

# RUTA P38 Y SU RELACIÓN CON EL SÍNDROME HEMOLÍTICO URÉMICO ATÍPICO

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

# C O N T E N I D O

- 01.** Descripción enfermedad:  
Síndrome Hemolítico Urémico Atípico (ORPHA: 2134)
- 
- 02.** Genes involucrados en la enfermedad.
- 
- 03.** Sistema complementario.
- 04.** Ruta p38.
- 
- 05.** Genes involucrados en la p38.
- 
- 06.** Conclusiones
- 
- 07.** Direcciones futuras

# SÍNDROME HEMOLÍTICO URÉMICO ATÍPICO (aHUS)

El aHUS al ser una enfermedad con **heterogeneidad genética**, posee varios mecanismos de herencia tanto autosómica dominante (**P<**), como autosómica recesiva (**P>**). También se ha reportado que puede tener herencia poligénica (Noris et al, 2021)

Adicionalmente, tiene una prevalencia mundial de 1-3 pacientes por millón de personas. Sin embargo en Europa es de 30-90 pacientes por millón de personas (Orphanet, 2021; Noris et al, 2021)

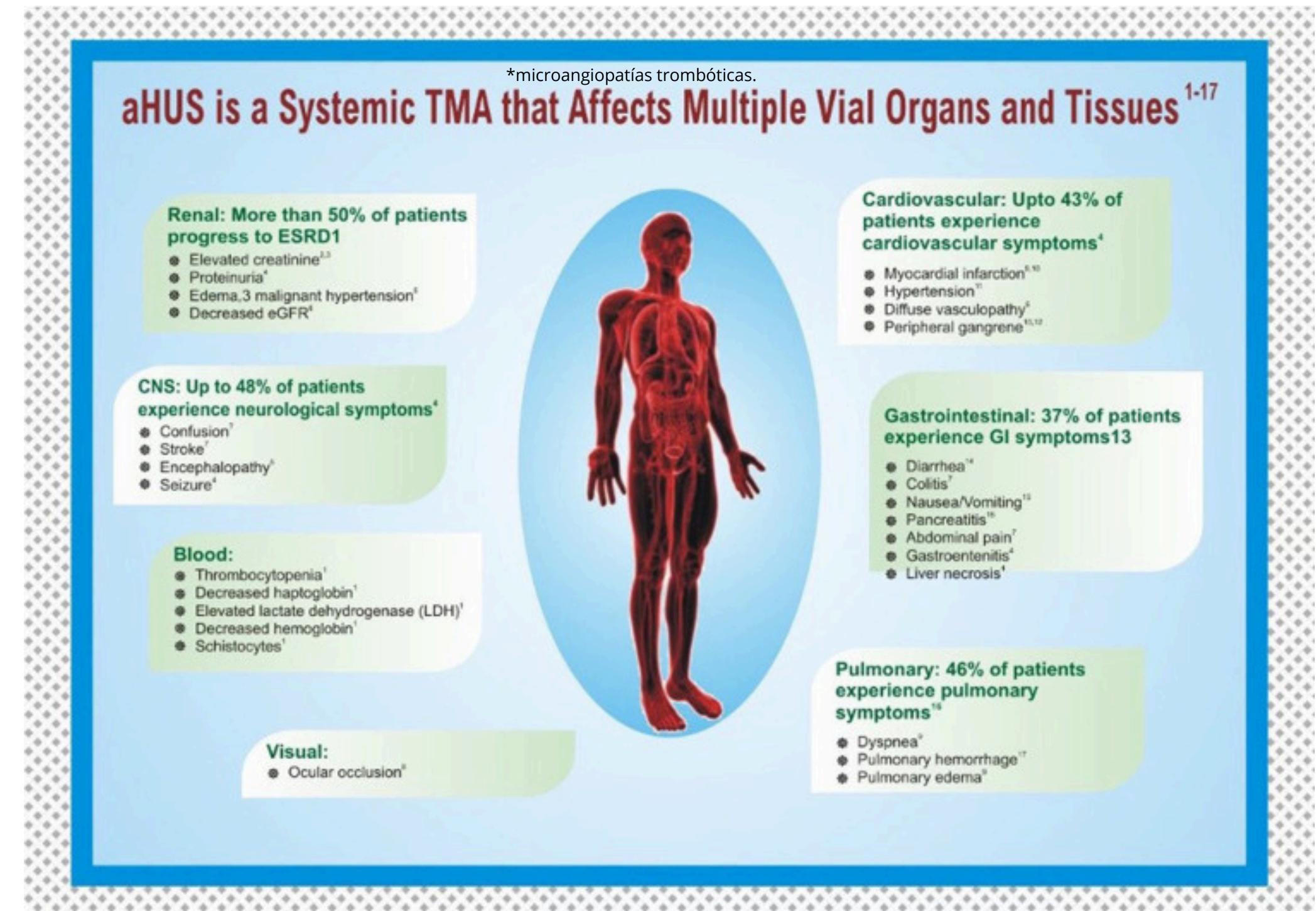


Imagen adaptado de Yerigeri et al. (2017).

