Bologna, March 7th 2018

# Undiagnosed Rare Disease Network Italy
# Update of the Bergamo's center


## Paraskevas Iatropoulos

Centro di Ricerche Cliniche per le Malattie Rare "Aldo e Cele Daccò"
IRCCS Istituto di Ricerche Farmacologiche Mario Negri
Bergamo, Italia


# THE MARIO NEGRI INSTITUTE FACILITIES

**1963**
Mario Negri Milano

*2007*
*new headquarters*

**1983**
Laboratori Negri Bergamo

*2010*
*new*
*headquarters*

**1992**
Clinical Research Center for
Rare Diseases
*Aldo e Cele Daccò*

# A Center dedicated to research projects

***Day Hospital & Outpatient clinics***

4 Nephrologists
2 Geneticists
1 Neurologist
1 Rheumatologist
1 Dermatologist

***Laboratories***

*Lab. Genetics (NGS)*
Lab. Biochemical studies
Microscopy
…

***Clinichal Research Center for Rare Diseases Istituto Mario Negri***

***Animal Care Unit***

*Mice & rats*

***Biomedical Engineering & Informatics***

***Lab. of Biostatistics***

# The Clinical Clinical Research Center for Rare Diseases is the Coordinator of the Regional Network of RDs in Lombardy

**46 Hospitals**
**642 Rare Diseases**
**60000 Patients in Lombardy**

Presidi regionali

Presidi regionali

Presidi regionali

Presidi regionali

**Registro Regionale ReLMaR**

**Centro di Coordinamento**

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

**Data Set Condiviso**

**Istituto Superiore di Sanità**

**Registro Nazionale**

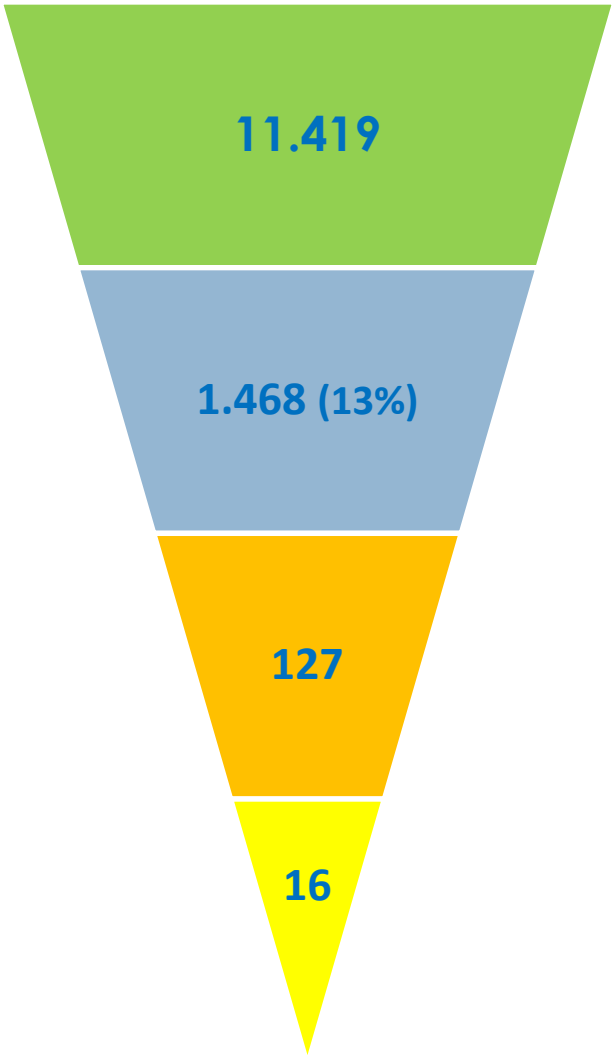
Analisi dei dati

Reports periodici

# ONGOING REGISTRIES

| | START DATE | NUMBER OF CASES | RELATED PROJECTS |
|---|---|---|---|
| Registry of recurrent and familial HUS and TTP | 1996 | 1260 | |
| Registry of MPGN / C3 Glomerulopathy | 2006 | 300 | |
| Registry of FSGS/SRNS | 2007 | 315 | |
| Regional Registry of Rare Diseases (Lombardy) | 2007 | 51.319 (Lombardy) 3.536 (other Regions) | |

