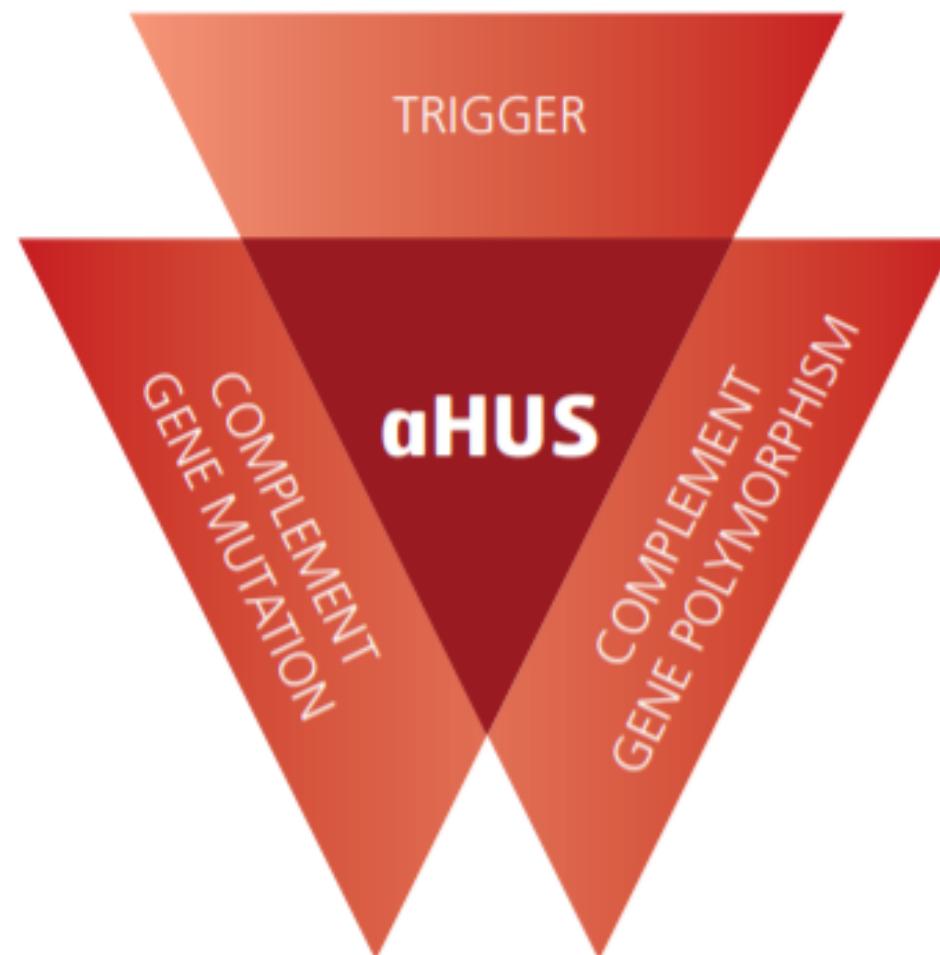


THE P38 SIGNALING PATHWAY AND ITS RELATIONSHIP WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME (AHUS)



Sarah Jimenez Rojas, Santiago Reinoso, Juanita Prada Mora, Silvana Gonzalez

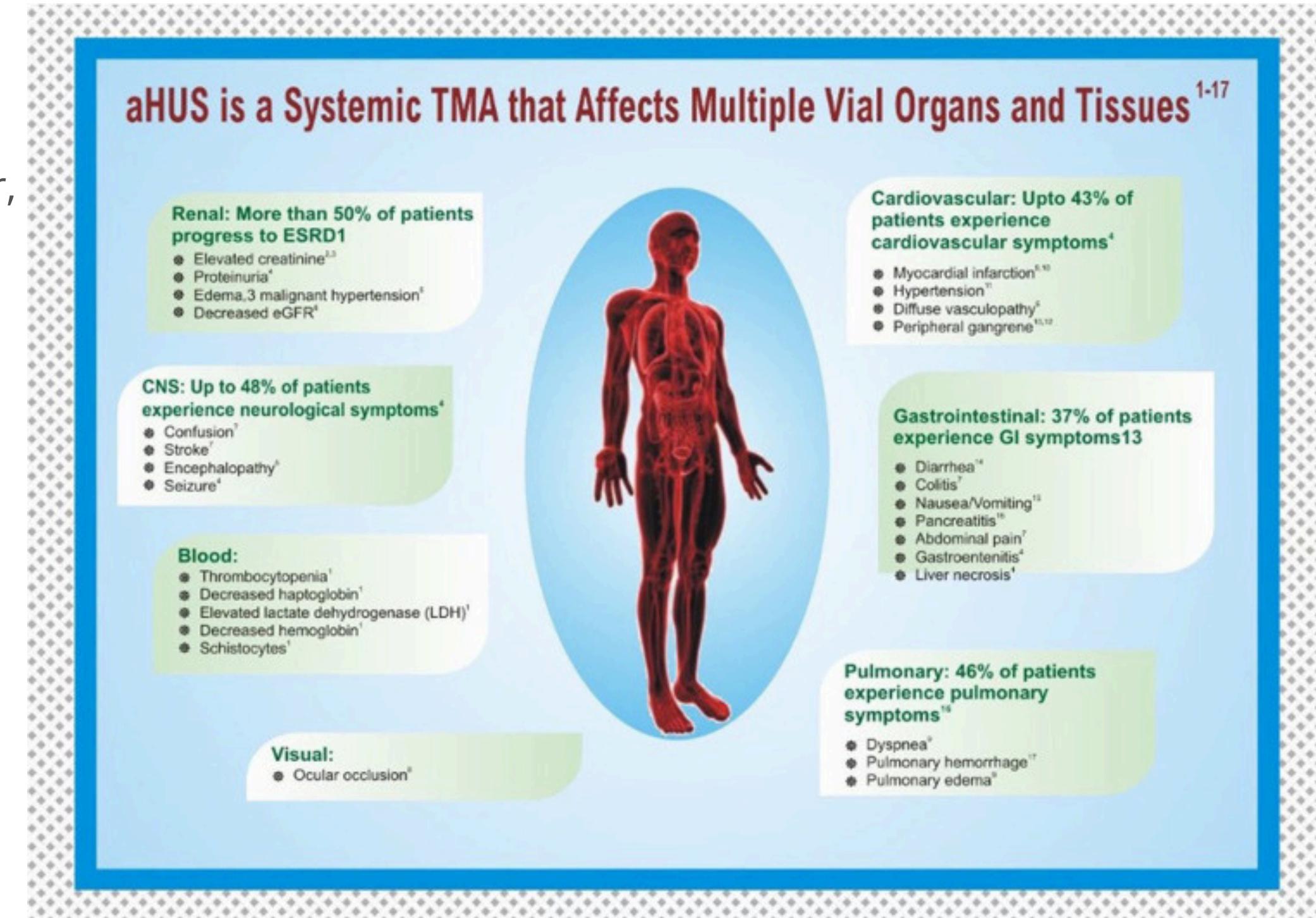
INDEX

-
- 01.** Description of the syndrome:
(ORPHA: 2134)
-
- 02.** Genes involved in the
syndrome
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- 03.** Complement system
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and its relation with the
complement system
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Justification, Experimental Design
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- 08.** Symptoms and treatment
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ATYPICAL HEMOLYTIC UREMIC SYNDROME (AHUS)

It has a global prevalence of 1-3 patients per million people. However, incidence in Europe increases to 30-90 patients per million people (Orphanet, 2021; Noris et al, 2021)

aHUS is disease with genetic heterogeneity, showing both autosomal dominant ($P<$) and autosomal recessive ($P>$). It has also been reported to have polygenic inheritance (Noris et al., 2021).



Adapted from Yerigeri et al. (2017).

GENES INVOLVED

C3, CD46 (MCP), CFB, CFH, CFHR1, CFHR3, CFHR4, CFHR5, CFI, DGKE, THBD, VTN (Noris et al, 2021).

[J Multidiscip Healthc.](#) 2023; 16: 2233–2249.

Published online 2023 Aug 4. doi: [10.2147/JMDH.S245620](https://doi.org/10.2147/JMDH.S245620)

PMCID: PMC10408684

PMID: [37560408](#)

Atypical Hemolytic-Uremic Syndrome: Genetic Basis, Clinical Manifestations, and a Multidisciplinary Approach to Management

Keval Yerigeri,¹ Saurav Kadatane,² Kai Mongan,³ Olivia Boyer,⁴ Linda L G Burke,⁵ Sidharth Kumar Sethi,⁶

| Genetic Testing in aHUS May Inform Long-term Patient Outcomes | | | |
|---|---|--|--|
| Genetic Abnormality | Frequency in Patients with aHUS ^{1-5,8-12} | ESRD or Death within 3 to 10 Years of Diagnosis, % of Patients ^{1,2,5,8,9,13} | Subsequent Disease Manifestation Post Transplant, @ of Kidney Grafts ^{1-3,5,8,14} |
| CFH mutations | 20%-52% | 66%-80% | 64%-90% |
| CFH autoantibodies and/or CFHR1-3 deletions | 5%-10% | 30%-63% | 20%-29% |
| CFI mutations | 4%-10% | 50%-72% | 45%-80% |
| THBD mutations | 3%-10% | 54%-60% | 100% (1/1)* |
| C3 mutations | 2%-10% | 56%-67% | 40%-70% |
| CFB mutations | 1%-4% | 70% | 100% (3/3)* |
| Isolated heterozygous MCP mutations ⁵ | 6%-15% | 6%-38%* | 0%-20% |
| DGKE mutations | -27% of patients diagnosed at≤1 year of age | 46% (6/13)* | 0% (0/3)* |
| CFH-H3 : 31% MCPggaa0 : 44% | | | |
| No identified mutation | 30%-50% | 32%-50% | 59% (17/29)* |

