare variants in complement factor I using a minigene assay

Cobey J. H. Donelson, Nicolo Ghiringhelli Borsa, Amanda O. Taylor, Richard J. H. Smith* and Yuzhou Zhang*

The regulatory serine protease, complement factor I (FI), in conjunction with one of its cofactors (FH, C4BP, MCP, or CR1), plays an essential role in controlling complement activity through inactivation of C3b and C4b. The functional impact by missense variants in the *CFI* gene, particularly those with minor allele frequencies of 0.01% to 0.1%, is infrequently studied. As such, these variants are typically classified as variants of uncertain significance (VUS) when they are identified by clinical testing. Herein, we utilized a minigene splicing assay to assess the functional impact of 36 ultra-rare variants of *CFI*. These variants were selected based on their minor allele frequencies (MAF) and their association with low-normal FI levels. Four variants lead to aberrant splicing–one 5′ consensus



Reference range for CFI: 18-44 mg/L
Definition of "low CFI" <25 mg/L
So p.Ala240Gly is "low-normal"

TABLE 2 Variant in-silico prediction and FI expression.

Variant	Protein	MAF±	Number of Pts in Cohort	Average FI expression (mg/L)	SpliceAI*	Human Splice Finder	Observed Effect
c.719C>A	p.Ala240Gly	0.02%	7	20.7	(-0.07)	ESE/ESS (-11)	No Effect

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Ashkenazi Jewish	172	29576	1	0.005816
Total	**272**	**1611298**	**1**	**0.0001688**

0.5% is far from being ultra-rare

Case 4

- Based on very high MAF data, it is most likely a benign *CFI* variant
- Functional data is not very convincing
- **Key point: beautiful experimental data never trumps weak genetics**

Case 5

Atypical HUS

heterozygous *CFH* missense variant (hotspot)

Bergamo

Case 5

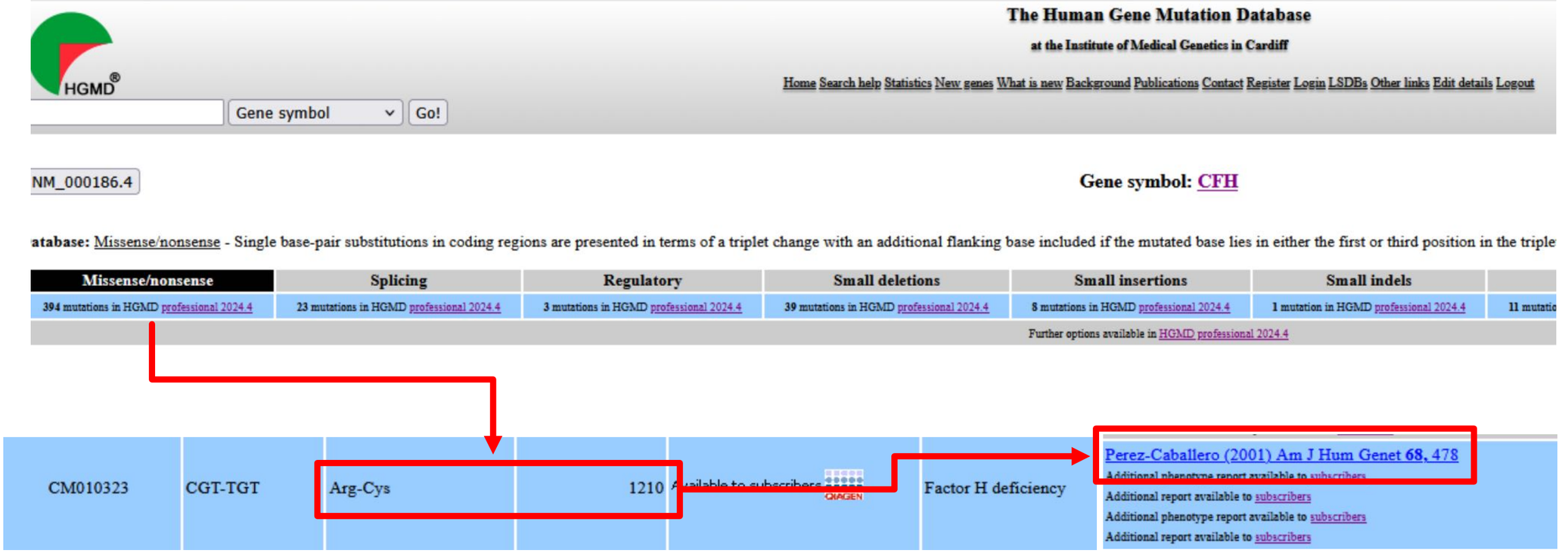
- 65-y patient hospitalized for:
  - Acute kidney injury (creatinine 3.5 mg/dL)
  - Low platelets 89,000
  - LDH 3631 U/L, haptoglobin <30, schistocvtes 1.4%
  - Hyperbilirubinemia
- Other data:
  - C3/C4 95/22 mg/dL
  - Blood pressure 172/115 mmHg