# GENES INVOLUCRADOS EN LA ENFERMEDAD

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,<sup>1</sup> Saurav Kadatane,<sup>2</sup> Kai Mongan,<sup>3</sup> Olivia Boyer,<sup>4</sup> Linda L G Burke,<sup>5</sup> Sidharth Kumar Sethi,<sup>6</sup>

## Genetic Testing in aHUS May Inform Long-term Patient Outcomes

| Genetic Abnormality                              | Frequency in Patients with aHUS <sup>1-6,9-12</sup> | ESRD or Death within 3 to 10 Years of Diagnosis, % of Patients <sup>1,2,6,8,9,13</sup> | Subsequent Disease Manifestation Post Transplant, @ of Kidney Grafts <sup>1-3,5,9,10</sup> |
|--|---|--|--|
| 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 <sup>5</sup> | 6%-15%  | 6%-38%*  | 0%-20%   |
| DGKE mutations                                   | -27% of patients diagnosed at≤1 year of age         | 46% (6/13)*  | 0% (0/3)*  |
| CFH or MCP risk haplotypes                       | CFH-H3 : 31%<br>MCPggaa0 : 44%                      |  |  |
| No identified mutation                           | 30%-50%   | 32%-50%  | 59% (17/29)*   |

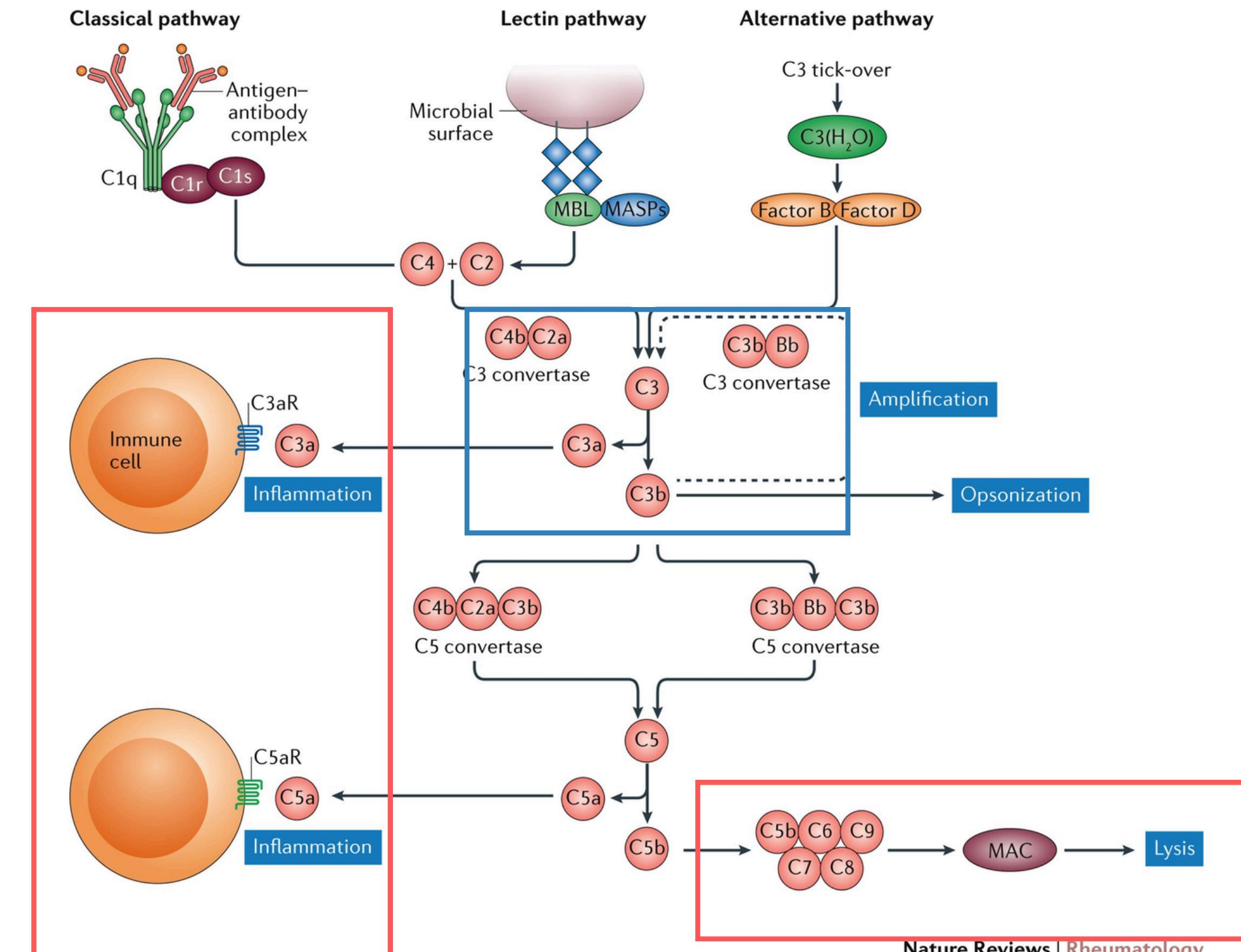
**Footnotes:** \*Plasminogen (PLG) mutations have not been included in this table because the outcomes of patients with aHUS and PLG mutations have not been reported\*\*; \*\*The ranges are based on kidney grafts that were affected by TMA manifestations. Some patients received multiple grafts. \*\*, (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, X<sup>2</sup> 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