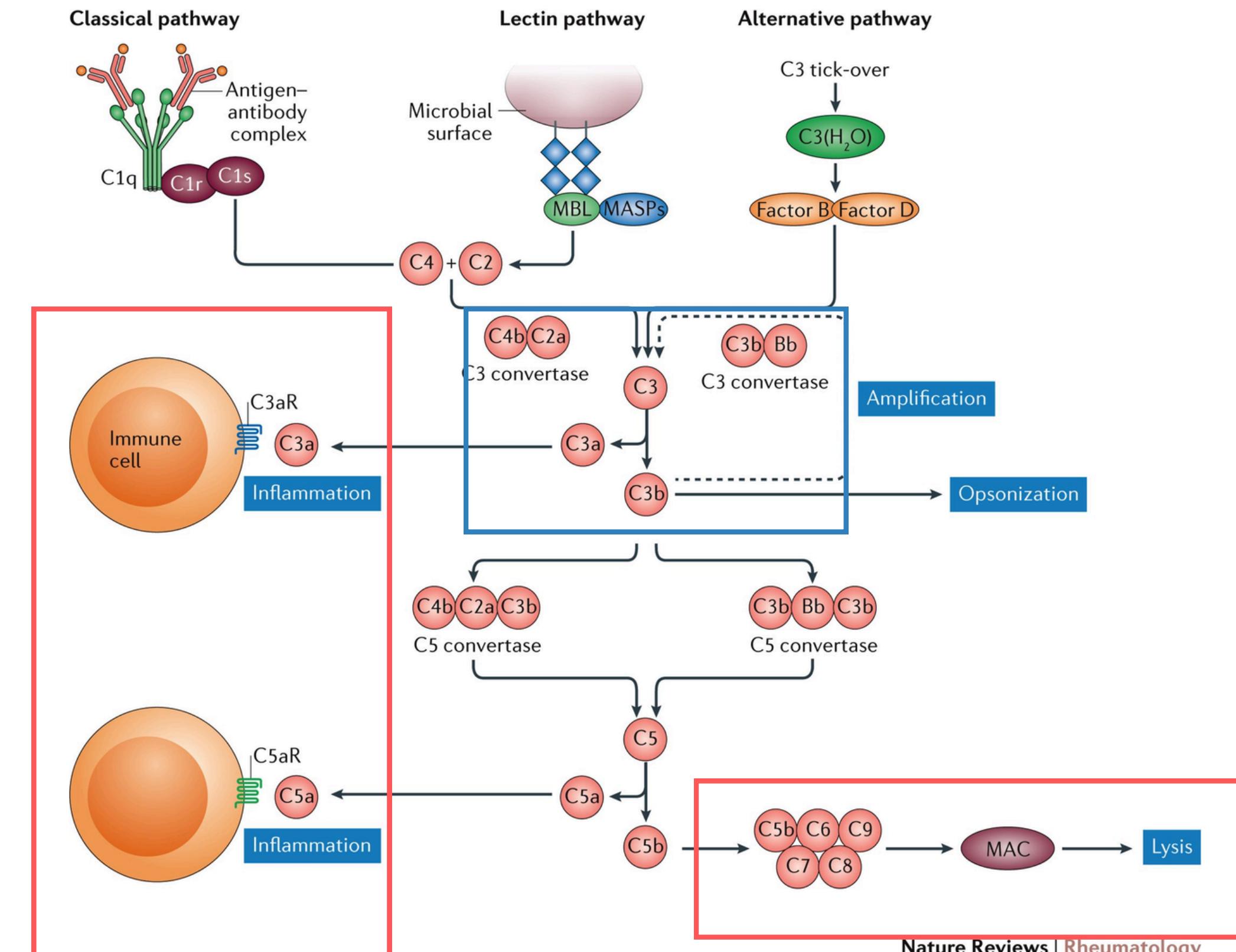
Foontes: *Plasminogen (PLG) mutations have not been included in this table because the outcomes of patients with aHUS and PLG mutations have not been reported**; **The ranges are based on kidney grafts that were affected by TMA manifestations. Some patients received multiple grafts. **, (n/N) of patients from one study. *The majority of patients with aHUS and MCP mutations studied in large cohorts had isolated heterozygous mutations. In one study, the rate of ESRD or death at 5 years of patients with aHUS and MCP mutations varied between adults and children: 63% (5/8) of patients >16 years of age compared with 17% (2/12) of patients <16 years of age, X² test P=0.03% (n/N) of patients from one study. 1% (n/N) of kidney grafts that failed by 1 year post transplant.

References 1. Noris M, Chin J Am Soc Nephrol 2010, 5 1844-1859. 2. Noris M, N Engl J Med 2009, 361 1676-1687. 3. da Cordoba S. Semin Thromb Hemost 2014, 40:422-430

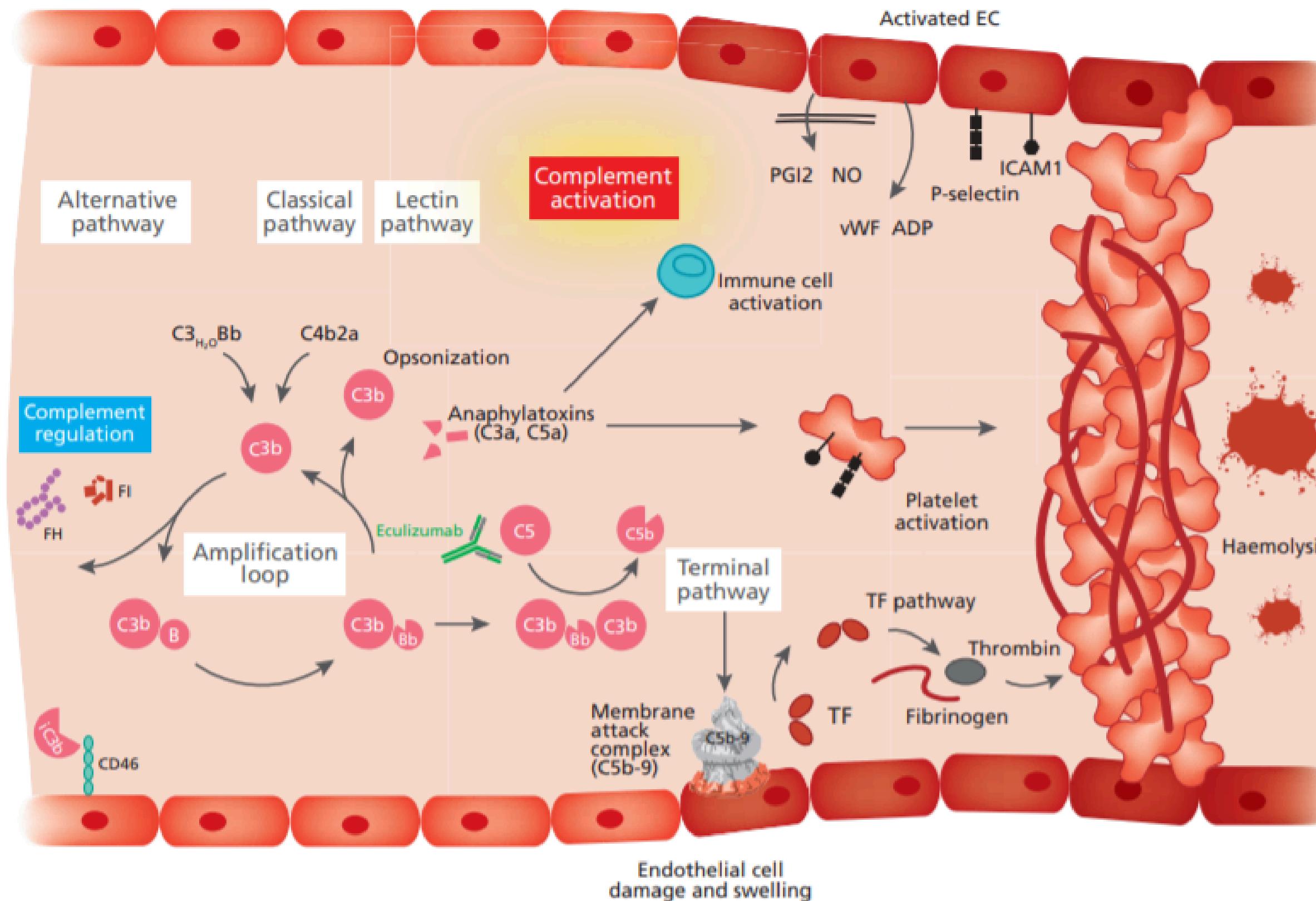
CFH, CFI, THBD, C3, CFB, MCP, DGKE

COMPLEMENT SYSTEM

Key genes with mutation in aHUS patients (related to symptoms)



COMPLEMENT SYSTEM IN AHUS



Adapted from Hui (2012)

1



RESEARCH REPORT

Whole-exome sequencing of a patient with severe and complex hemostatic abnormalities reveals a possible contributing frameshift mutation in C3AR1

Eva Leinøe,¹ Ove Juul Nielsen,¹ Lars Jønson,² and Maria Rossing²

¹Department of Hematology, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark;

²Center for Genomic Medicine, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark

C3A1 is a receptor for complement factor C3a

2

Stem Cell Reports

Article



OPEN ACCESS

Patient-specific iPSC-derived endothelial cells reveal aberrant p38 MAPK signaling in atypical hemolytic uremic syndrome

Danni Zhou,^{1,4,5,15} Ying Tan,^{2,6,7,8,15} Xiaoling Liu,^{2,6,7,8} Ling Tang,^{1,4,5} Hao Wang,^{11,12} Jiaxi Shen,^{1,4,5} Wei Wang,¹³ Lenan Zhuang,¹⁴ Juan Tao,^{2,6,7,8} Jun Su,^{1,4,5} Tingyu Gong,¹ Xiaorong Liu,^{3,*} Ping Liang,^{1,4,5,*} Feng Yu,^{2,6,7,8,9,*} and Minghui Zhao^{2,6,7,8,10}