Case 5

- Treatments:
  - HD
  - Antihypertensive treatment
  - Eculizumab
- Genetics: heterozygous p.R1210C variant in *CFH*

Free online resources to help you

- **HMGD (The Human Gene Mutation Database)**
- gnomAD (Genome Aggregation Database)
- ClinVar (public archive of interpretations of genetic variants)
- OMIM (Online Catalog of Human Genes and Genetic Disorders)


HGMD®
The Human Gene Mutation Database
at the Institute of Medical Genetics in Cardiff
Home Search help Statistics New genes What is new Background Publications Contact Register Login LSDBs Other links Edit details Logout
Gene symbol
Go!
NM_000186.4
Gene symbol: CFH
atabase: Missense/nonsense - Single base-pair substitutions in coding regions are presented in terms of a triplet change with an additional flanking base included if the mutated base lies in either the first or third position in the triple
Missense/nonsense
Splicing
Regulatory
Small deletions
Small insertions
Small indels
394 mutations in HGMD professional 2024.4
23 mutations in HGMD professional 2024.4
3 mutations in HGMD professional 2024.4
39 mutations in HGMD professional 2024.4
8 mutations in HGMD professional 2024.4
1 mutation in HGMD professional 2024.4
Further options available in HGMD professional 2024.4
CM010323
CGT-TGT
Arg-Cys
1210
Factor H deficiency
Perez-Caballero (2001) Am J Hum Genet 68, 478
Additional report available to subscribers
Additional phenotype report available to subscribers
Additional report available to subscribers

Free online resources to help you

- HMGD (The Human Gene Mutation Database)
- **gnomAD (Genome Aggregation Database)**
- ClinVar (public archive of interpretations of genetic variants)
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SNV: 1-196747245-C-T(GRCh38)

Copy variant ID | Gene page | Dataset: gnomAD v4.1.0

	Exomes	Genomes	Total
Filters	Pass	Pass	Discrepant frequencies
Allele Count	194	27	221
Allele Number	1461694	152178	1613872
Allele Frequency	0.0001327	0.0001774	0.0001369
Grpmax Filtering AF (95% confidence)	0.0001388	0.0002428	0.0001502
Number of homozygotes	0	0	0

External Resources

- dbSNP (rs121913059)
- UCSC
- ClinVar (16558)
- ClinGen Allele Registry (CA128563)
- All of Us

Feedback

Report an issue with this variant

Genetic Ancestry Group Frequencies

gnomAD | HGDP | 1KG | Local Ancestry

Genetic Ancestry Group	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (non-Finnish)	200	1179908	0	0.0001695
Remaining	10	62472	0	0.0001601
Admixed American	6	59998	0	0.0001000
African/African American	3	74916	0	0.00004004
European (Finnish)	1	64028	0	0.00001562
South Asian	1	91080	0	0.00001098
Ashkenazi Jewish	0	29598	0	0.000
East Asian	0	44880	0	0.000
Middle Eastern	0	6080	0	0.000
Amish	0	912	0	0.000
XX	106	812366	0	0.0001305
XY	115	801506	0	0.0001435
Total	**221**	**1613872**	**0**	**0.0001369**

missense

1. CFH
   1. ENST00000367429.9
      MANE Select transcript for CFH
      HGVSp: p.Arg1210Cys
      HGVSc: c.3628C>T
      Domains: PF00084 (Pfam), and 23 more

non coding transcript exon

1. CFH
   1. ENST00000466229.5
      HGVSc: n.6726C>T

In Silico Predictors

CADD: 0.181	**Benign**
REVEL: 0.280	**Benign**
SpliceAI: 0.00	No effect
Pangolin: 0.0300	No effect
phyloP: -4.47	Low conservation
PolyPhen (max): 0.280	**Likely Benign**

Note The SpliceAI and Pangolin predictions displayed here were precomputed by Illumina and Invitae. For more detailed and up to date SpliceAI and Pangolin predictions, please visit our SpliceAI Lookup browser.