# SISTEMA COMPLETO

Principales genes con mutaciones de pacientes con aHUS relacionados con los síntomas



Nature Reviews | Rheumatology

# SISTEMA COMPLETO EN AHUS

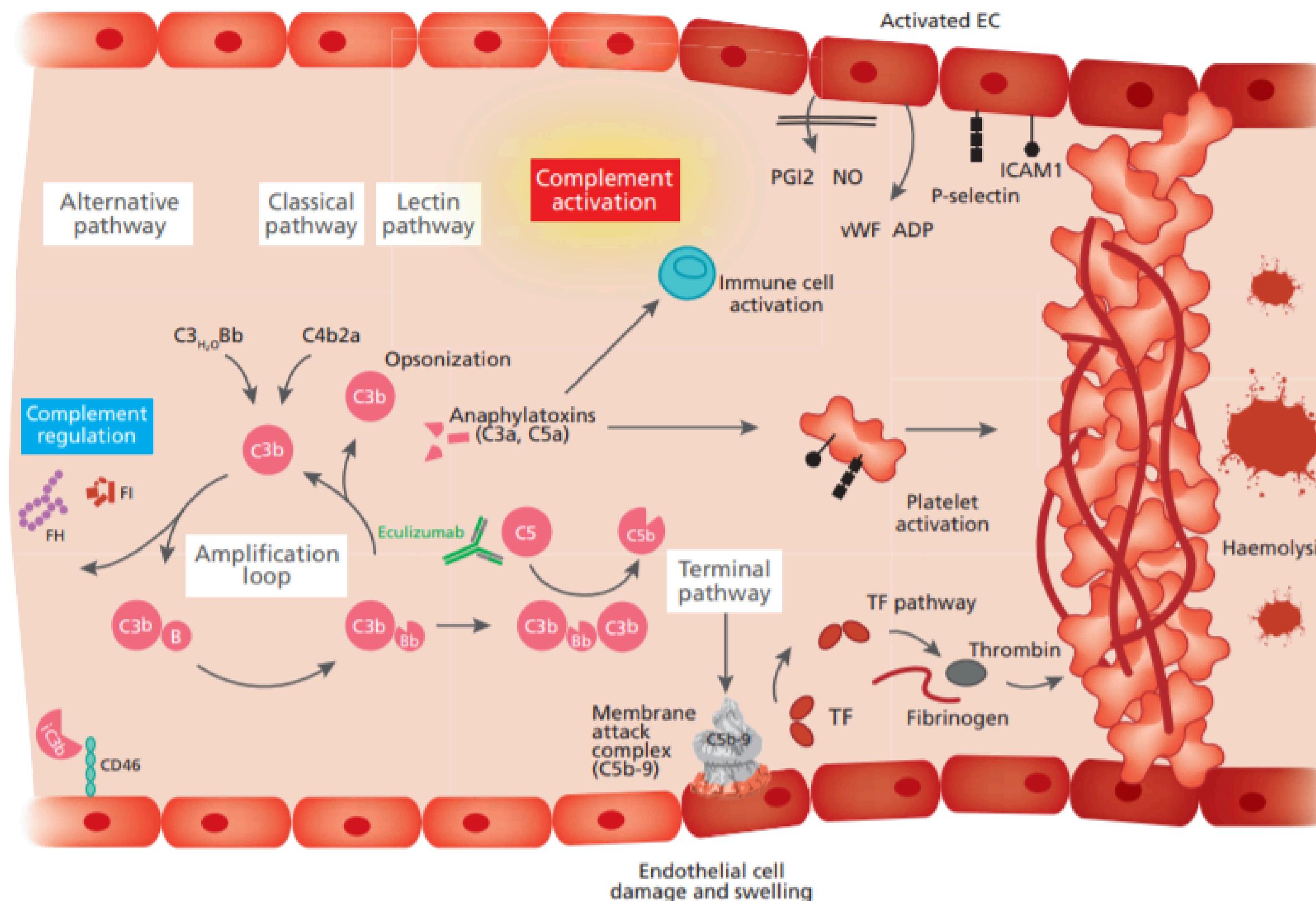


Imagen adaptado de Hui (2012)