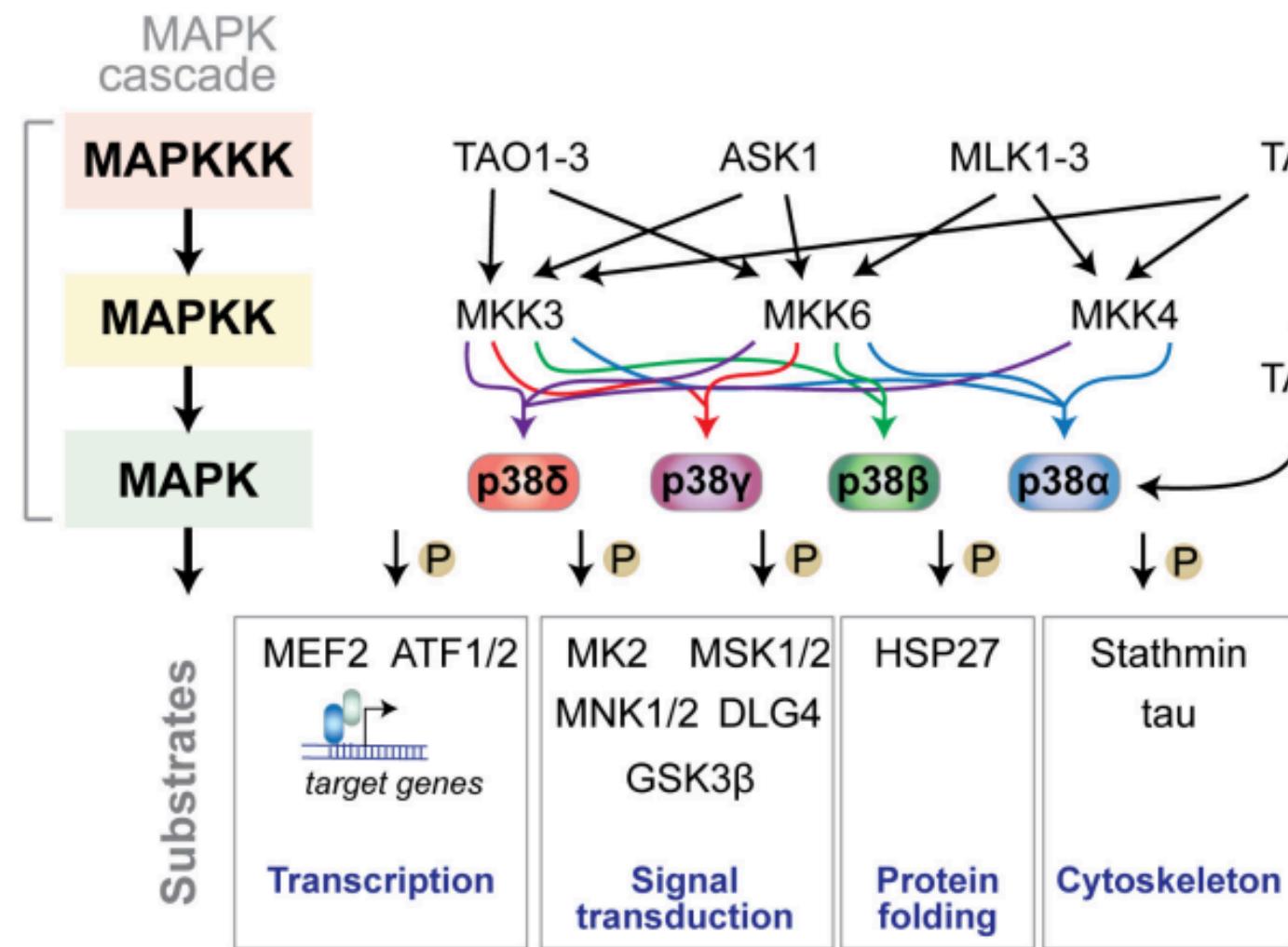
A significant decrease in p38 signaling was observed



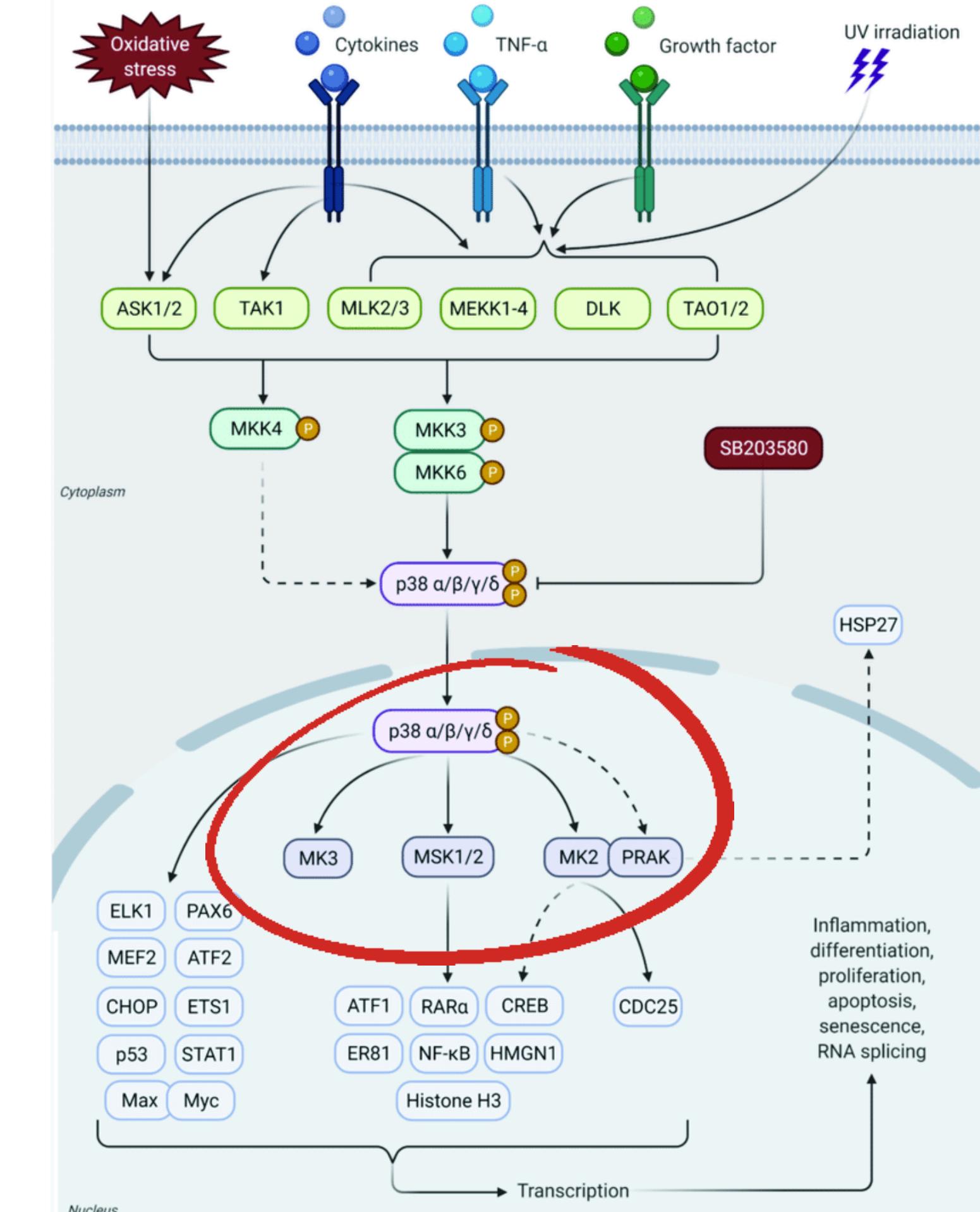
SIGNALING PATHWAY P38/MAPK

Four isoforms of protein kinase p38:

- p38 α (*MAPK14*)
- p38 β (*MAPK11*)
- p38 γ (*MAPK12*)
- p38 δ (*MAPK13*)



Adapted from Asih et al., 2020



Taken from Pua et al., 2022

COMPLEMENT SYSTEM AND P38

Relationship with p38

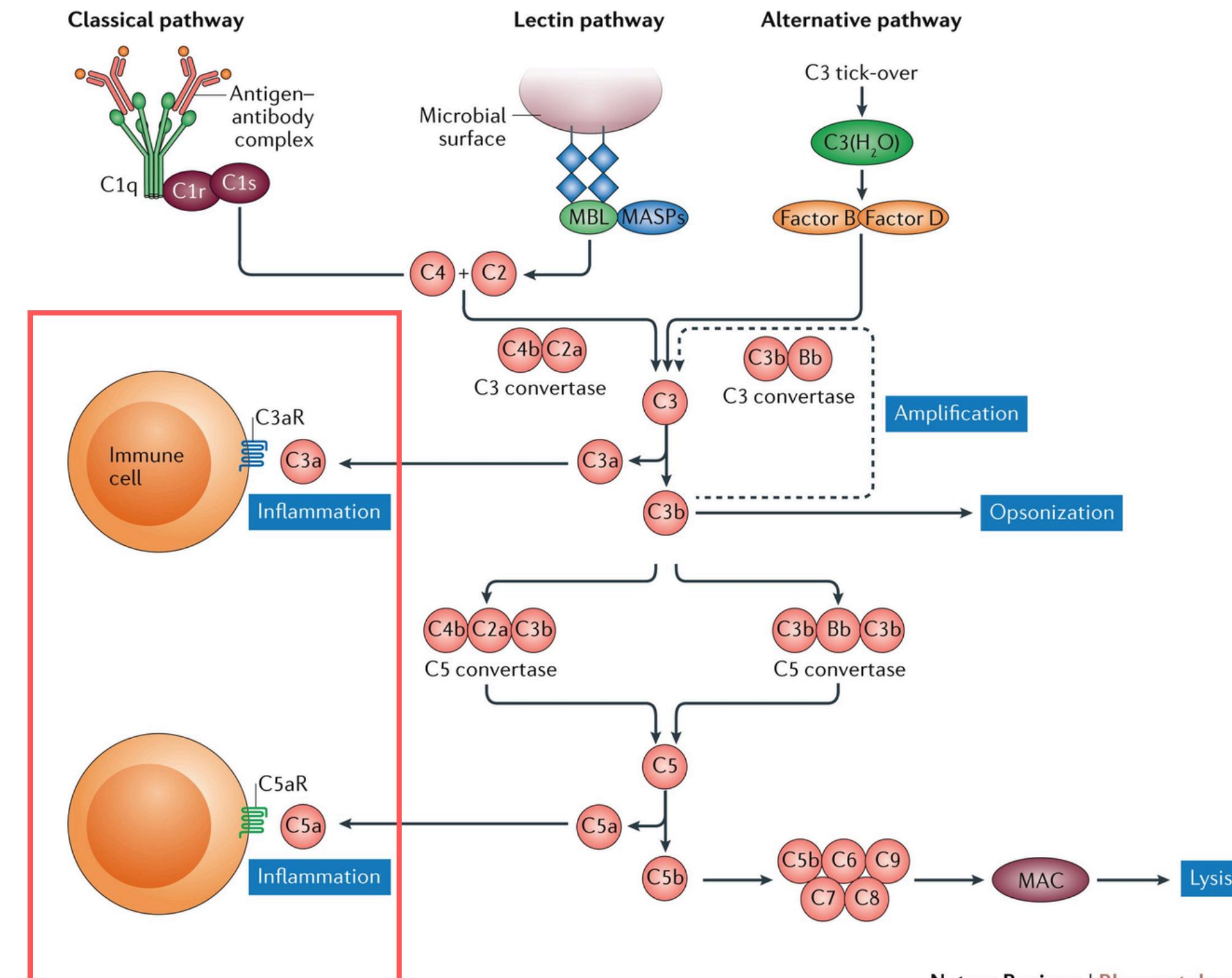
1. p38 MAPK
(MKK6=MAPK14)

regulates C3
expression

(Lei et al., 2016)

2. C5a is activated through
p38 macrophages

(Maranto et al., 2011)



RESEARCH QUESTION

What is the relationship between p38 signaling pathway and the symptomatology and severity of aHUS?