# THE DATABASE OF THE DOCUMENTATION CENTRE FOR RARE DISEASES (1993-2017)




RARE DISEASE CASES SUBMITTED TO MULTIDISCIPLINARY TEAM EVALUATION
- 34% LOMBARDY
- 66% OTHER ITALIAN REGIONS

UNDIAGNOSED CASES ADDRESSED TO REVALUATION AT REFERENCE CENTRES

MONITORED CASES
*(UNDIAGNOSED FOLLOWING CAREFUL PERIODIC REVALUATIONS)*

CASES SELECTED FOR GENOMIC AND FUNCTIONAL ANALYSES

- 1 family including 2 patients

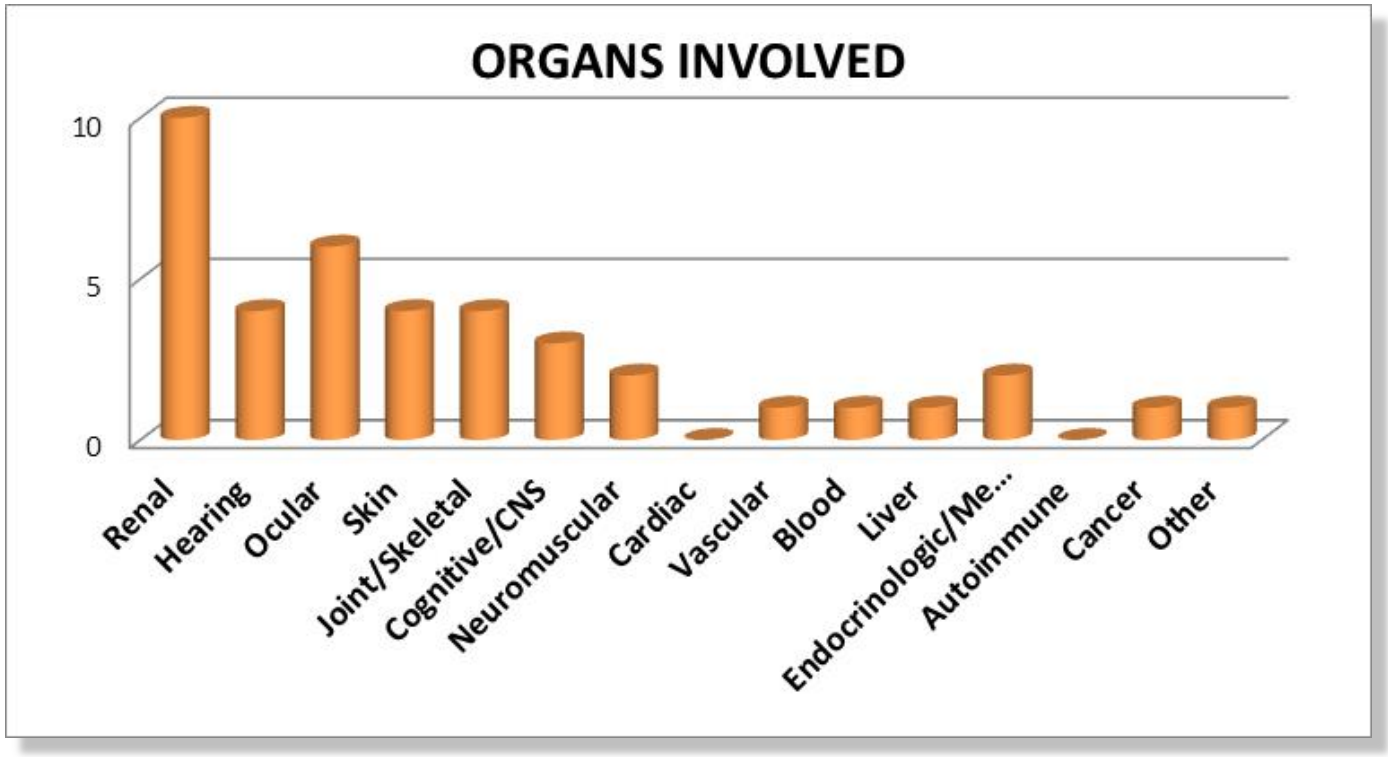
NIH Undiagnosed Diseases Program

- 15 unrelated families (cases) including 31 patients
  - 12 cases with peculiar complex phenotype
  - 3 cases with clinical but not molecular diagnosis

udnp ITALY UnDiagnosed Network Program Italy

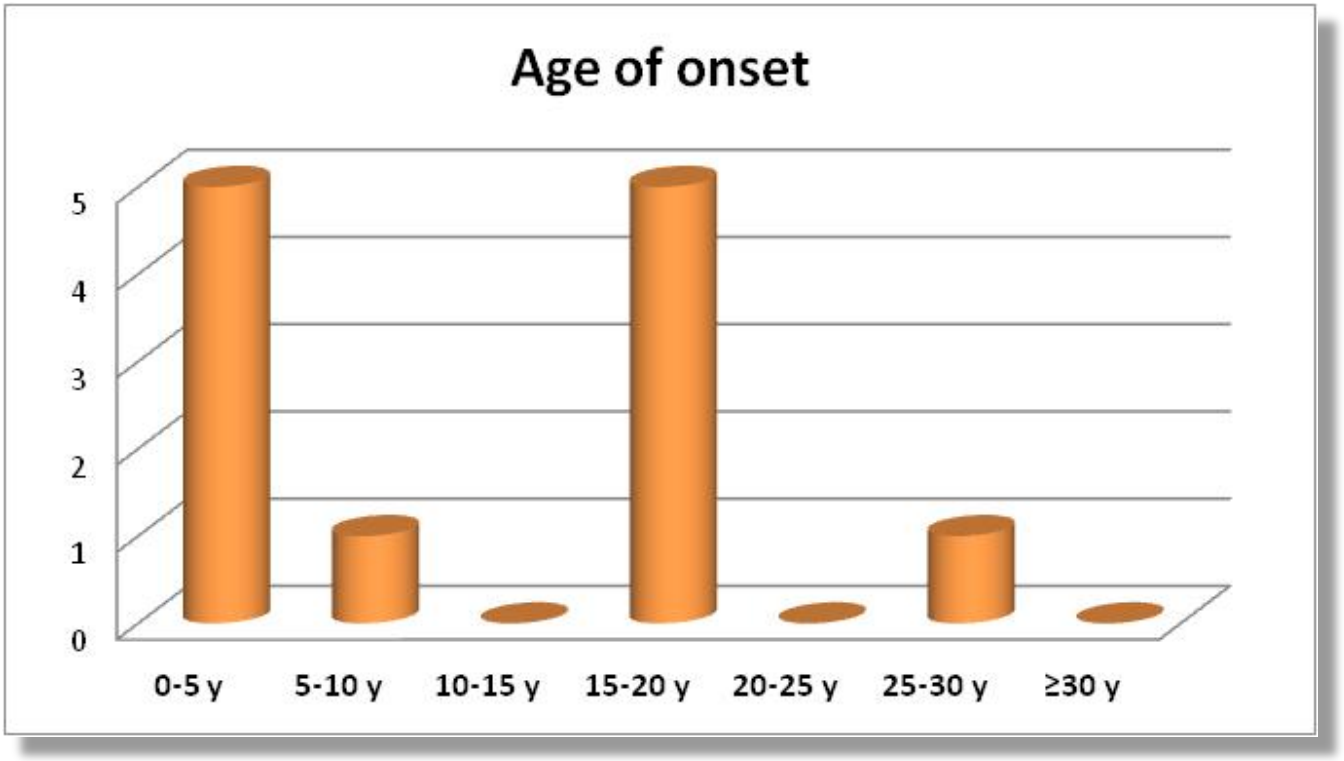
# Characteristics of patients with peculiar complex phenotype

All 12 cases with peculiar phenotype show multi-organ involvement.