1

# Stem Cell Reports

**Article**



OPEN ACCESS

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

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

Se observó una disminución significativa de las señalización de p38

2



RESEARCH REPORT

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

Eva Leinøe,<sup>1</sup> Ove Juul Nielsen,<sup>1</sup> Lars Jønson,<sup>2</sup> and Maria Rossing<sup>2</sup>

<sup>1</sup>Department of Hematology, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark;

<sup>2</sup>Center for Genomic Medicine, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark

C3A1 is a receptor for complement factor C3a

# RUTA DE SEÑALIZACIÓN CELULAR P38/MAPK

Cuatro isoformas de la proteína quinasa p38:

- p38 $\alpha$  (*MAPK14*)
- p38 $\beta$  (*MAPK11*)
- p38 $\gamma$  (*MAPK12*)
- p38 $\delta$  (*MAPK13*)

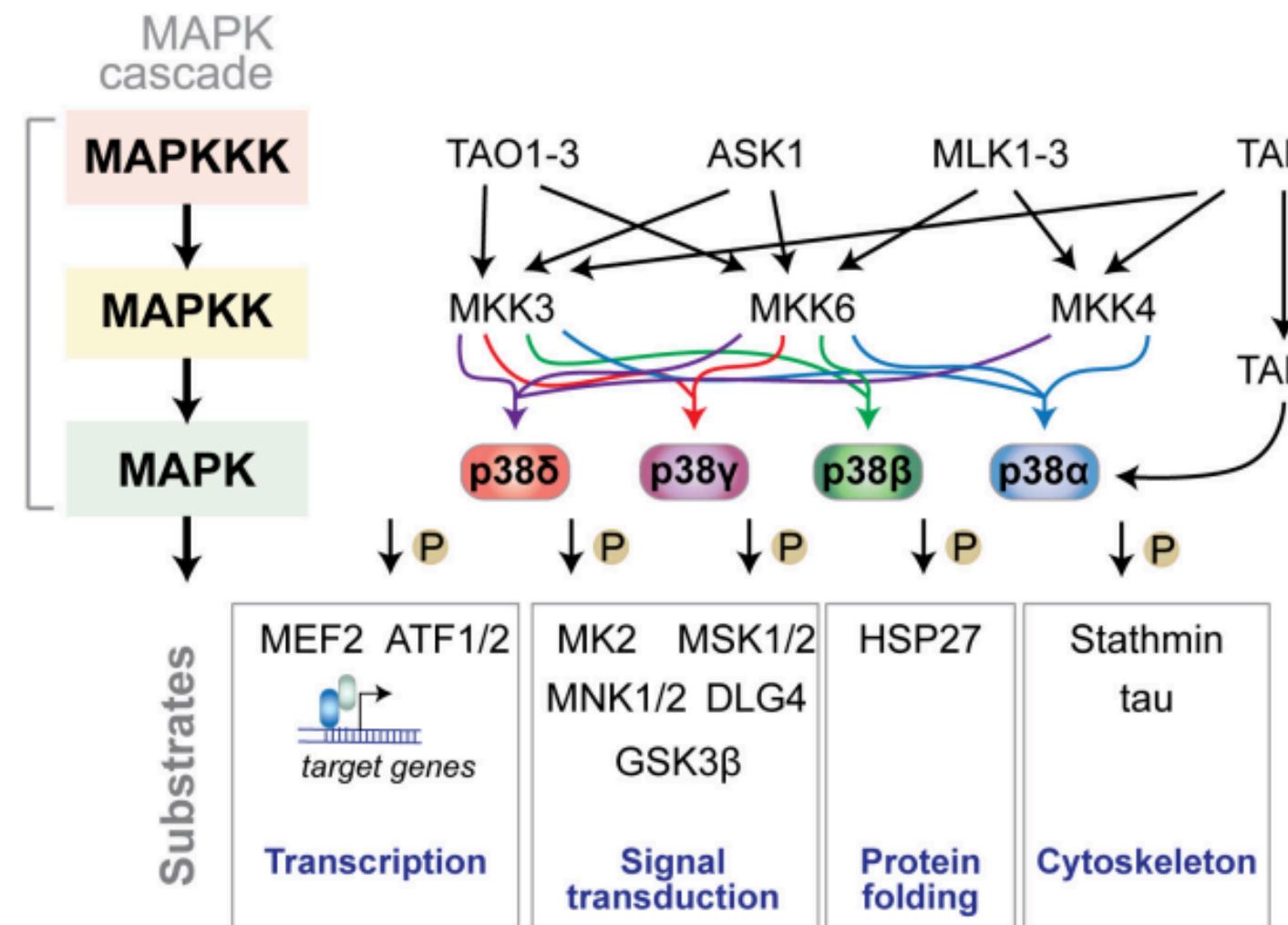


Imagen adaptada de Asih et al., 2020

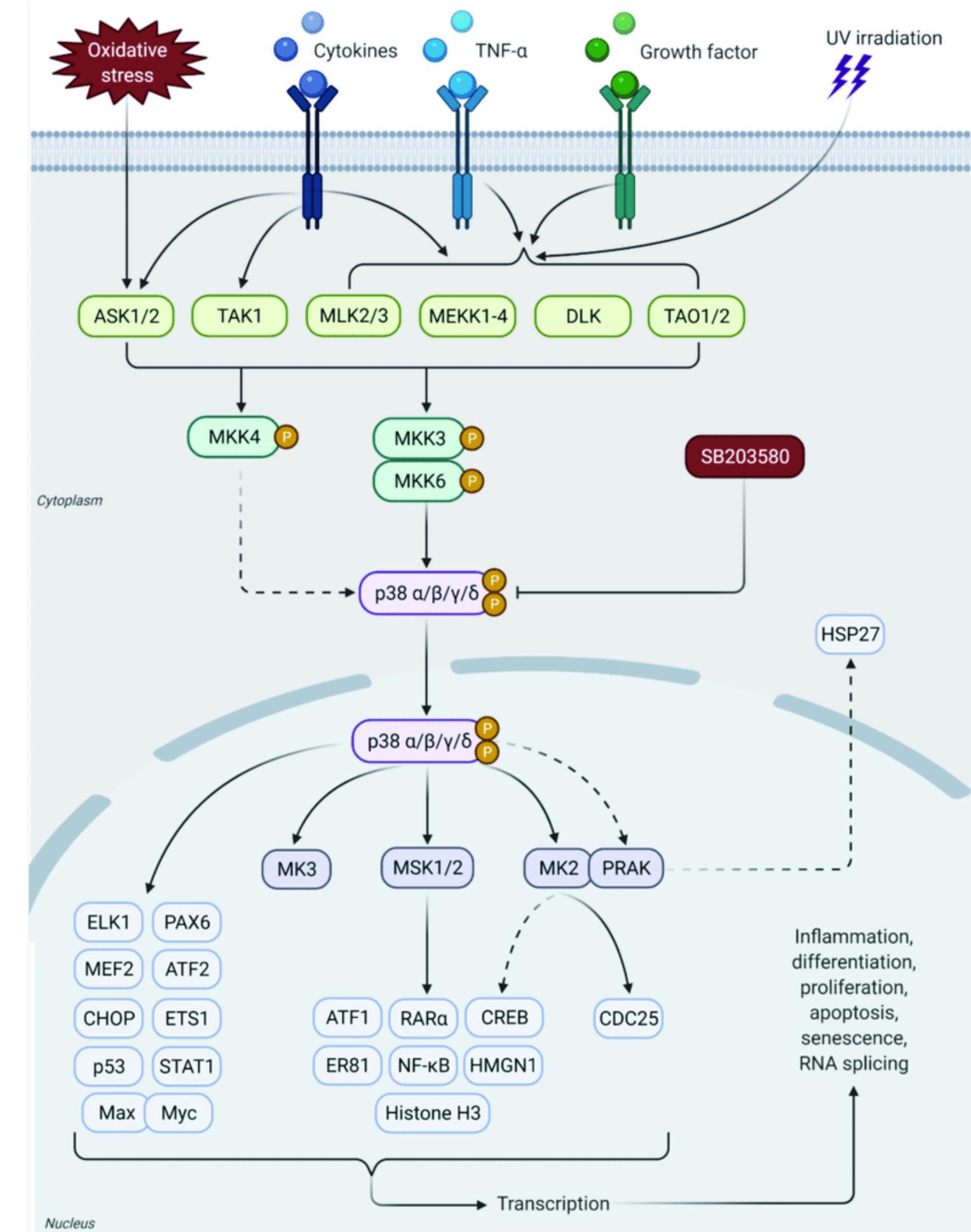


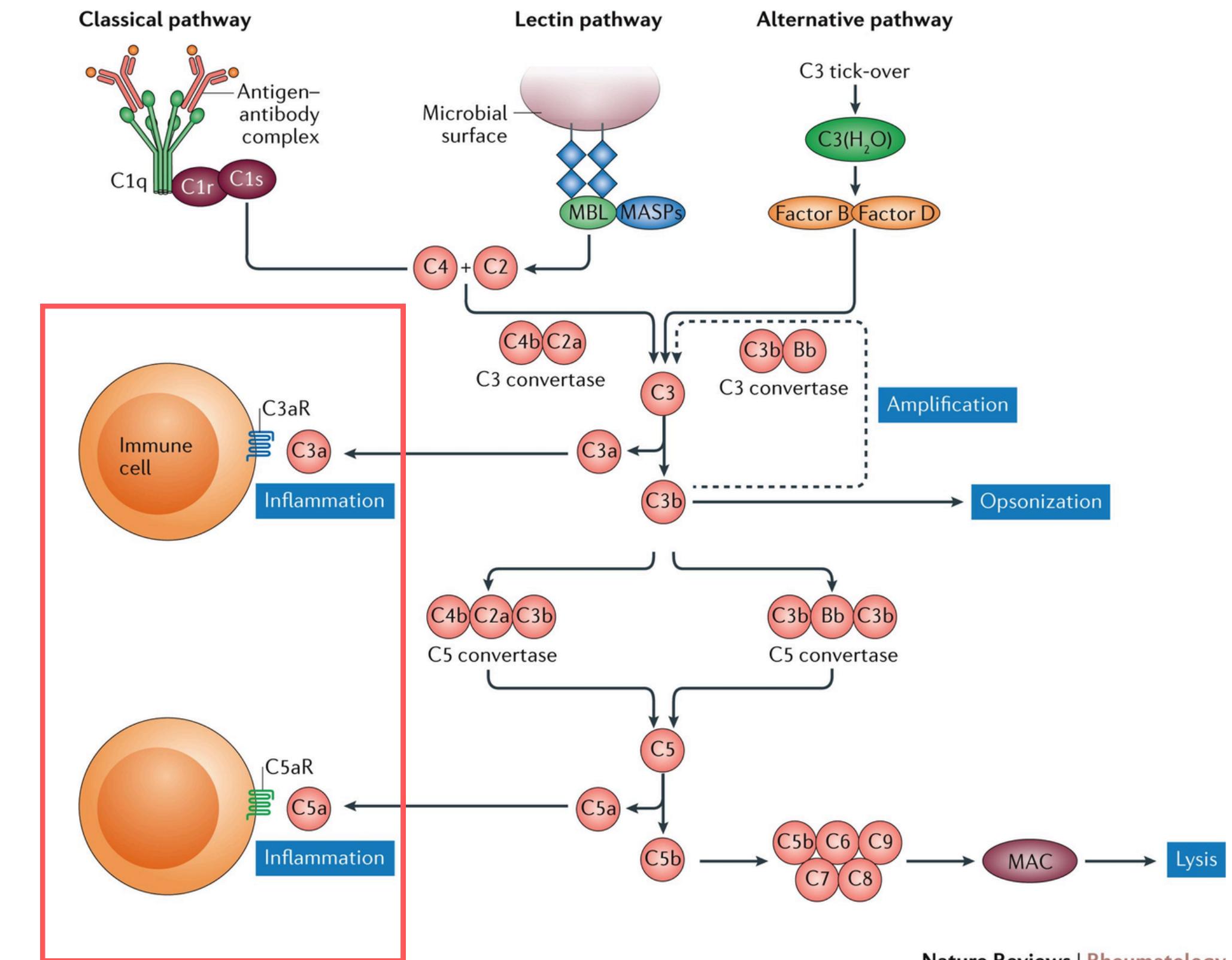