=

**P38 signaling + Symptomatology cause by
pathway the complement systems ?**

=

New perspectives to the genetics of aHUS

OBJECTIVES

**Understand the Role of p38
MAPK Pathway**

**Analyze Variant Effects on
Protein Function**

**Evaluate Protein Interactions
and Pathway Networks**

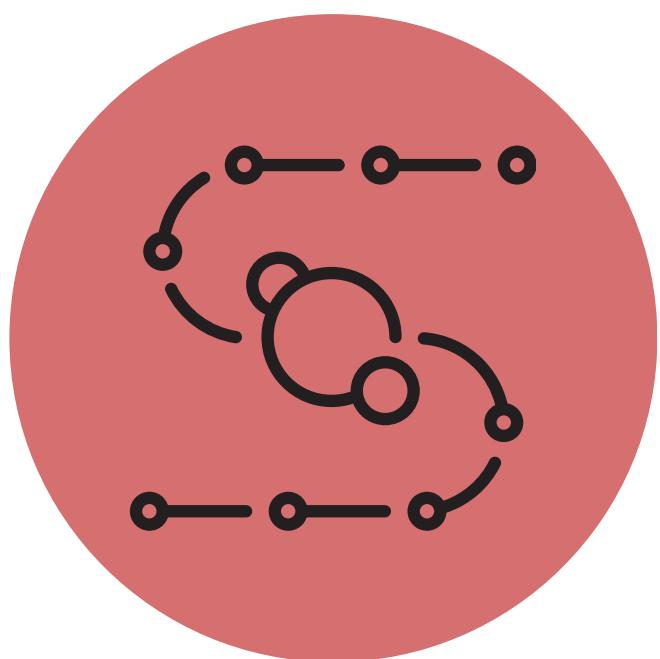
**Recognize Therapeutic
Targets**

JUSTIFICATION

Exploring aHUS through bioinformatics provides us with key insights for advancements in understanding and managing the aHUS:



Genetic Basis



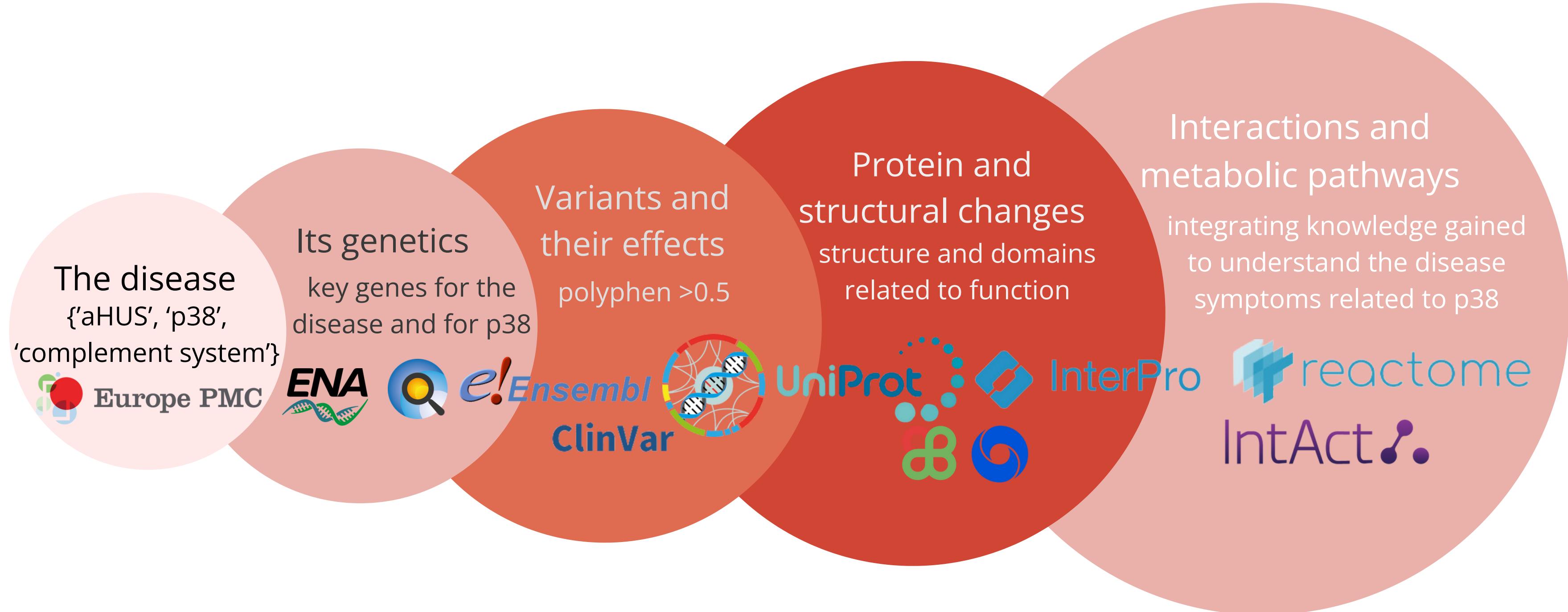
Pathway Information



Bioinformatics

EXPERIMENTAL DESIGN

Each circle represent an inclusive step



VARIANTS OF MAPKS

- MAPK14

| Chr | Position | Variant ID | Alleles | Class | Most Severe Consequence Type | Most Severe Protein Substitution Score | | |
|-----|----------|------------|---------|-------|------------------------------|--|------|--|
| | | | | | | PolyPhen2 | Sift | |
| 6 | 36024540 | - | G/C | SNV | missense_variant | 0.737 | 0 | |
| 6 | 36024541 | - | A/T | SNV | missense_variant | 0.631 | 0.01 | |
| 6 | 36024753 | - | C/A | SNV | missense_variant | 0.98 | 0 | |
| 6 | 36052721 | - | G/A | SNV | missense_variant | 0.662 | 0.18 | |
| 6 | 36052776 | - | C/T | SNV | missense_variant | 1 | 0 | |
| 6 | 36075831 | - | C/A | SNV | missense_variant | 0.837 | 0.01 | |

- MAPK12

| Chr | Position | Variant ID | Alleles | Class | Most Severe Consequence Type | Most Severe Protein Substitution Score | | |
|-----|----------|------------|---------|-------|------------------------------|--|------|--|
| | | | | | | PolyPhen2 | Sift | |
| 22 | 50243732 | - | C/A | SNV | missense_variant | 0.872 | 0 | |
| 22 | 50243760 | - | G/A | SNV | missense_variant | 0.998 | 0.03 | |
| 22 | 50243786 | - | T/C | SNV | missense_variant | 0.999 | 0 | |
| 22 | 50243805 | - | C/A | SNV | missense_variant | 0.981 | 0.02 | |
| 22 | 50243871 | - | A/G | SNV | missense_variant | 0.994 | 0.01 | |
| 22 | 50243897 | - | G/C | SNV | missense_variant | 0.53 | 0.09 | |
| 22 | 50243909 | - | G/A | SNV | missense_variant | 0.968 | 0 | |
| 22 | 50243922 | - | G/T | SNV | missense_variant | 0.692 | 0.13 | |
| 22 | 50244017 | - | T/C | SNV | missense_variant | 1 | 0 | |
| 22 | 50244041 | - | C/T | SNV | missense_variant | 0.999 | 0.05 | |

- MAPK11

| Chr | Position | Variant ID | Alleles | Class | Most Severe Consequence Type | Most Severe Protein Substitution Score | | |
|-----|----------|------------|---------|-------|------------------------------|--|------|--|
| | | | | | | PolyPhen2 | Sift | |
| 22 | 50261178 | - | G/A | SNV | missense_variant | 0.941 | 0.02 | |
| 22 | 50261196 | - | G/A | SNV | missense_variant | 0.999 | 0.01 | |
| 22 | 50261216 | - | T/A | SNV | missense_variant | 1 | 0 | |
| 22 | 50261229 | - | C/G | SNV | missense_variant | 0.997 | 0.51 | |
| 22 | 50261240 | - | G/A | SNV | missense_variant | 1 | 0 | |
| 22 | 50261244 | - | G/A | SNV | missense_variant | 1 | 0 | |
| 22 | 50261284 | - | G/T | SNV | missense_variant | 0.922 | 0 | |
| 22 | 50261385 | - | C/T | SNV | missense_variant | 0.982 | 0 | |
| 22 | 50265420 | - | C/T | SNV | missense_variant | 0.701 | 0.01 | |
| 22 | 50265597 | - | C/T | SNV | missense_variant | 0.968 | 0.23 | |

- MAPK13

| Chr | Position | Variant ID | Alleles | Class | Most Severe Consequence Type | Most Severe Protein Substitution Score | | |
|-----|----------|------------|---------|-------|------------------------------|--|------|--|
| | | | | | | PolyPhen2 | Sift | |
| 6 | 36130701 | - | G/A | SNV | missense_variant | 0.981 | 0 | |
| 6 | 36131273 | - | C/T | SNV | missense_variant | 0.906 | 0 | |
| 6 | 36131296 | - | G/A | SNV | missense_variant | 0.557 | 0.2 | |
| 6 | 36136040 | - | G/A | SNV | missense_variant | 0.954 | 0 | |
| 6 | 36136726 | - | G/A | SNV | missense_variant | 0.999 | 0 | |
| 6 | 36136905 | - | A/G | SNV | missense_variant | 0.99 | 0 | |
| 6 | 36138930 | - | C/T | SNV | missense_variant | 1 | 0 | |
| 6 | 36138971 | - | C/T | SNV | missense_variant | 0.92 | 0.01 | |



PATTERN: MAPK ISOFORMS MUTATION

| | | | |
|----------------|-------|---|--|
| ► Binding site | 30-38 | } | Common binding and actives sites for these proteins |
| ► Binding site | 53 | | |
| ► Active site | 168 | | |

