HYSTORY:

The Registry was established in 1996 under the coordination of the Clinical Research Center for Rare Diseases Aldo e Cele Daccò.

AIMS OF THE REGISTRY:
- understanding the pathogenesis of HUS/TTP
- studying the genetic and biochemical abnormalities of HUS/TTP
- collecting clinical and genetic data of patients and their families
- finding the best therapeutic approach for patients
- giving up-to-date information to physicians and families
THE THROMBOTIC MICROANGIOPATHY

The term “thrombotic microangiopathy” (TMA) defines a lesion of vessel wall thickening (mainly arterioles and capillaries), intraluminal platelet thrombosis and partial or complete obstruction of the vessel lumina.

**HUS** → microangiopathic haemolysis, thrombocytopenia and renal failure

**TTP** → microangiopathic hemolysis, thrombocytopenia and cerebral lesions

**HUS and TTP are two clinically defined syndromes**

**with shared pathology of thrombotic microangiopathy**
FORMS OF HUS/TTP:

The most common form of HUS in children (typical HUS), with predominant renal failure, is triggered by a particular gastro-intestinal infection (Shigatoxin producing *Escherichia Coli*).

This form usually has a good prognosis.

There are also rare forms of HUS, usually without gastro-intestinal infection (atypical HUS - aHUS), that have a poorer prognosis:

- recurrent form (when the patient has relapses of the disease)
- familial form (when there are at least 2 affected subjects in the same family)

TTP is the most common form of TMA in adults and manifests with prevalent neurological symptoms. Also in TTP, familial and recurrent forms are recognised.
THERAPY OF HUS/TTP:

Early plasma-exchange or plasma infusion of an health donor is the current therapy for acute phases of the disease.

Dialysis is necessary if there is an acute renal failure.
There are a lot of research studies ongoing about HUS/TTP to understand the pathogenesis and to find the specific therapies of the disease.

Researchers are studying the role of substances of the blood coagulation and particularly some proteins of the complement system, and are studying the genetic aspects of HUS/TTP.

As for therapy: research is working on the optimisation of plasma treatment and towards new therapeutic approach for patients.
WHAT WE ARE DOING TO BETTER UNDERSTAND aHUS

**GENETIC AND BIOCHEMICAL STUDIES ON:**

*Factor H - CFH* - A circulating protein mainly produced by the liver and involved in the regulation of the complement system. Mutations have been found in around 30% of patients.

*Factor I - CFI* - A circulating serine protease mainly produced by the liver and involved in the regulation of the complement system. Mutations have been found in around 5-10% of patients.

*Membrane Cofactor Protein - MCP* - A surface-bound complement regulator associated with a milder form of aHUS. Mutations have been found in around 10% of patients.

*Complement Component 3 - C3* - Mutations have been found in around 5-10% of patients.

*Factor B - CFB* - Is part of the alternative complement pathway. Mutations are rare and have been found in 1-4% of patients with aHUS.

*Thrombomodulin - THBD* - An endothelial glycoprotein with anticoagulant properties that modulates complement activation on cell surfaces. Mutations have been found in around 5% of patients with aHUS.

ADAMTS13 - the Von Willebrand Factor cleaving protease - an enzyme which degrades the VWF multimers, preventing platelet adhesion and aggregation in the microcirculation. The plasma levels of ADAMTS13 protease, particularly in patients with TTP, are absent or very low due to a congenital deficiency (ADAMTS13 mutations) or due to an acquired defective activity (autoantibodies anti-ADAMTS13).

WHAT HAVE FOUND IN aHUS and TTP

Our researchers* found 26 different mutations in CFH, 13 in MCP, 10 in CFI, 12 in C3, 6 in THBD and 1 in CFB from 273 aHUS patients referred to the Registry.

Our researchers^ found also 7 different mutations in ADAMTS13 gene from patients with congenital TTP referred to the Registry.

* Noris M et al. CJASN 2010, 5(10):1844-59
^ Noris M. et al. JASN 2005, 16:1177-83
MUTATIONS FOUND IN FACTOR H GENE FROM aHUS PATIENTS REFERRED TO THE REGISTRY

MUTATIONS FOUND IN \textbf{MCP} GENE FROM aHUS PATIENTS REFERRED TO THE REGISTRY

- C35X
- C35Y (n=3)
- R59X (n=4)
- 48aa del
- P50T
- Y155D
- T267fs270X
- F242C
- (858-872)del+D277N+P278S
- 192T>C+193-198delC99R
- (96-129)del+G130I+Y132T+L133X

MUTATIONS FOUND IN FACTOR I GENE FROM aHUS PATIENTS REFERRED TO THE REGISTRY

- T72S
- A240G
- G261D (n=2)
- R317W
- G349R
- I357M
- W399R
- L484V+Q485G+W486X
- E554V
- D519N

MUTATIONS FOUND IN **C3** GENE FROM aHUS PATIENTS REFERRED TO THE REGISTRY

MUTATIONS FOUND IN *THBD* GENE FROM aHUS PATIENTS REFERRED TO THE REGISTRY

Delvaeye, Noris et al, NEJM 2009, 361:345-357
MUTATIONS FOUND IN **CFB** GENE FROM aHUS PATIENTS REFERRED TO THE REGISTRY

MUTATIONS FOUND IN *ADAMTS13* GENE FROM TTP PATIENTS REFERRED TO THE REGISTRY

Extensive research has established an association between aHUS and uncontrolled activation of the alternative pathway of the complement system.

We have recently studied the relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype.