Imagen tomada de Pua et al., 2022

# SISTEMA COMPLETO

## Relación con p38

1. p38 MAPK  
(MKK6=MPAK14) regula la expresión de C3  
(Lei et al., 2016)

2. C5a activa a través de la p38 macrófagos  
(Maranto et al., 2011)



# PREGUNTA DE INVESTIGACIÓN

¿Qué relación hay entre la ruta de señalización p38 y la sintomatología y severidad del aHUS?

=

¿ La ruta de **Sintomatología** causada por el  
señalización **P38 + sistema complemento** ?

=

Nueva perspectiva al aspecto genético de aHUS

# MAPK14: ¿SINTOMATOLOGÍA Y TRATAMIENTO?



MAPK14



Se reportan estos y varios casos donde una mutación (SNP) resulta ser benigna para el paciente (enfermedad no reportada)

|     |  |                 |  |  |  |
|-----|--|-----------------|--|--|--|
| -3  |  | ENSG00000112062 | 'lipopolysaccharide' vs 'none' in 'systemic-onset juvenile idiopathic arthritis'     | disease, stimulus  | A multidimensional blood stimulation assay reveals immune alterations underlying systemic juvenile idiopathic arthritis [RNA-Seq]  |
| 1.2 |  | ENSG00000112062 | 'inflammatory bowel disease' vs 'normal' in 'none; blood; normal tissue' at '0 week' | block, cohort, disease, organism part, sampling site, time | A functional genomics predictive network model identifies regulators of inflammatory bowel disease: Microarray Analysis of Human Blood and Intestinal Biopsy Samples from a Phase 2b, Double-blind, Placebo-controlled Study of Ustekinumab in Crohn's Disease |

Sintomatología trombótica/ hemolítica reportada en los pacientes de estos artículos



# VARIANTES DE LAS 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      |      |

# VARIANTES DE LAS MAPKS

- MAPK14 (MKK6)

| 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 |  |

Variantes sin sentido con un efecto en la estructura de proteína (PolyPhen2 > 0.5)

Impairs MAP2K6/MKK6-dependent autophosphorylation. [1 Publication]

Manual assertion based on experiment'

Differential activation of p38 mitogen-activated protein kinase isoforms depending on signal strength.