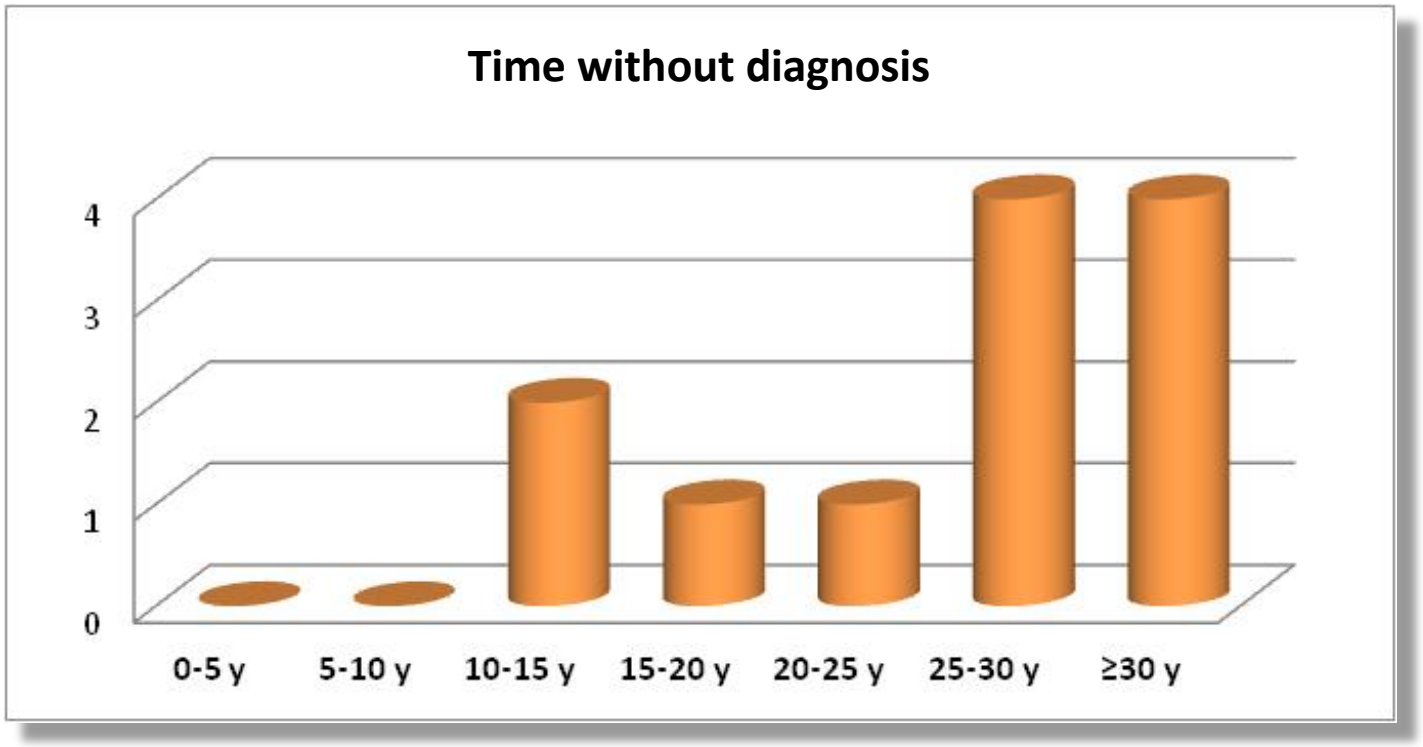
# Our Undiagnosed cases usually developed the disease in childhood or adolescence

Disease onset in patients with multi-organ involvement occurs mainly in children and adolescents (mean ±s.d. age of onset of 10 ±9 years).



# Undiagnosed cases are characterized by long diagnostic delay

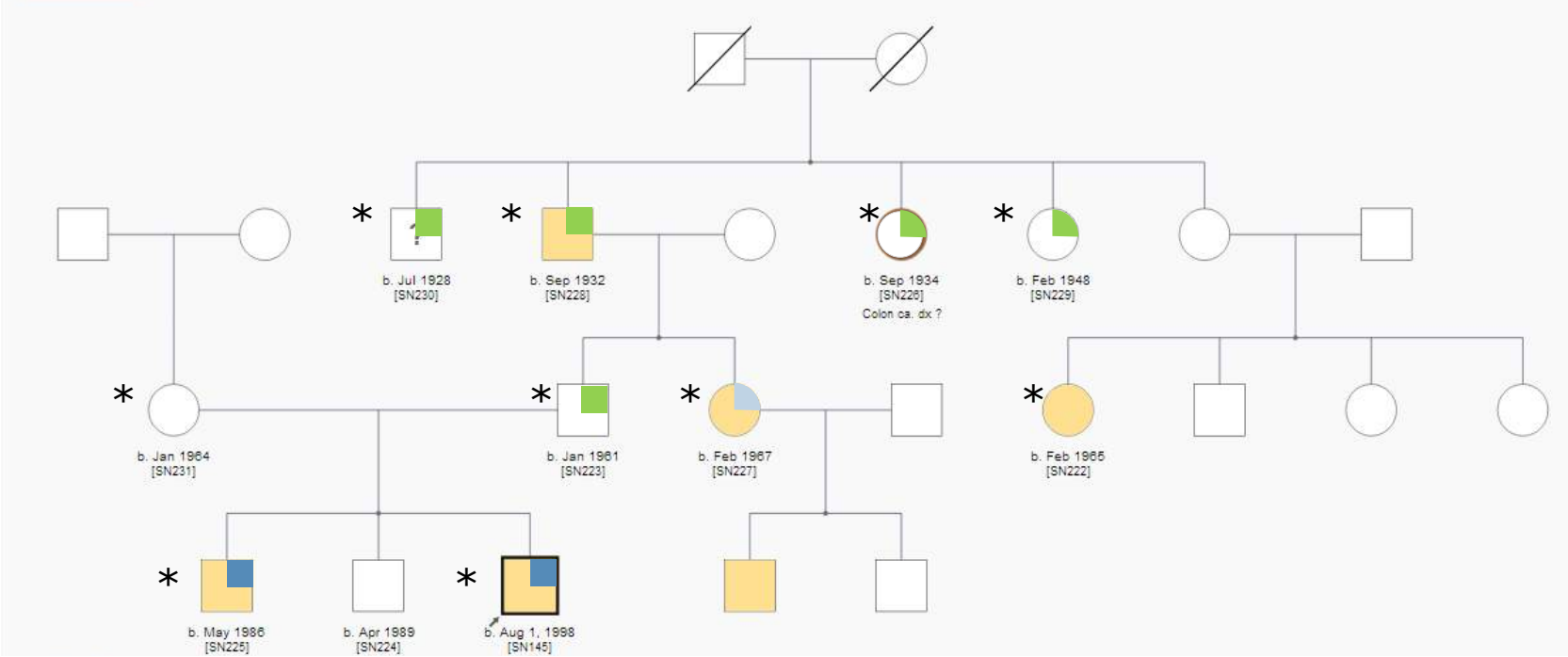
All cases with multi-organ involvement have not received a conclusive diagnosis after a mean (±s.d.) time of 27 (±10) years from disease onset.



| Family CODE | Affected (collected samples) | Unaffected (collected samples) | UDN Italy (ISS) DB | UDN Internat. DB | Exome |
|---|---|---|---|---|---|
| 1.SO | 5 (5) | 6 (6) | + | | Ongoing |
| 2.TR | 1 (1) | 3 (3) | + | + | Ongoing |
| 3.DI | 1 (1) | 2 (2) | + | + | |
| 4.MAST | 1 (1) | 2 | + | + | Ongoing |
| 5.MA | 1 (1) | 2 (2) | + | | Ongoing |
| 6.IA | 1 (1) | 3 (3) | + | + | |
| 7.PA | 3 (3) | 5 (5) | + | | |
| 8.DO | 9 (9) | 1 (1) | + | | |
| 9.CI | 1 (1) | 3 (3) | + | | |
| 10.AM | 1 | - | + | | |
| 11.GU | 1 | - | + | | |
| 12. SOL | 1 (1) | 2 (2) | + | | |
| 13. FU | 1 (1) | 3 (3) | + | | |
| 14.SI * | 2 (2) | 1 (1) | | | |
| 15.LO | 2 (2) | - | | | |
| **Total** | **31 (29)** | **33 (31)** | **13** | **4** | **2** |