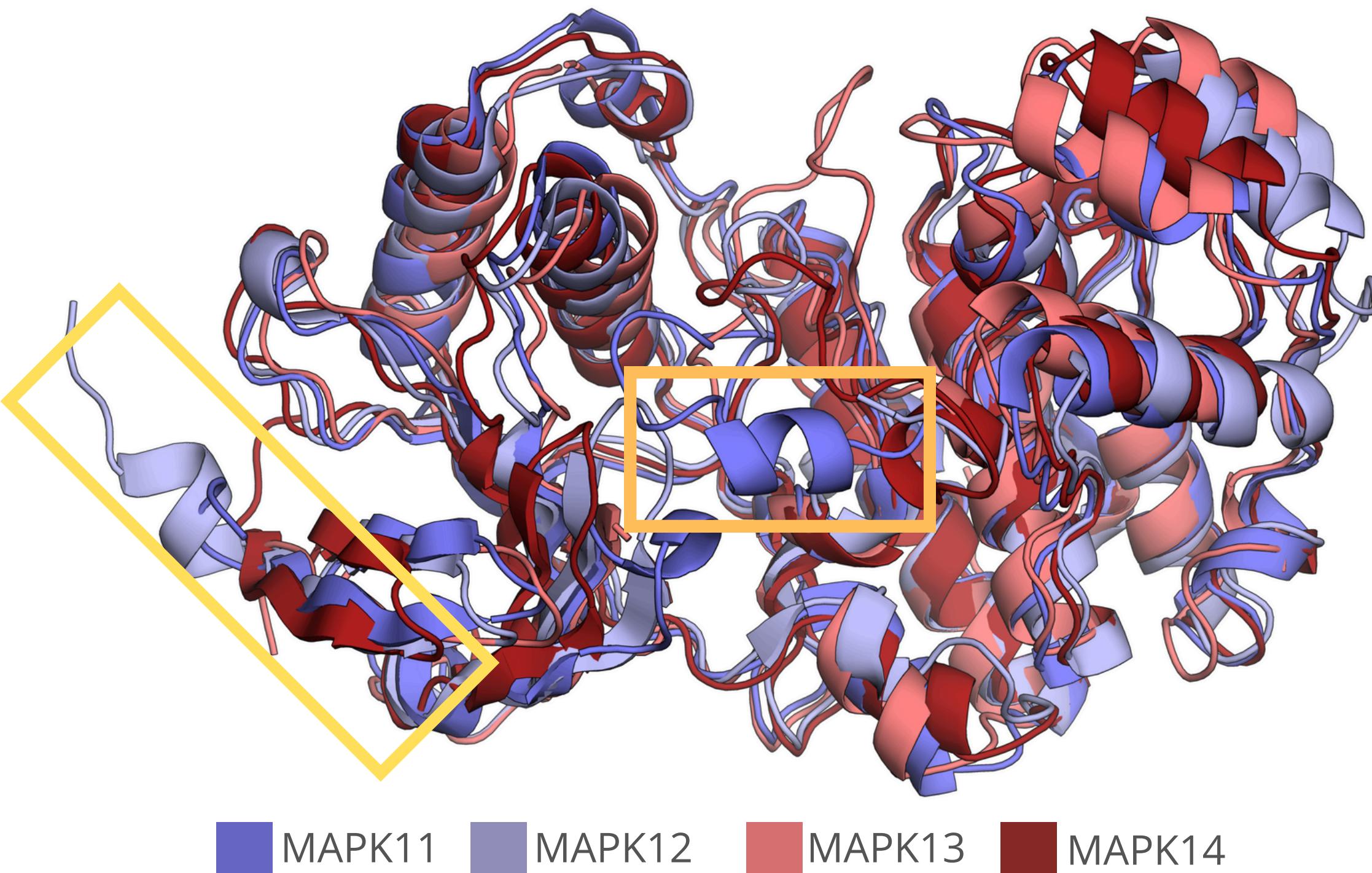
Common variants:

- aa180-182: Lowered Kinase activity and/or inactivation
- aa185: Loss of function

MAPK14 reported variants

- aa53-177: Loss of Kinase activity
- aa54 (polyphen = 0.737): Impairs autophosphorilation

STRUCTURAL SIMILARITIES BETWEEN MAPKS



Minimal differences
in the **TXY motif** and
N-terminus

D Prot_kinase_dom - IPR000719
SMART: S_TKc - SM00220
PROFILE: PROTEIN_KINASE_DOM - PS5001
PFAM: Pkinase - PF00069

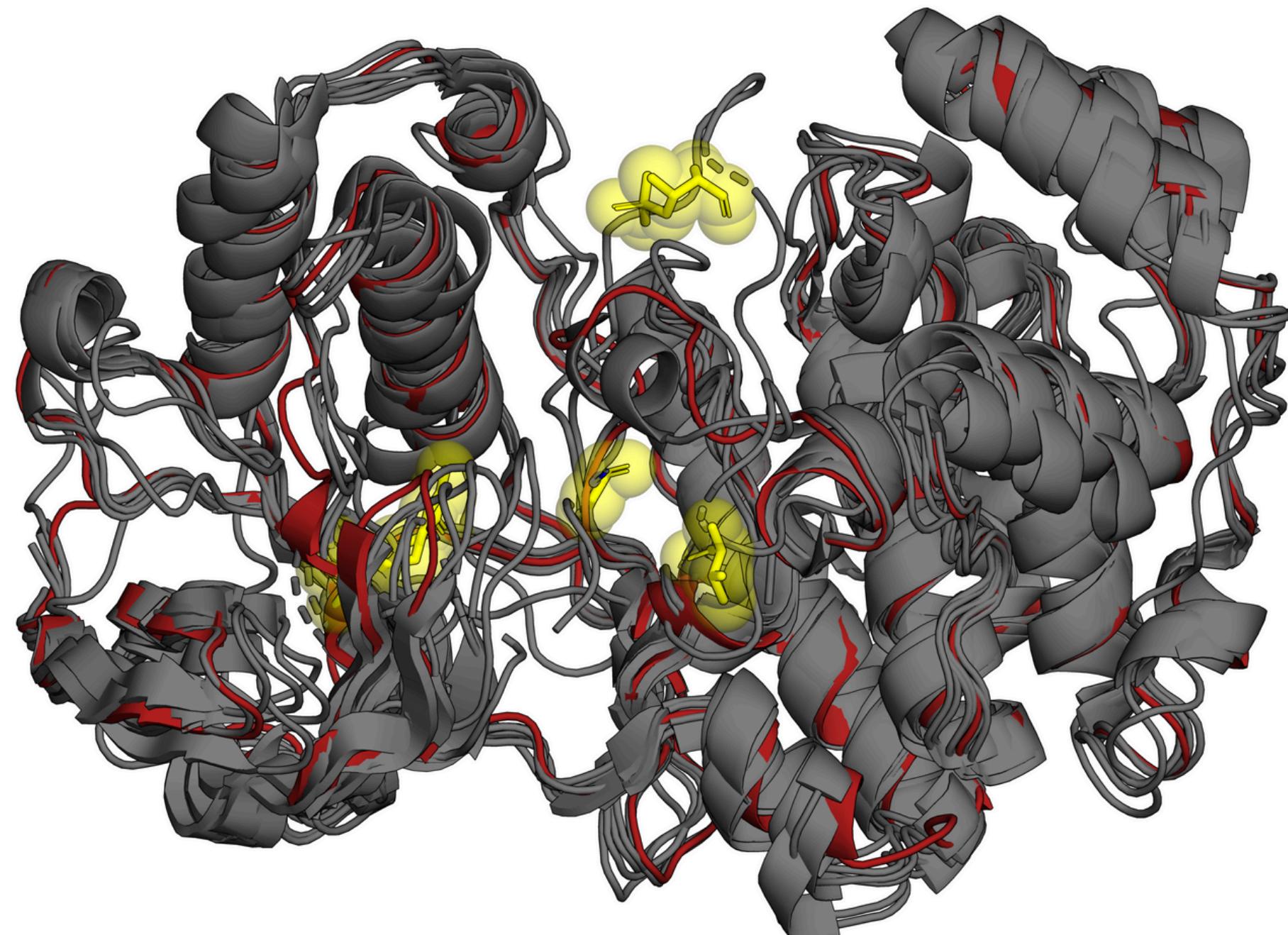
STKc_p38beta

STKc_p38gamma

STKc_p38delta

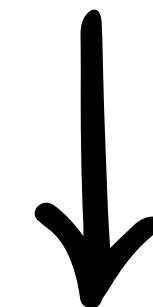
STKc_p38alpha

MAPK14 STRUCTURAL VARIANTS

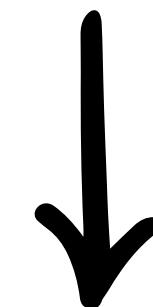


■ MAPK14 WT ■ MAPK14 variants ● Mutations

Most **mutations** were found to be around the core of the protein, near the **TXY motif**