Relative role of genetic complement abnormalities in aHUS

**AGE AT ONSET**

<table>
<thead>
<tr>
<th>Protein</th>
<th>0 - 2</th>
<th>3 - 10</th>
<th>11 - 16</th>
<th>17 - 34</th>
<th>35 - 54</th>
<th>&gt;55</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>CFH</em></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td><em>CFI</em></td>
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<tr>
<td><em>C3</em></td>
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<tr>
<td><em>THBD</em></td>
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<tr>
<td><em>MCP</em></td>
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<tr>
<td>Non mut</td>
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</tbody>
</table>

*Noris M. et al. CJASN 2010, 5(10):1844-59*
Relative role of genetic complement abnormalities in aHUS
TRIGGERING /UNDERLYING CONDITION

Relative role of genetic complement abnormalities in aHUS
OUTCOME OF THE FIRST EPISODE

Relative role of genetic complement abnormalities in aHUS
LONG TERM OUTCOME

Relative role of genetic complement abnormalities in aHUS RESPONSE to PLASMA IN aHUS PATIENTS with *CFH* MUTATIONS


*Partial remission: hematological normalization with renal sequelae*
Relative role of genetic complement abnormalities in aHUS RESPONSE to PLASMA IN aHUS with **CFI** or **C3** MUTATIONS

- **CFI**
  - ESRD or death: 75%
  - Remission (complete or partial): 25%

- **C3**
  - ESRD or death: 43%
  - Remission (complete or partial): 57%

Relative role of genetic complement abnormalities in aHUS outcome in patients with \textit{MCP} mutations

- Plasma infusion or exchange: 97%
- No plasma: 100%

Relative role of genetic complement abnormalities in aHUS
Outcome of kidney graft for aHUS depend on the genetic background

Among patients with CFH mutations, 12 of 17 kidney grafts were lost for aHUS recurrence, acute rejection, or thrombosis within 1 year.

Among patients with CFI mutations, aHUS recurrence occurred in 4 out of 6 grafts within 1 year.

Among patients with C3 mutations, aHUS recurrence occurred in 3 out of 7 kidney grafts.

Among patients with MCP mutations, no HUS recurrence was observed.

These data underline the need of genetic screening for complement abnormalities for identification of patients who could safely benefit from kidney transplant.

### Flow-chart for biochemical-genetic analyses in patients with aHUS and TTP

<table>
<thead>
<tr>
<th><strong>Analysis</strong></th>
<th><strong>Indication</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAMTS13 activity</td>
<td>All patients with aHUS and TTP</td>
</tr>
<tr>
<td>ADAMTS13 autoantibodies research</td>
<td>If reduction/deficiency of ADAMTS13 activity</td>
</tr>
<tr>
<td>Sequencing of <strong>ADAMTS13</strong> gene</td>
<td>If congenital ADAMTS13 deficiency (no autoantibodies)</td>
</tr>
<tr>
<td>Serum complement (C3, C4, FH)</td>
<td>All patients with aHUS</td>
</tr>
<tr>
<td>Sequencing of <strong>CFH</strong> gene</td>
<td>All patients with aHUS</td>
</tr>
<tr>
<td>Sequencing of <strong>CFI</strong> gene</td>
<td>Pts with aHUS, without CFH mutations</td>
</tr>
<tr>
<td>Sequencing of <strong>MCP</strong> gene</td>
<td>Pts with aHUS, without CFH/CFI mutations</td>
</tr>
<tr>
<td>Sequencing of <strong>C3</strong> gene</td>
<td>Pts with aHUS, without CFH/CFI/MCP mutations</td>
</tr>
<tr>
<td>Sequencing of <strong>THBD</strong> gene</td>
<td>Pts with aHUS, without CFH/CFI/MCP/C3 mutations</td>
</tr>
<tr>
<td>Sequencing of <strong>CFB</strong> gene</td>
<td>on a research basis only at present</td>
</tr>
<tr>
<td>Factor H auto-antibodies</td>
<td>on a research basis only at present</td>
</tr>
</tbody>
</table>
PARTICIPATING CENTERS OF THE INTERNATIONAL REGISTRY OF HEMOLYTIC UREMIC SYNDROME AND THROMBOTIC THROMBOCYTOPENIC PURPURA:

- Italian Centers: 100
- Abroad Centers: 80

U.S.A
CANADA
ARGENTINA
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S. ARABIA
R.S.A.
SPAIN
PORTUGAL
UK
DENMARK
BELGIUM
GERMANY
RUSSIA
ESTHONIA
POLAND
CZECH R.
SWITZERLAND
SERBIA
GREECE
TURKEY
INDIA
MALAYSIA
JAPAN
AUSTRALIA

THE INTERNATIONAL REGISTRY OF HUS/TTP:
PATIENTS DATA

<table>
<thead>
<tr>
<th></th>
<th>HUS</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial forms</strong></td>
<td>96 (within 48 families)</td>
<td>24 (within 15 families)</td>
</tr>
<tr>
<td><strong>Recurrent forms</strong></td>
<td>114</td>
<td>48</td>
</tr>
<tr>
<td><strong>Sporadic forms</strong></td>
<td>370</td>
<td>78</td>
</tr>
<tr>
<td><strong>Tot. 580</strong></td>
<td></td>
<td><strong>Tot. 150</strong></td>
</tr>
</tbody>
</table>
We perform biochemical and genetic analyses for patients with atypical form of HUS and TTP. For information and for other questions and for any other questions, please contact:

Coordinator: Prof. Giuseppe Remuzzi
Clinical Research Center for Rare Diseases Aldo e Cele Daccò
Mario Negri Institute for Pharmacological Research
Via G.B. Camozzi, 3 - 24020 Ranica (BG) Italy
Phone: +39-35-4535304
Fax: +39-35-4535373
E-mail: raredis@marionegri.it

Contact persons: Elena Bresin, MD
Erica Daina, MD
Sara Gamba, RN