***** Diagnosed as X-linked Alport syndrome, COL4A5-associated
(previous genetic analysis of COL4A3-5 genes with negative results)

# SN145 family




Childhood-onset Nephropathy

Severe myopia &
Retinal pigmentary abnormalities

Cataract at 45 y-o

Late-onset hearing impairment

* DNA available

# SN145- Investigations

- Alport and Alport-like genes *COL4A5*, *COL4A3*, *COL4A4* and *MYH9:*

  no mutations

- Genetic panel for isolated and syndromic glomerulopathies (93 genes):

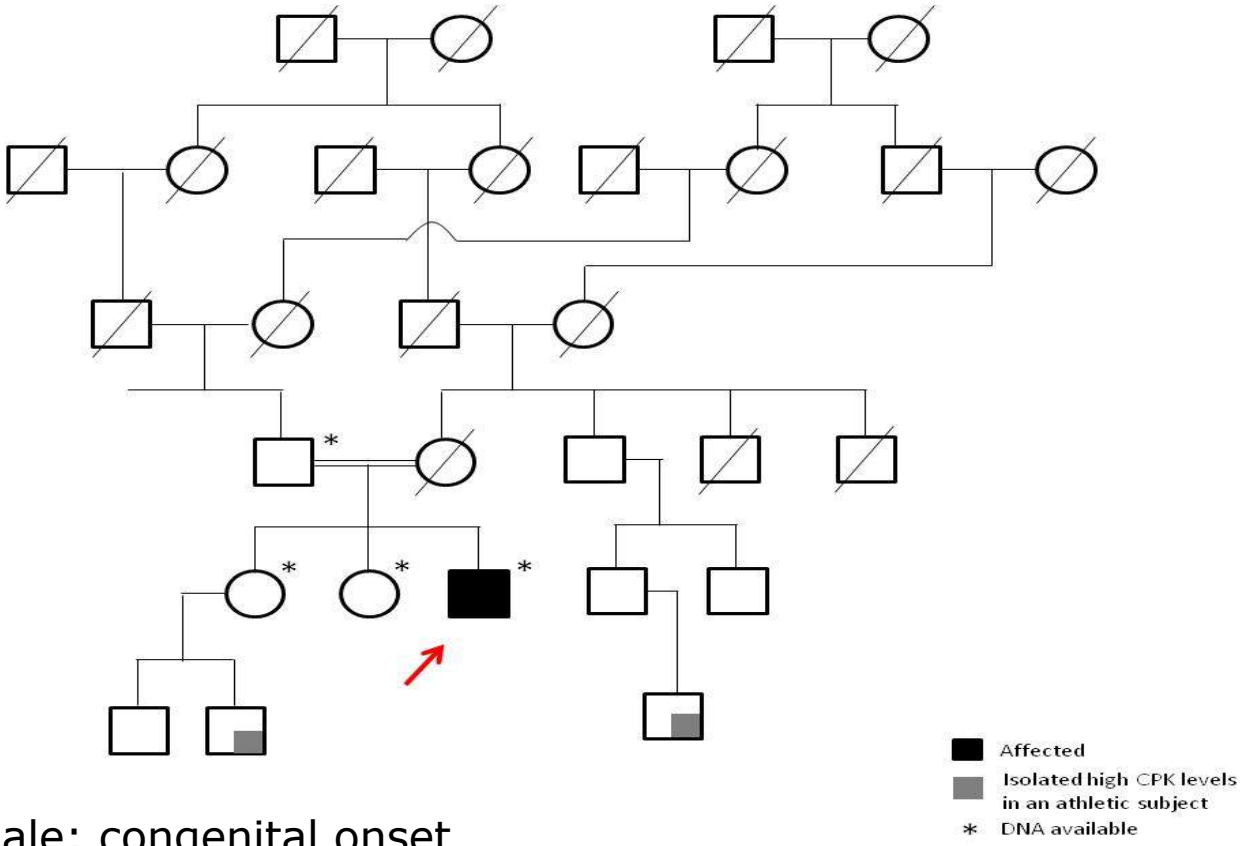
  no mutations

- Analysis of Exome sequecing ongoing

# Results of the Exome Seq in SN145 pedigree

| Exome sequencing | Number of variations |
|---|---|
| Total rare variants (MAF <0.01) putative functional variants identified in the proband | 353 |
| … very rare (MAF < 0.001) functional variants identified in the proband | 175 |
| … shared with other affected members of the family | 14 |
| … predicted to be damaging | 11 |

# TRGI168




- 49 y.o. male; congenital onset
- No family history for renal, ocular or neural diseases
- Family history for isolated high blood CPK levels
- Parents' consanguinity

# TRGI168 – Clinical signs

- Retinal cone-rod degeneration, color blindness, optic nerve atrophy and reduced visual acuity (1/10) diagnosed at 5 y of age
- Muscle irritability/fasciculations and high CPK blood levels at age 20
- Non-alcoholic steatohepatitis at age 32 y
- Chronic subdural hematoma at age 35 y
- Linear morphea (face) with negative inflammatory indexes at 35 y
- Mixed glomerular-tubular nephropathy and renal impairment at 36 y (ESRD at 45 y)
- Papillary thyroid carcinoma at 47 y

# TRGI168 - Investigations

- Genetic panel for isolated and syndromic glomerulopathies (93 genes):

**homozygous FAT1 p.R1953T (c.5858G>C)**

- Not present in public databases (AF=0 in 1000 Genomes, 6500 ESP e ExAC).
- Predicted damaging in 8 out of 10 software/algorithms used in our laboratory including Polyphen (HVAR=0.984 => 'probably damaging') and CADD (15.2).

| Feature | Previous cases* | Present case |
|---|---|---|
| **Urinary Tract Abnormalities** | 4/4 | + |
| - Proteinuria | 4/4 | + |
| - Nephrotic syndrome | 4/4 | - |
| - Hematuria | 4/4 | + |
| - Chronic kidney disease | 1/4 | + |
| - Tubular abnormalities | 4/4 | + |
| - Vescicoureteral reflux | 1/4 | - |
| **Neoplastic disorders** | 2/4 | + |
| - Ewing sarcoma | 1/4 | - |
| - Hodgkin lymphoma | 1/4 | - |
| - Papillary thyroid carcinoma | 0/4 | + |
| **Central Nervous System Abnormalities** | 2/4 | - |
| - Hydrocephalus | 1/4 | - |
| - Intellectual disability | 1/4 | - |
| - Pachygyria | 1/4 | - |
| - Blepharoptosis | 1/4 | - |
| **Ocular Abnormalities** | 0/4 | + |
| - Optic nerve atrophy | 0/4 | + |
| - Retinal cone-rod degeneration | | |
| - Blindness | | |
| **Muscular abnormalities** | | |
| - Fasciculation / muscle hyper-irritability | | |
| - High blood CK levels | | |
| **Miscellaneous** | | |
| - Pulmonary artery stenosis | 1/4 | - |
| - Linear morphea (face) | 0/4 | + |
| - Chronic subdural hematoma | 0/4 | + |
| - Primary hyperparathyroidism | 0/4 | + |
| - Nonalcoholic steatohepatitis | 0/4 | + |