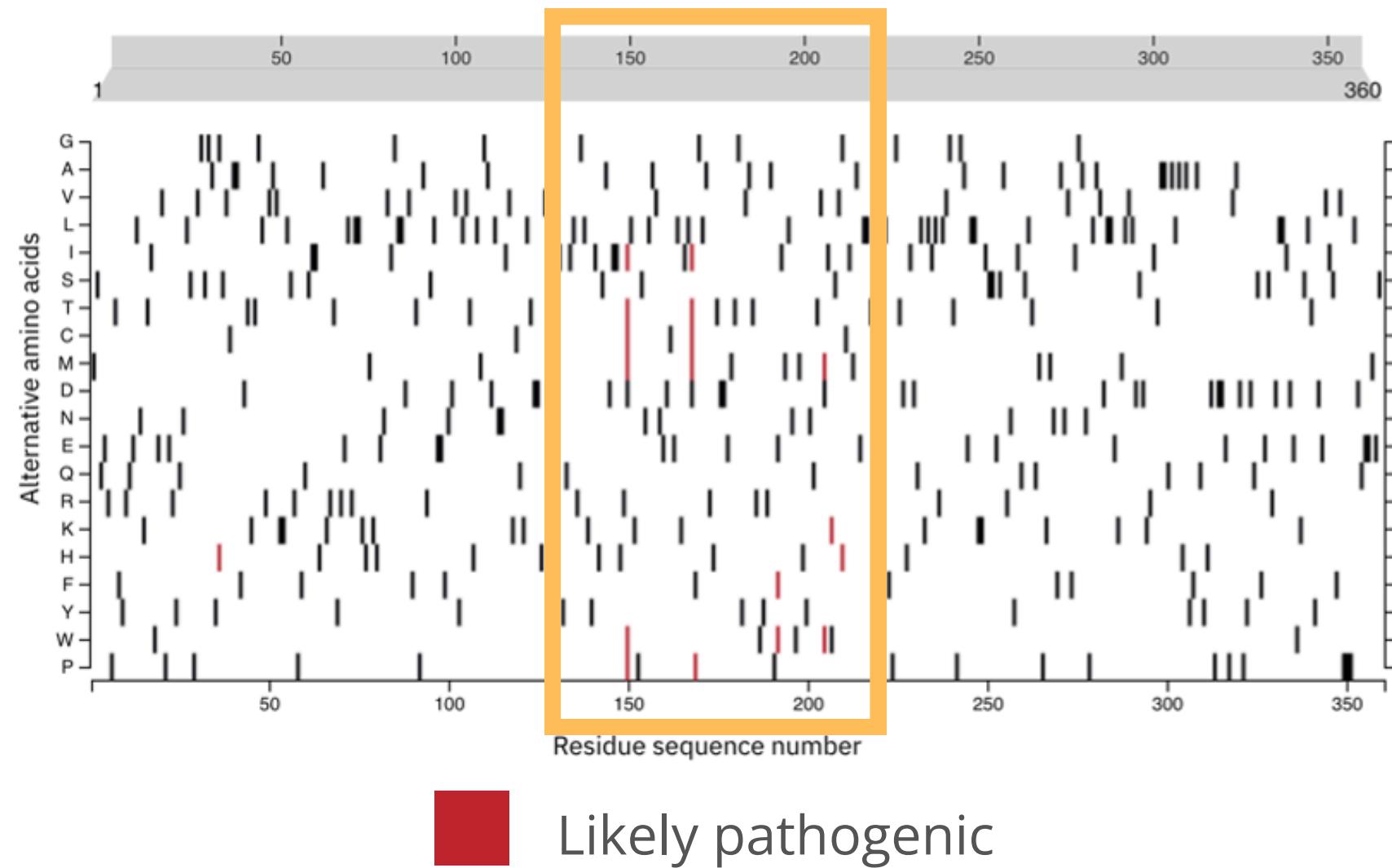
Effect on
phosphorylation



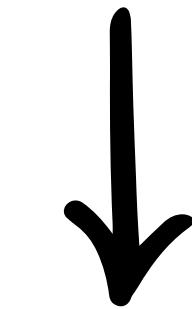
Defect on the **p38**
signaling pathway

OTHER MAPK14 MUTATIONS'S LOCATION

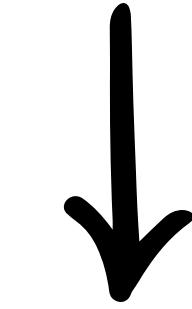
AlphaMissense Pathogenicity Heatmap



Most **mutations** could be near the TXY motif



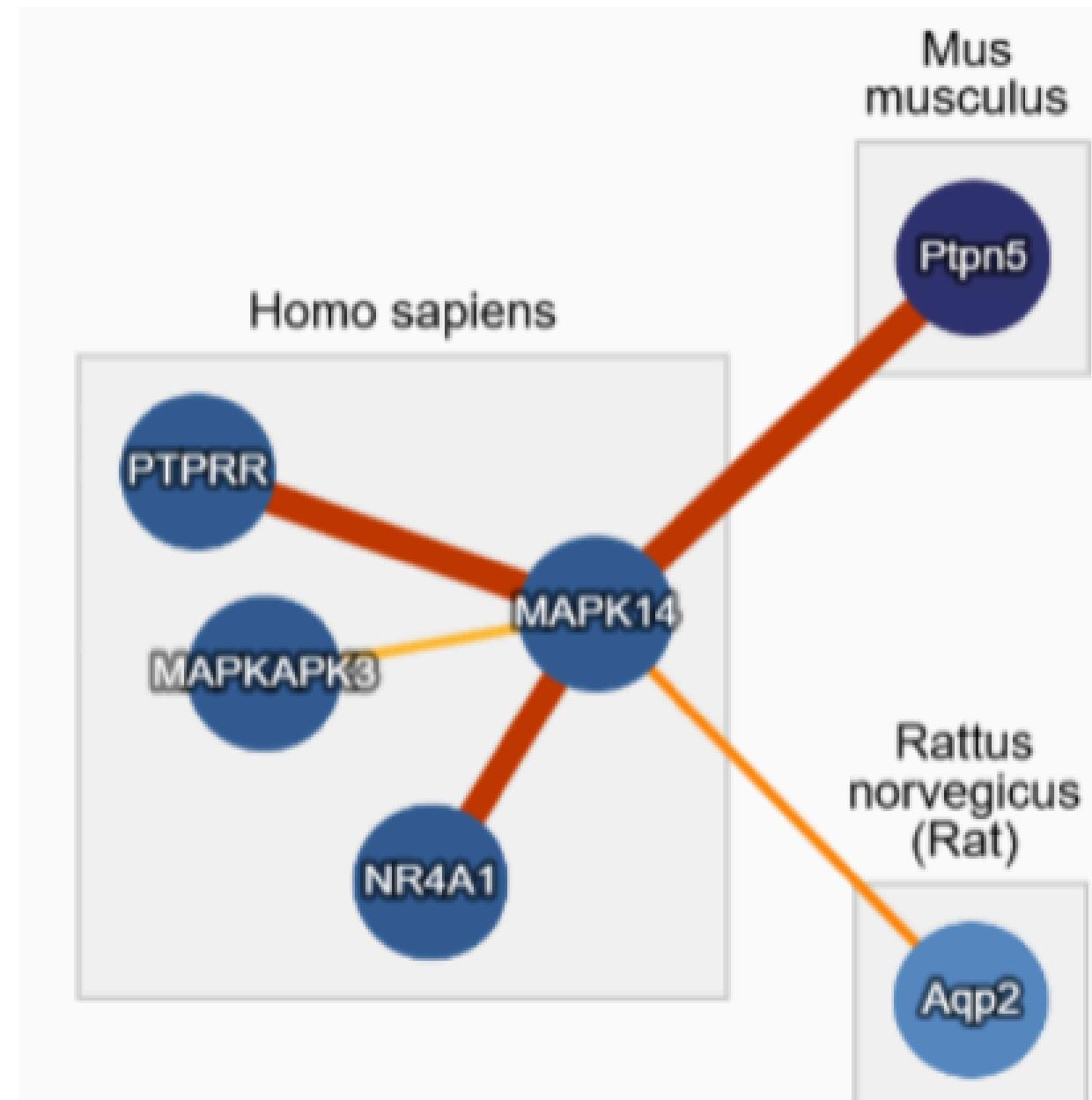
Effect on phosphorylation



Defect on the p38 signaling pathway



MAPK14 AND ITS INTERACTIONS



1. PTPRR

Part of the tyrosine phosphatase family.
Sequesters the MAPK14 to regulate its activation

2. NR4A1

Nuclear receptor involved in homeostasis, regulation of inflammatory response and response in vascular lesions

MAPK13 AND ITS INTERACTIONS

1. PRKD1

MAPK13 phosphorylates the PRKD1 reducing the insulin secretion

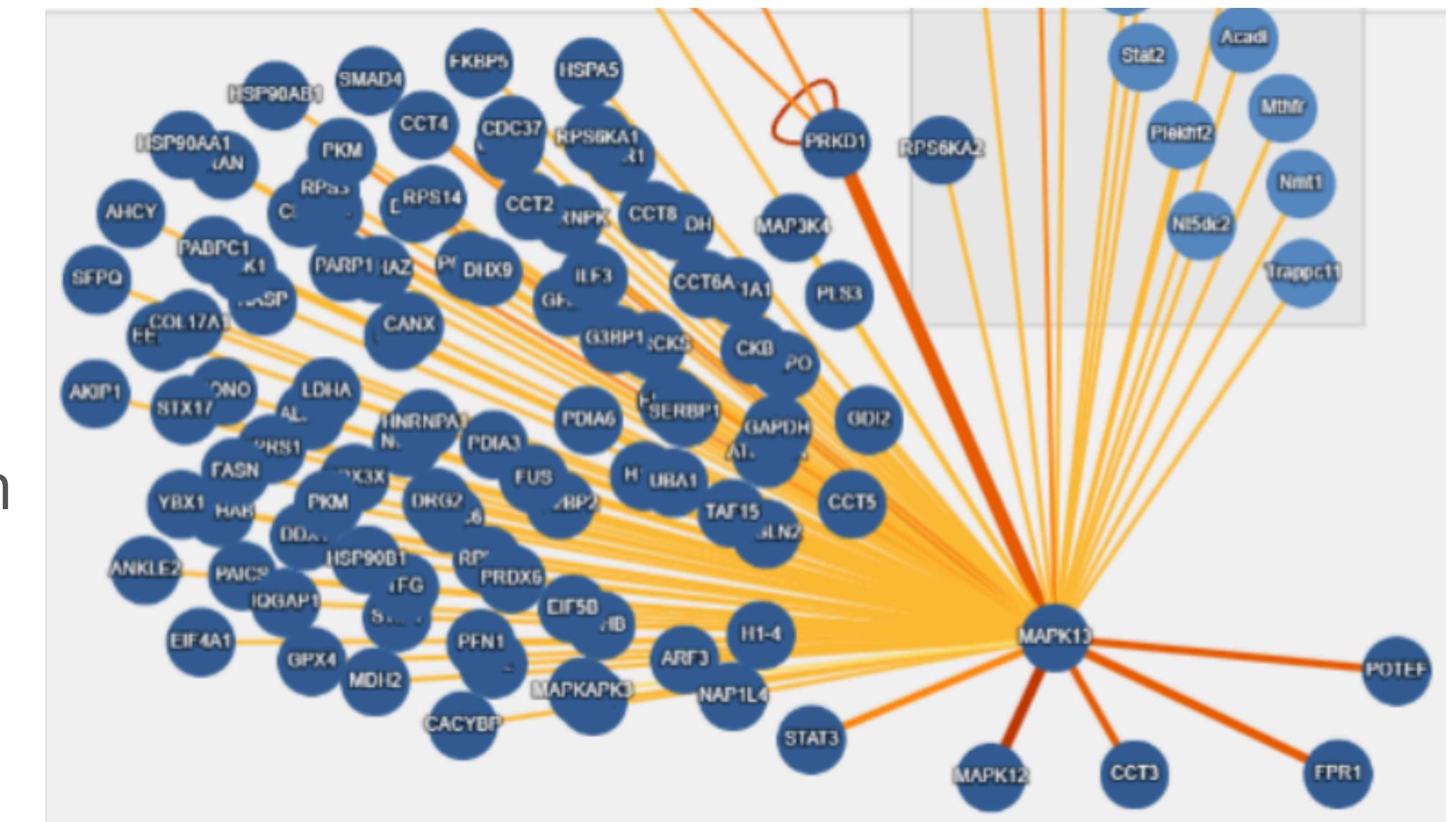
2. FPR1

MAPK13 phosphorylates the FPR1, which blocks the GRK2 and facilitates neutrophils migrations.