Alonso G., Ambrosino C., Jones M., Nebreda A.R.

[View abstract](#)

PubMed [ ] Europe PMC [ ] J. Biol. Chem. 275:40641-40648 (2000) [ ] Cited in [2] [ ]

2 ENSE00003491453 [36,052,699](#) [36,052,828](#)

Parte del exon dos del gene *MAPK14*

- ▶ Mutagenesis 34 Lowered kinase activity. [1 Publication]
- ▶ Natural variant VAR\_042270 51 in a gastric adenocarcinoma sample; somatic mutation [1 Publication]
- ▶ Mutagenesis 53 Loss of kinase activity. [1 Publication]
- ▶ Mutagenesis 54 Impairs MAP2K6/MKK6-dependent autophosphorylation. [1 Publication]
- ▶ Mutagenesis 69 Lowered kinase activity. [1 Publication]

Efecto en la autofosforilación

Protein summary [ ? ]

Protein domains for ENSP0000229795.3

Add/remove tracks | Share | Export image | Reset configuration | Reset track order

ENSP0000229795.3 Low complexity (Seq) Exon: ENSE0003491453 Location 6:36027808-36111236

AlphaFold DB import First aa 39 (3rd base)

Superfamily Last aa 82

SMART Start phase 2

Prints End phase 2

Pfam Length 130bp, 43 1/3 aa

PROSITE profiles Protein kinase domain

Entre los aa 39-82, específicamente el aa54

# CONCLUSIONES

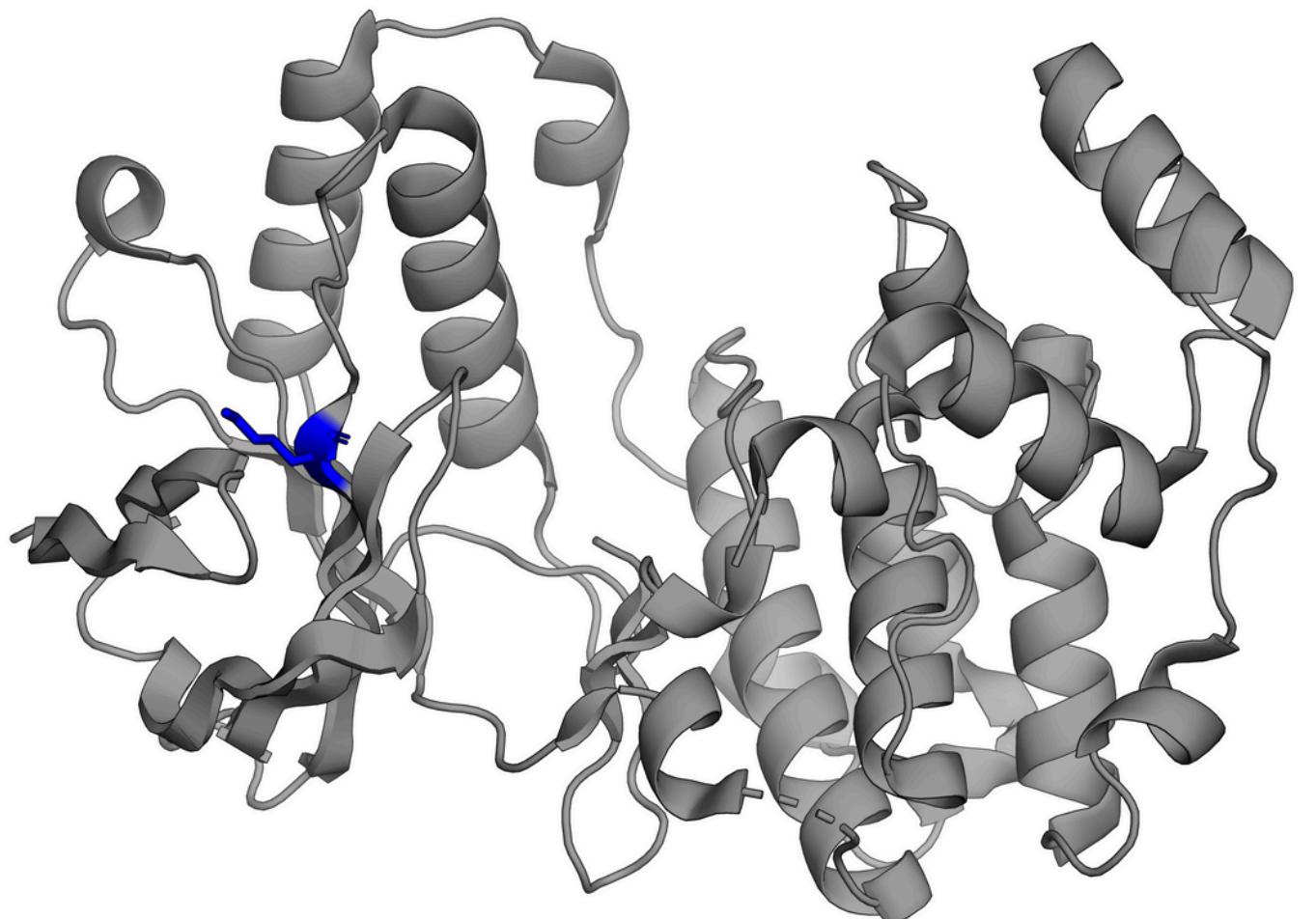
- La identificación de la p38 como una vía de señalización que contribuye a las disfunciones endoteliales en la enfermedad.
- Esta vía de señalización (p38 MAPK) puede ser un objetivo terapéutico para el tratamiento de la enfermedad.
- *MAPK14* parece ser un gen de gran interés debido a qué se encuentra directamente relacionado a la función principal de la p38 y variantes de este afectan estructuralmente su función, adicionalmente, se reporta expresión diferencial para sintomatología hemolítica y podría ser benigna para el tratamiento de la enfermedad