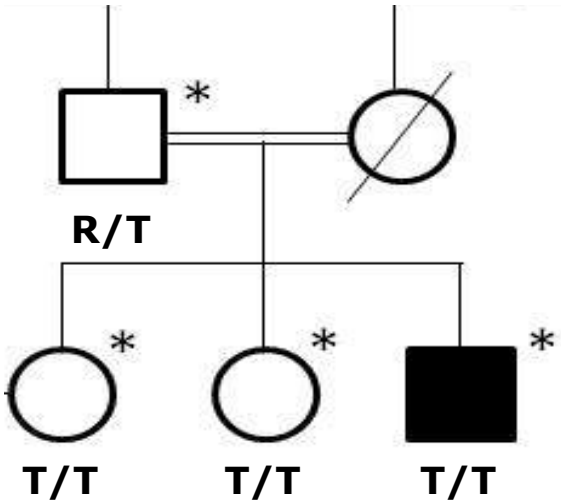
*Gee, Nat Commun 2016;7:10822.

OPEN ACCESS Freely available online PLOS | GENETICS

Deregulation of the Protocadherin Gene *FAT1* Alters Muscle Shapes: Implications for the Pathogenesis of Facioscapulohumeral Dystrophy

Nathalie Caruso[1], Balàzs Herberth[1], Marc Bartoli[2], Francesca Puppo[2], Julie Dumonceaux[3], Angela Zimmermann[1], Simon Denadai[1], Marie Lebossé[1], Stephane Roche[2], Linda Geng[4], Frederique Magdinier[2], Shahram Attarian[2,5], Rafaelle Bernard[2,6], Flavio Maina[1], Nicolas Levy[2,6], Françoise Helmbacher[1]*

# TRGI168 –FAT1 R1953T

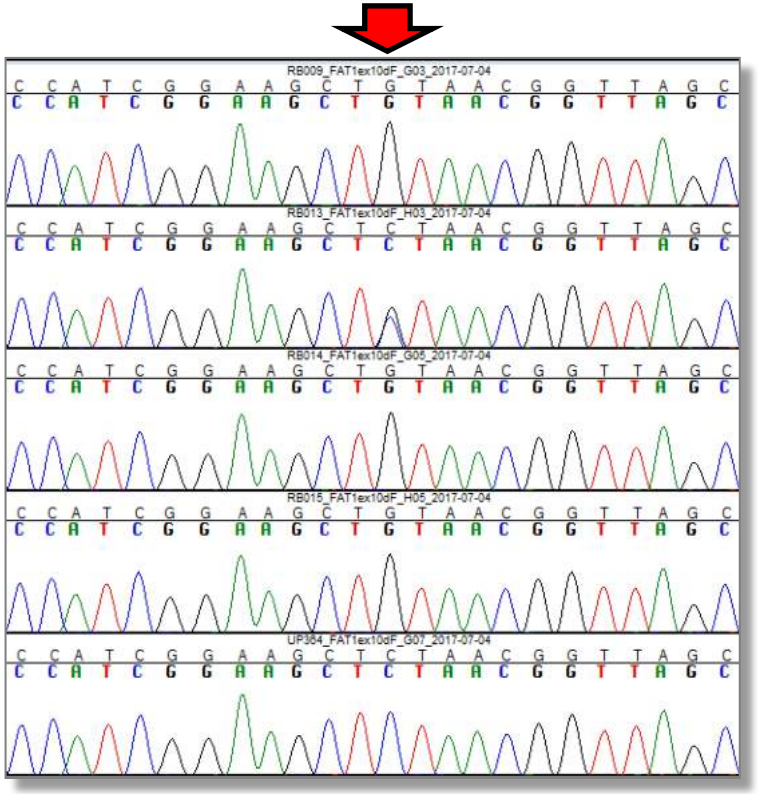



- The homozygous FAT1 R1953T variant is also present in both older healthy sisters
- Is the FAT1 R1953T an incidental finding not associated with the disease?
- Is it associated with the disease and the disease is not monogenic?

# Results of the Exome Seq in TRGI168 and his two sisters

| Exome sequencing | Number of variations |
|---|---|
| Total Homozygous variants identified in the affected patient that are heterozygous/wild type for unaffected sisters | 27,941 |
| … Functional variants | 654 |
| … Functional variants with MAF < 0.001 | 14 |
| … Predicted to be damaging | 8 |

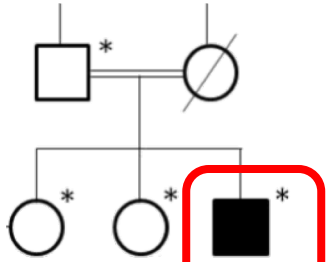
# FAT1 variants was not detected by the Whole Exome Sequencing


The FAT1 variant was identified with the NGS glomerulopathy panel and confirmed by Sanger sequencing.

It was not detected by Whole Exome Sequencing.

# Likely Pathogenetic Variants in genes associated with diseases that overlap with the patient's phenotype



| Gene | Aa change | Frequency in ExAC population | Damage prediction§ | REF | ALT | RB014 | RB015 | RB009 | Known related disease |
|---|---|---|---|---|---|---|---|---|---|
| **POC1B** chr12:89492072 | p.R106* | 0 | 4/4 | G | A | GA | GA | AA | **Cone-rode dystrophy:**<br>- Autosomal recessive<br>- Reduced visual acuity<br>- Color vision defects<br>- Altered electroretinography<br>- Polycystic kidney |
| **HSD17B10** chrX:53433778 | p.G46S | 0 | 3/10 | C | T | CT | CC | T | **HSD10 mitochondrial disease:**<br>- X-Linked Dominant<br>- Highly variable phenotype and severity<br>- Hearing loss<br>- Early onset<br>- Visual loss (Optic atrophy, Retinal degeneration)<br>- Intellectual disability, Hypotonia, Seizures, Spasticity, Cortical atrophy, hypotonia<br>- Progressive neurodegeneration |
| **TTN** chr2:178745715 | p.E5562V | 0 | 6/8 | T | A | TA | TT | AA | **Limb-girdle muscular dystrophy 2J:**<br>- Autosomal recessive<br>- Muscle weakness<br>- EMG: myopathic changes<br>- N or ↑ serum creatine kinase.<br>- No: cardiomyopathy or facial muscle involvement<br>- Severe disability, Loss of ambulation<br>- Muscle biopsy: dystrophic changes and fatty infiltration. |

§Damage prediction software: SIFT, Polyphen2 HVAR, Polyphen2 HDIV, LRT, Mutation Taster, Mutation Assessor, GERP, CADD, SiPhy and FATHMM.