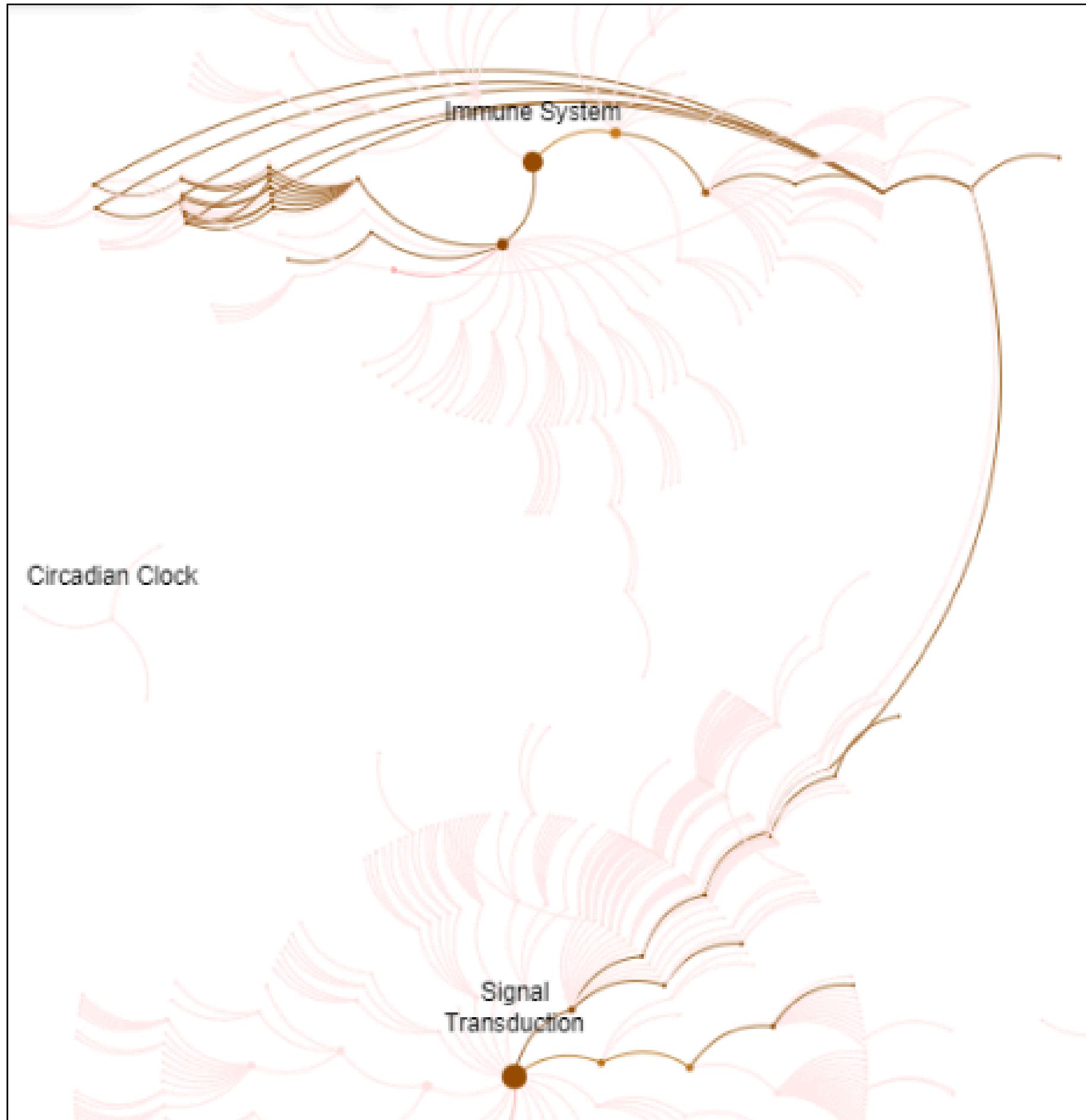
3. STAT3

Indirect interaction.

BCA phosphorylase MAPK13, increasing its restriction activity.

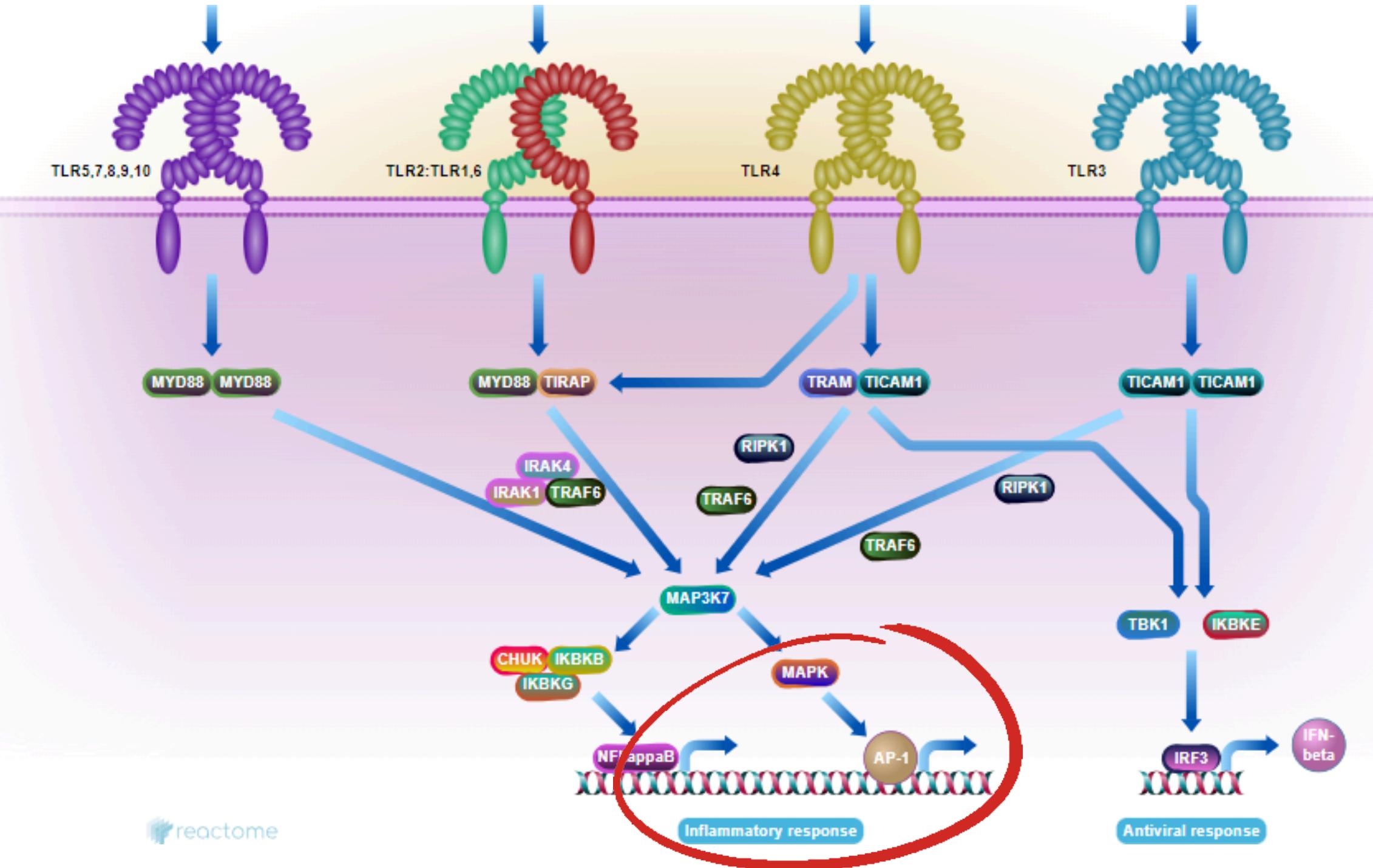


BCA phosphorylase STAT3, blocking its activation.



MAPKs are primarily present in
the **Immune system** and in the
Signal transduction

IMMUNE SYSTEM: TOOL-LIKE RECEPTORS



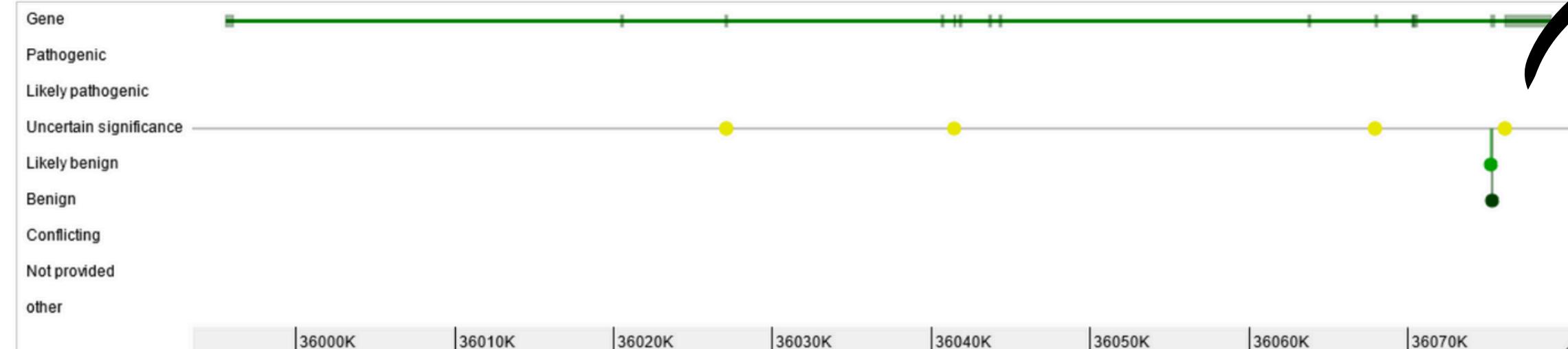
Relationship with
inflammatory
responses (AP-1)

aHUS involves uncontrolled activation of the complement system, which leads to widespread inflammation within the blood vessels

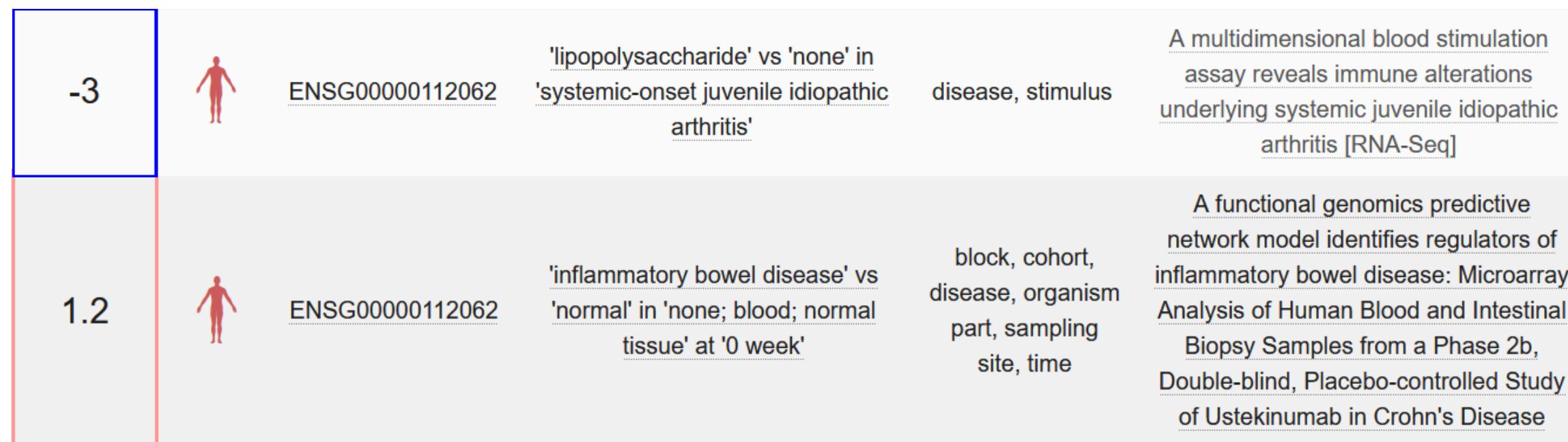
MAPK14: ¿SYMPTOMS AND TREATMENT?