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NM_000186.4(CFH):c.3628C>T (p.Arg1210Cys) Cite Follow Print Download

Germline

Classification

Conflicting classifications of pathogenicity
Pathogenic(6); Uncertain significance(3)
9 out of 14 submissions contributed to this classification

Conditions - Germline

Condition	Classification (# of submissions)	Review status	Last evaluated	Variation/condition record
Factor H deficiency	Pathogenic (1)	★★★★	Jul 1, 2015	RCV000018025.29
Hemolytic uremic syndrome, atypical, susceptibility to, 1	risk factor (2)	★★★★	Jul 1, 2015	RCV000018026.16
Age related macular degeneration 4	Pathogenic (2)	★★★★	Aug 9, 2018	RCV000022540.12
CFH-Related Dense Deposit Disease / Membranoproliferative Glomerulonephritis Type II	Uncertain significance (1)	★★★★	Jun 16, 2017	RCV001099303.4
Basal laminar drusen	Uncertain significance (1)	★★★★	Jun 16, 2017	RCV001099304.4

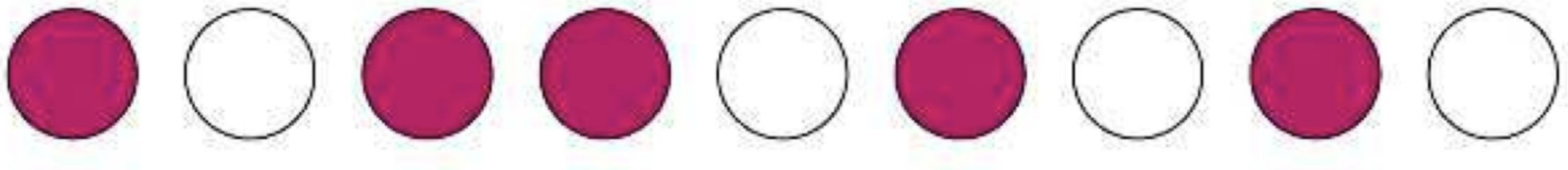
extremely heterogeneous phenotype

More about *CFH* p.R1210C

- Unusual variant ➡ generates covalent complexes between FH and human serum albumin
  - Formation of FH-HSA complexes impairs accessibility to all FH functional domains
  - These data suggest that p.R1210C is a unique C-terminal *CFH* variant that behaves as a partial FH deficiency, predisposing individuals to *diverse pathologies*

More about *CFH* p.R1210C

- We identified
  - 25 p.R1210C carriers in a aHUS cohort (n=1030)
  - 2 in the C3G cohort (n=187)
  - 5 in the AMD cohort (n=259)
  - none in a control group (n=330)
- Both affected and healthy individuals among p.R1210 carriers
  - illustrates **incomplete penetrance** for the 3 diseases



Variable penetrance

Variable expressivity

In the Recalde's paper all aHUS patients with the p.R1210C, they all carried at least one additional genetic risk factor (variant or risk haplotypes)

Case 5: heterozygous *CFH* H3 risk haplotype homozygous $CD46_{ggaac}$ risk haplotype

Conclusions for p.R1210C: pathogenic

- **Evidence Against Pathogenicity**
  - The variant is not ultrarare (max MAF: 1.7×10^{-4}).
  - In silico predictions classify it as likely benign
- **Evidence Supporting Pathogenicity**
  - Occurs at a known mutational hotspot
  - Previously reported as pathogenic by multiple independent sources
  - Higher prevalence in affected individuals compared with controls
  - Functional studies demonstrate deleterious effects on protein activity
- **Additional Considerations**
  - The variant is associated with variable phenotypes and incomplete penetrance
  - Clinical expression and penetrance appear to depend on the presence of additional genetic or environmental risk factors

Thank you!

Any questions?