# Putative Damaging variants in genes not associated with features of the patient's phenotype

| Gene | Aa change | Frequency in ExAC population | PS | Info/Known related disease |
|---|---|---|---|---|
| **STRA8** chr7:135240663 | p.F69V | 0 | PS=9/10 | **Code for:** Stimulated By Retinoic Acid 8<br>**Function**: Meiosis-Inducer<br>**Disease:** Reproductive system disorder (spermatogenesis and oogenesis). |

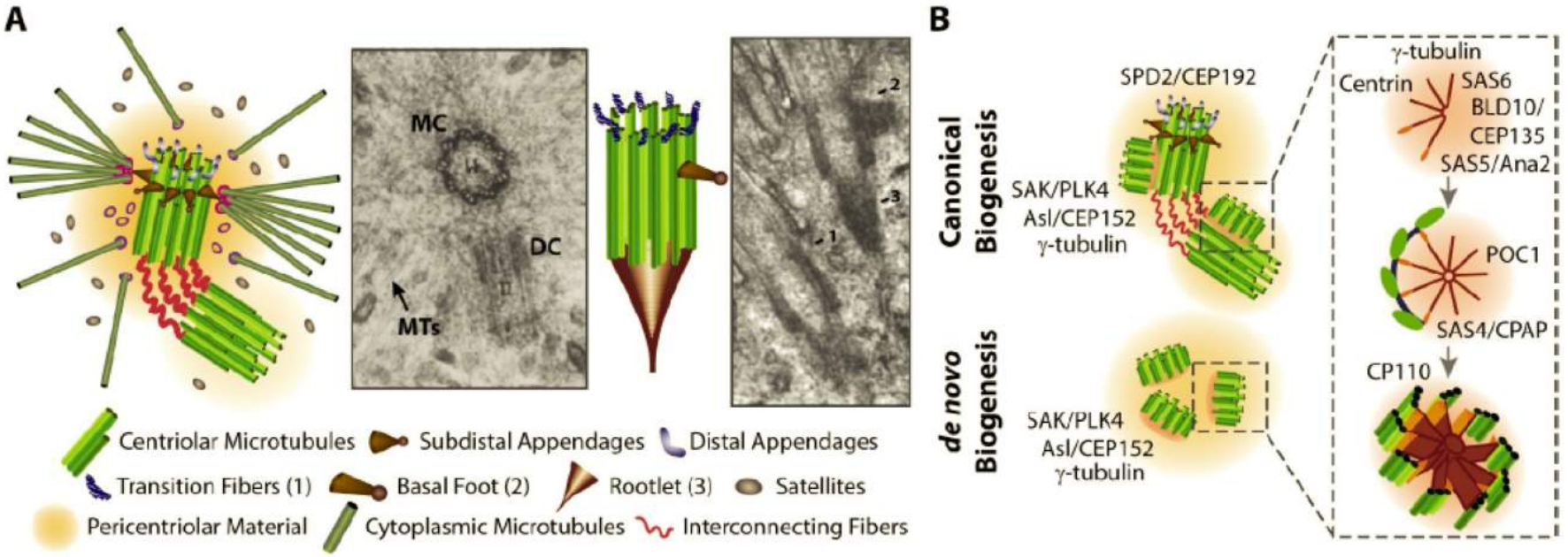
# Putative Damaging variants in genes not associated any disease

| Gene | Aa change | Frequency in ExAC population | PS | Protein and function |
|---|---|---|---|---|
| **GCC2** chr2:108469672 | p.D115H | 0.000008 | PS=9/10 | **Code for**: GRIP AND COILED-COIL DOMAIN-CONTAINING PROTEIN 2 **Function:** vesicular transport between endosomes and the Golgi |
| **FCGBP** chr19:39906191 | p.V1190A | 0 | PS=3/7 | **Code for:** Fc FRAGMENT OF IgG-BINDING PROTEIN **Function:** may be involved in maintenance of the mucosal structure. |
| **ASB11** chrX:15297648 | p.V99L | 0.00007 | PS=7/10 | **Code for:** ANKYRIN REPEAT- AND SOCS BOX-CONTAINING PROTEIN 11 **Function:** Neurodevelopment; misexpression of ASB11 caused impaired neurogenesis and myogenesis in zebrafish |
| **CFAP47** chrX:36366986 | p.I3015T | 0 | PS=6/10 | **Code for:** cilia and flagella associated protein 47 **Function**: not available |

# POC1B mutations and human disease

- POC1B was first associated with cone-rod retinal dystrophy in 2014
- Five pedigrees described with mutations in POC1B so far.
- All patients present cone-rod retinal dystrophy.
- One (1/5) pedigree presents polycystic kindey disease.

*Beck BB ,Hum Mutat 2014*
*Roosing S, Am J Hum Genet 2014*
*Durlu, JAMA Ophthalm 2014*
*Jin X, Ophthalm Genet 2018*




*Carvalho-Santos Z, JCB 2011*

| Features present in the case | FAT1 | POC1B | HSD17B10 | TTN |
|---|---|---|---|---|
| **Urinary Tract Abnormalities** | Resolved ? | Resolved | - | - |
| - Proteinuria | Resolved ? | - | - | - |
| - Hematuria | Resolved ? | - | - | - |
| - Chronic kidney disease | Resolved ? | Resolved | - | - |
| - Tubular abnormalities | Resolved ? | Resolved | - | - |
| - Renal cyst | - | Resolved | - | - |
| **Neoplastic disorders** | Resolved ? | - | - | - |
| - Papillary thyroid carcinoma | - | - | - | - |
| **Central Nervous System Abnormalities** | - | - | - | Resolved |
| - Chronic subdural hematoma | - | - | - | Resolved |
| **Ocular Abnormalities** | - | Resolved | Resolved? | - |
| - Optic nerve atrophy | - | | Resolved? | - |
| - Retinal cone-rod degeneration | - | Resolved | - | - |
| - Blindness | - | Resolved | Resolved? | - |
| - Colorblindness | - | Resolved | - | - |
| **Muscular abnormalities** | - | - | - | Resolved |
| - Fasciculation / muscle hyper-irritability | - | - | - | - |
| - High blood CK levels | - | - | - | Resolved |
| **Miscellaneous** | - | - | - | - |
| - Linear morphea (face) | - | - | - | - |
| - Primary hyperparathyroidism | - | - | - | - |
| - Nonalcoholic steatohepatitis | - | - | - | - |

# Thanks!

**IRCCS – Istituto di Ricerche Farmacologiche *Mario Negri***

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Dr. Samantha Solini
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Dr. Manuela Curreri
Ing. Laura Bottanelli
Dr. Elena Bresin
Sara Gamba