Graphical view of search results ▾

▶ GRCh37



There are cases reported where a SNP mutation results beneficial for the patient (but no disease reported)

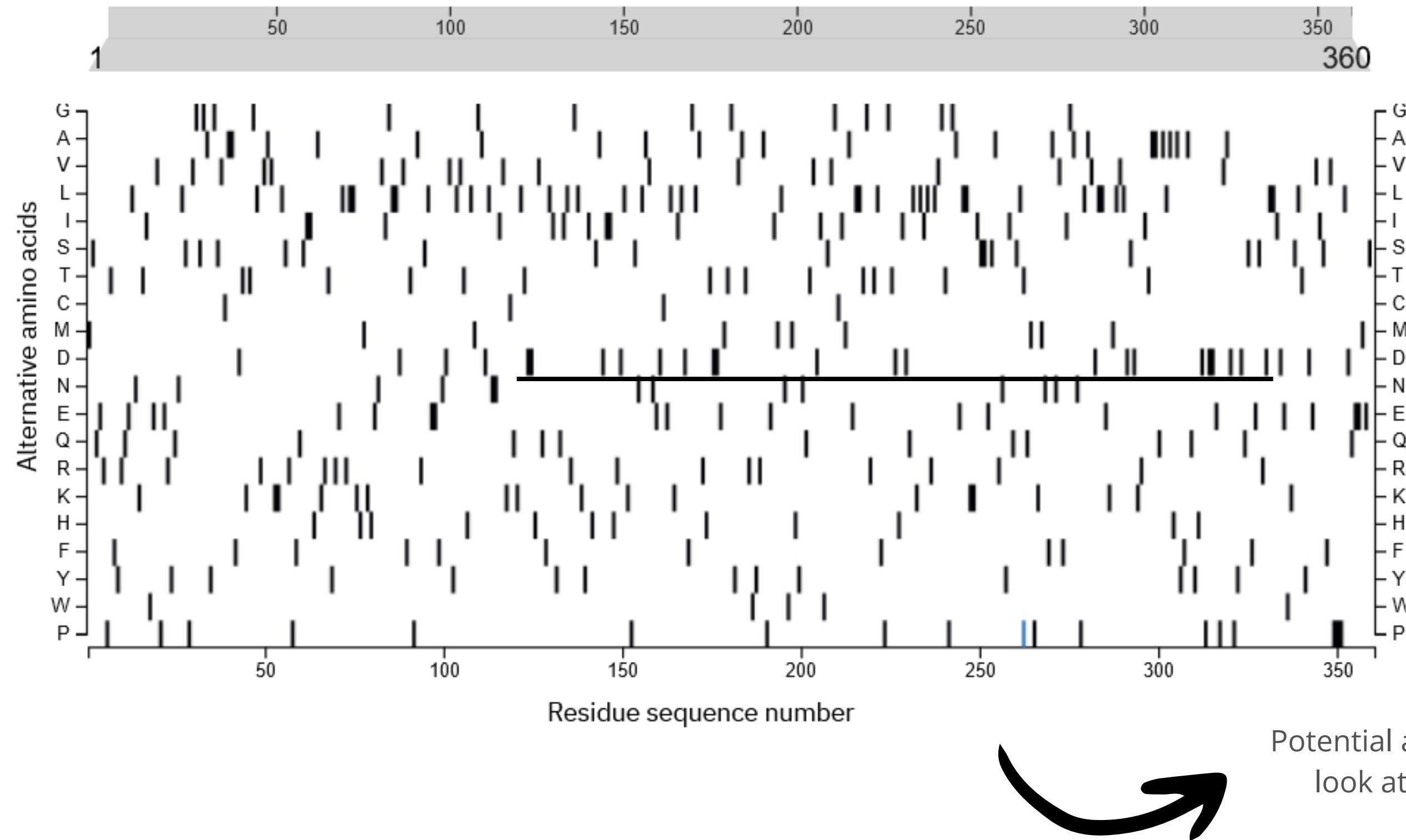


Thrombotic symptoms reported for patients when overexpressed



ClinVar
Clinically relevant variation

MAPK14: ¿SYMPTOMS AND TREATMENT?



CONCLUSIONS

- The P38 pathway is primarily related to the **immune system**, and contributes to the endothelial dysfunctions. This relationship highlights its importance in the regulation of inflammatory responses and vascular health.
- The P38 pathway come out to be a important resource for the development of **therapeutic targets**.
- The **MAPK14** presented an intersenting bond with the symptoms of the aHUS. Variants that impact its function have been reported, suggesting a new genetic connection to the development of aHUS.

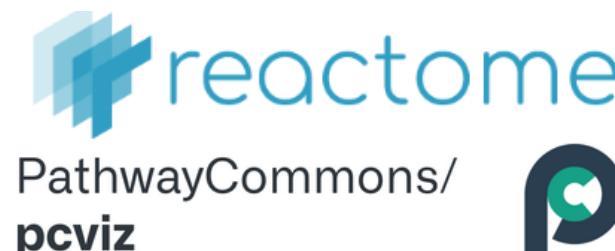
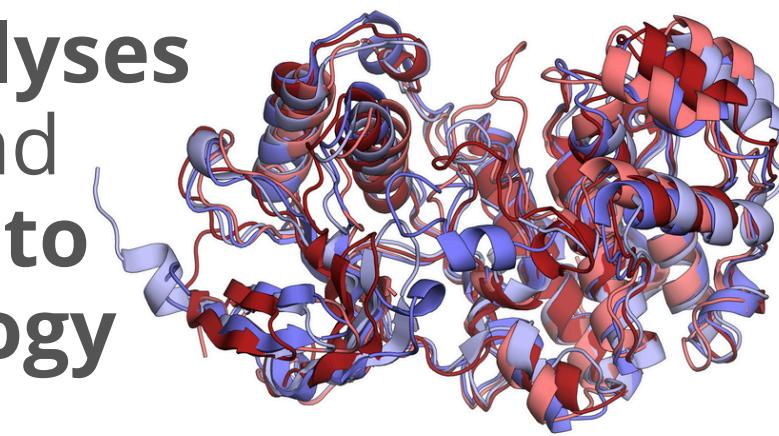
FUTURE DIRECTIONS

Short-term



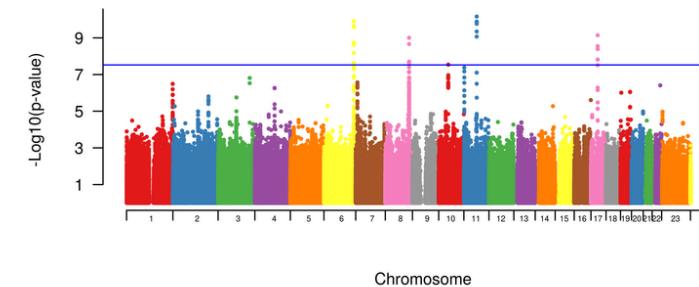
Identify **biomarkers related to p38 activation**, also associated with the **severity of aHUS**

Experimental analyses of p38 isoforms and their contribution to the symptomatology of aHUS



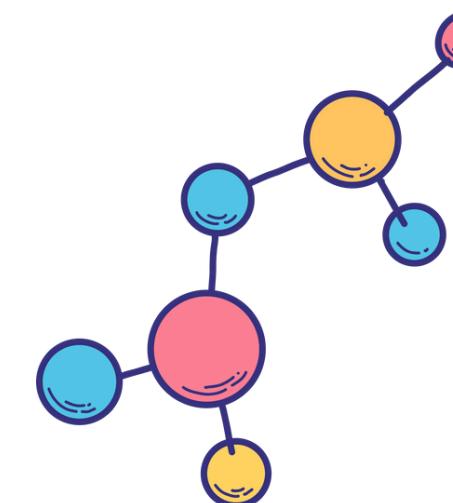
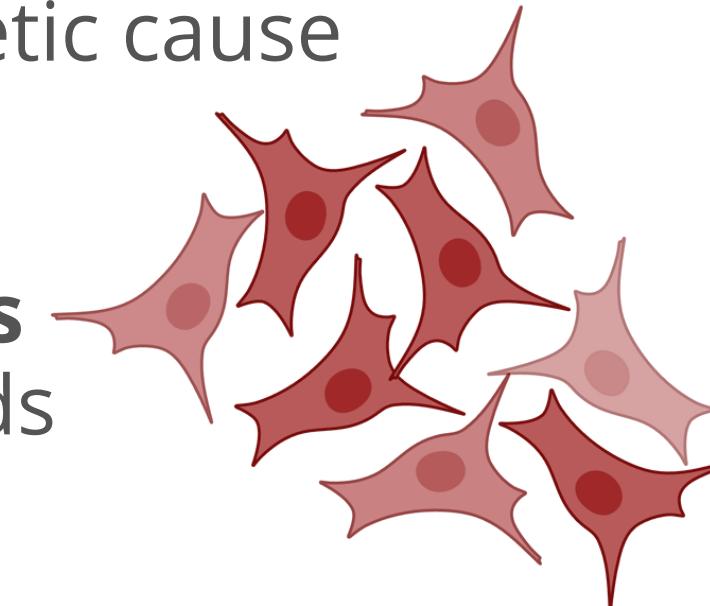
Use of Reactome and Pathway Commons to **model systemic disruptions in signaling pathways**

Long-term



Conduct GWAS in aHUS patients to identify novel variants, especially the cases without known genetic cause

Clinical validation of p38 MAPKs mutations in cell lines or organoids



Screen for **small molecules that modulate the p38 MAPK pathway**

REPOSITORY AND PRESENTATION ACCESS



GitHub



Presentation

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T H A N K S