(Zhou D et al, 2021)

# DIRECCIONES FUTURAS

## A futuro cercano

- Relación variante-gen-proteína-(función)sintomatología para las MAPKs con un enfoque en la relación estructura-función
- Revisar la ontología de los genes y proteínas a trabajar
- Estudiar la expresión de las MAPKs en relación a los órganos más afectados en aHUS (ej. riñon)



MAPK14 (8vke) con el **54K** en el dominio kinasa

## A futuro lejano

- Dar una nueva perspectiva genética de aHUS en relación a la p38
- Juntar los conocimiento independientes en un nuevo *state of the art* para aHUS

M U C H A S  
G R A C I A S

# Referencias

- Pua, Lesley & Mai, Chun-Wai & Chung, Felicia & Khoo, Alan & Leong, Chee-Onn & Lim, Wei Meng & Hii, Ling-Wei. (2022). Functional Roles of JNK and p38 MAPK Signaling in Nasopharyngeal Carcinoma. International Journal of Molecular Sciences. 23. 1108. 10.3390/ijms23031108.
- Asih, P.R., Prikas, E., Stefanoska, K., Tan, A.R., Ahel, H.I., & Ittner, A. (2020). Functions of p38 MAP Kinases in the Central Nervous System. Frontiers in Molecular Neuroscience, 13.
- Noris M, Bresin E, Mele C, et al. Genetic Atypical Hemolytic-Uremic Syndrome. 2007 Nov 16 [Updated 2021 Sep 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1367/>
- Yerigeri, K., et al. (2023). Atypical Hemolytic-Uremic Syndrome: Genetic Basis, Clinical Manifestations, and a Multidisciplinary Approach to Management. Journal of Multidisciplinary Healthcare, 16:2233-2249, <https://doi.org/10.2147/JMDH.S245620>.
- Zhou D, Tan Y, Liu X, Tang L, Wang H, Shen J, Wang W, Zhuang L, Tao J, Su J, Gong T, Liu X, Liang P, Yu F, Zhao M. Patient-specific iPSC-derived endothelial cells reveal aberrant p38 MAPK signaling in atypical hemolytic uremic syndrome. Stem Cell Reports. 2021 Sep 14;16(9):2305-2319. doi: 10.1016/j.stemcr.2021.07.011. Epub 2021 Aug 12. PMID: 34388364; PMCID: PMC8452517.
- Harwell, D. (2024, February 6). Taylor Swift threatens legal action against student who tracks her jet. Washington Post. <https://www.washingtonpost.com/technology/2024/02/06/taylor-swift-jet-tracking-legal-threat/>
- Higgins, E. (2015, October 8). MH17 - The Open Source Evidence. Bellingcat. <https://www.bellingcat.com/news/uk-and-europe/2015/10/08/mh17-the-open-source-evidence/>
- Langston, J. (2024, February 7). "It is public information after all:" UCF student tracking Taylor Swift's jet responds to threat of legal action. WKMG; WKMG News 6 & ClickOrlando. <https://www.clickorlando.com/news/local/2024/02/07/it-is-public-information-after-all-ucf-student-tracking-taylor-swifts-jet-responds-to-threat-of-legal-action/>
- Larraz, I. (2022, October 26). Las herramientas de OSINT para rastrear vuelos se abren espacio entre los activistas. Newtral. <https://www.newtral.es/rastrear-vuelos-privados/20221026/>
- Wendling, M. (2024, February 11). Jack Sweeney: The planespotting student who angers Taylor Swift and Elon Musk. Www.bbc.com. <https://www.bbc.com/news/world-us-canada-68248168>
- Orphanet. (2021). Orphanet: Atypical hemolytic uremic syndrome. Orpha.net. <https://www.orpha.net/en/disease/detail/2134>