Dr. Ariela Benigni
Prof. Giuseppe Remuzzi

**Undiagnosed Disease Network Program**

All partners from Torino, Roma, L'Aquila, Ferrara and Udine

Partially funded by
**Undiagnosed Rare Diseases: a joint Italy - USA project**

*Jackson Pollock, Blue Poles 1952*

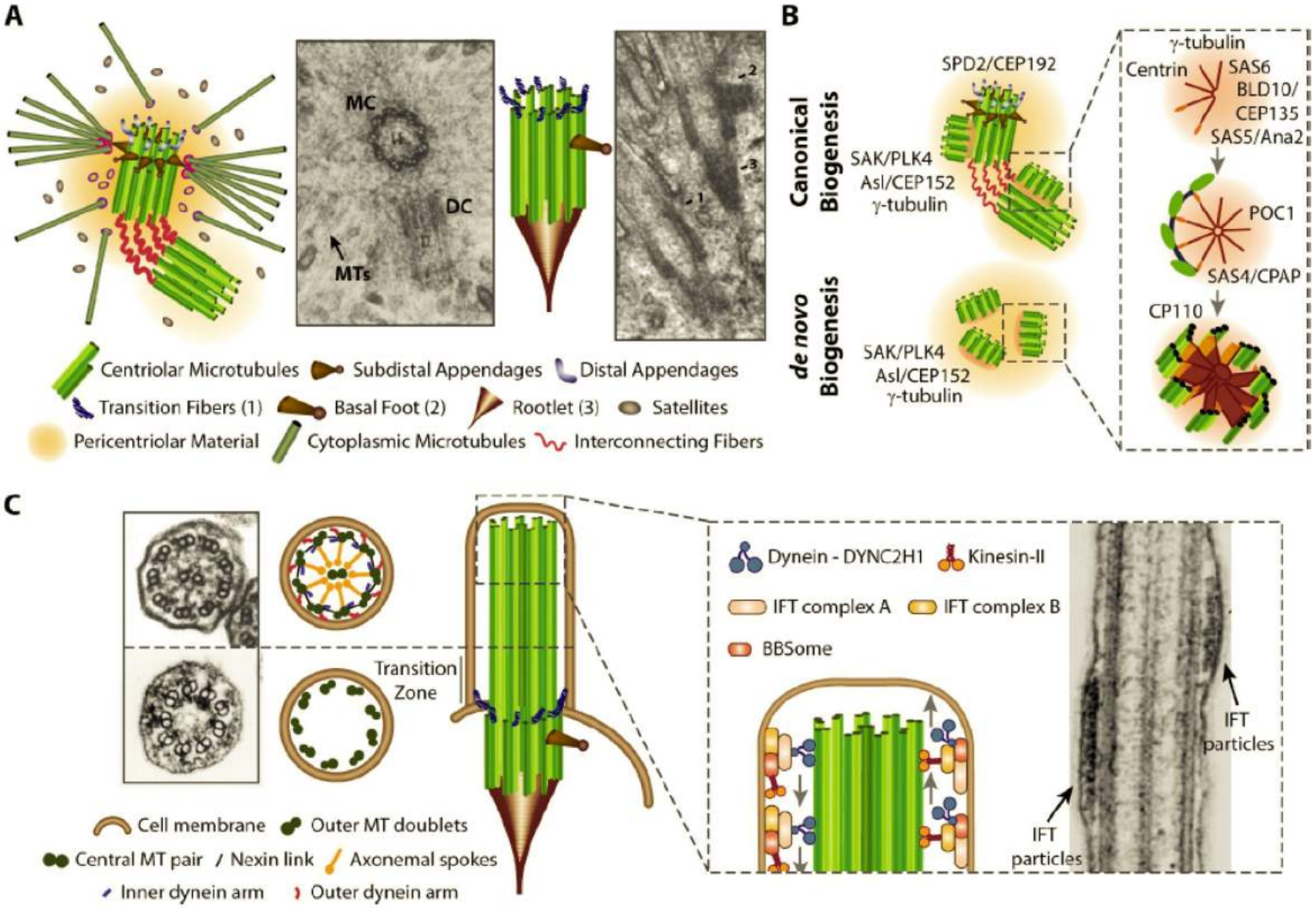
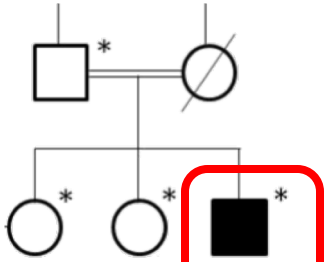



Figure 1. **Structure and biogenesis of centrosomes and cilia.** (A) On the left, a schematic and EM micrograph (reproduced from Vorobjev and Chentsov, 1982) of an animal prometaphase centrosome composed of mother (MC) and daughter (DC) centriole arranged in an orthogonal fashion. The mother centriole harbors subdistal and distal appendages. On the right, a schematic and EM longitudinal section (reproduced with permission from the *Journal of Cell Science;* Sorokin, 1968) of a basal body from rat lung multiciliated cells bearing rootlets and lateral/distal appendages. (B) Key regulatory and structural components in CBB biogenesis (canonical [top] and de novo [bottom]; Azimzadeh and Marshall, 2010). (C) Schematic of the basal body, when docked at the cell membrane and growing the axoneme of cilia/flagella. EM cross section of tracheal motile cilia (top: reproduced from Satir and Dirksen (1985) in *Handbook of Physiology* with permission from the American Physiology Association) and renal nonmotile primary cilia (bottom: image courtesy of H. Zentgraf, German Cancer Research Center, Heidelberg, Germany). Cilia/flagella are assembled via the intraflagellar transport (IFT) system. EM longitudinal section of the *Chlamydomonas* flagellum adapted from Pedersen et al. (2006) with permission from Elsevier.

| Features present in the case | FAT1 | POC1B | HSD17B10 | TTN | ADAMSTL2 | LRP1B | INPP5E |
|---|---|---|---|---|---|---|---|
| **Urinary Tract Abnormalities** | Resolved ? | Resolved | - | - | - | - | ? |
| - Proteinuria | Resolved ? | - | - | - | - | - | - |
| - Hematuria | Resolved ? | - | - | - | - | - | - |
| - Chronic kidney disease | Resolved ? | Resolved | - | - | - | - | ? |
| - Tubular abnormalities | Resolved ? | Resolved | - | - | - | - | ? |
| - Renal cyst | - | Resolved | - | - | - | - | ? |
| **Neoplastic disorders** | Resolved ? | - | - | - | - | Resolved | - |
| - Papillary thyroid carcinoma | - | - | - | - | - | Resolved | - |
| **Central Nervous System Abnormalities** | - | - | - | Resolved | - | - | - |
| - Chronic subdural hematoma | - | - | - | Resolved | - | - | - |
| **Ocular Abnormalities** | - | Resolved | Resolved? | - | - | - | ? |
| - Optic nerve atrophy | - | | Resolved? | - | - | - | ? |
| - Retinal cone-rod degeneration | - | Resolved | - | - | - | - | ? |
| - Blindness | - | Resolved | Resolved? | - | - | - | ? |
| - Colorblindness | - | Resolved | - | - | - | - | - |
| **Muscular abnormalities** | - | - | - | Resolved | - | - | - |
| - Fasciculation / muscle hyper-irritability | - | - | - | - | - | - | - |
| - High blood CK levels | - | - | - | Resolved | - | - | - |

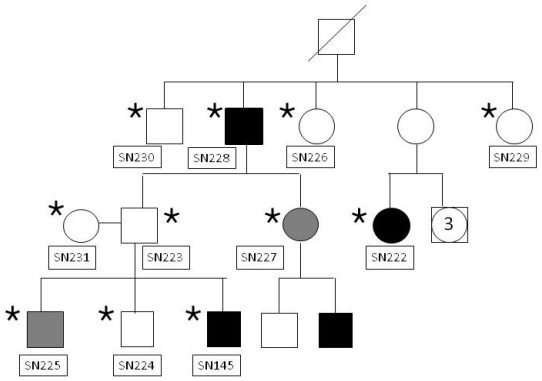
# Damaging variants with phenotypic expression

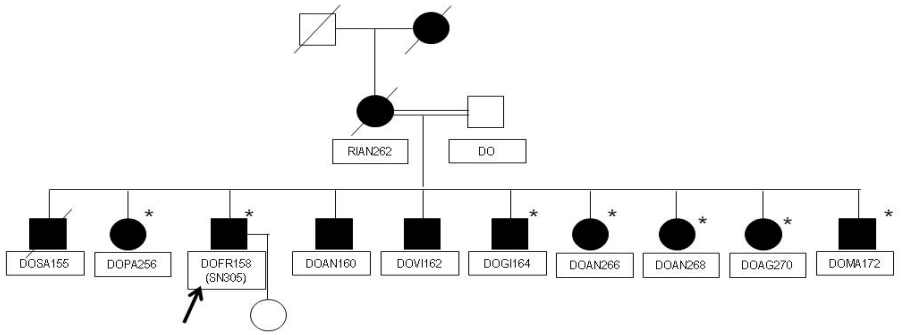


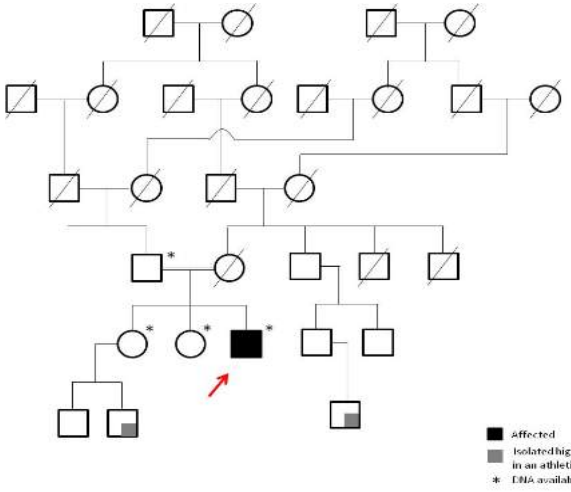
| Gene | Aa change | Frequency in ExAC population | Damage prediction§ | CADD | REF | ALT | RB014 | RB015 | RB009 | Known related disease |
|---|---|---|---|---|---|---|---|---|---|---|
| **ADAMTSL2** chr9:133554507 | p.V364I | 0 | 2/10 | 0.04 | G | A | GA | GG | AA | **Geleophysic dysplasia 1 (AR)**<br>- Short stature<br>- Cardiovascular involvement<br>- Airways stenosis<br>- Hepatomegaly<br>- Skeletal abnormalities<br>- Thickened skin<br>- Neuro: Developmental delayand Seizures |
| **LRP1B** chr2:140598659 | p.R2389T | 0 | 9/10 | 24.5 | C | G | CC | CC | CG | Down-expression of LRP1B as been observed in renal cell carcinoma and thyroid cancer |
| **INPP5E** chr9:136434088 | p.D328A | 0 | 9/10 | 22.9 | T | G | TT | TT | TG | **Joubert syndrome (AR):**<br>- Macrocephaly<br>- Ocular: optic nerve and retinal anomalies.<br>- Facial dysmorphism<br>- Renal cysts<br>- Neuro: Mental retardation, Ataxia, Hypotonia, brainstem anomalies, cerebellar vermis hypoplasia, Behavioral manifestations<br>-Variable phenotype<br><br>-**MORMS (AR):**<br>-Mental retardation<br>-Truncal obesity<br>-Retinal dystrophy/ Cataract/ blindness<br>-Micropenis syndrome |

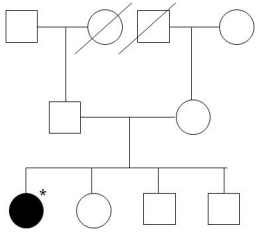
§Damage prediction software: SIFT, Polyphen2 HVAR, Polyphen2 HDIV, LRT, Mutation Taster, Mutation Assessor, GERP, CADD, SiPhy and FATHMM.

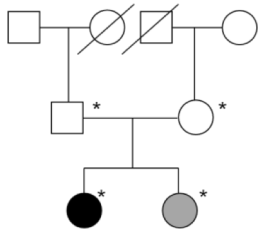
# Examples of Cases registered on Phenotips platform

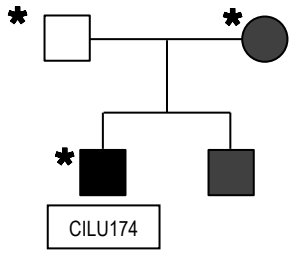


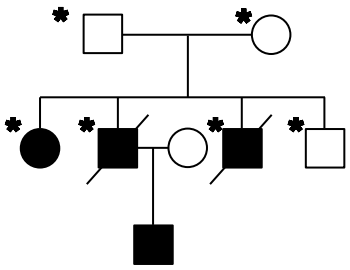



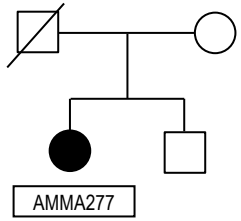



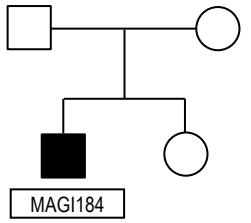









*We did not find likely pathogenetic variants in any gene associated with glomerular or tubular nephropathy.*

# Criteri per valutare il contributo di ogni centro – Punti di discussione

- Valutare ogni caso (trio sporadico/famiglia) e assegnare un punteggio

| Criterio | Punti |
|---|---|
| Caso grave ad esordio precoce | 1 |
| Caso con consanguineità (AR) / autosomico dominante con LOD score atteso ≥2 | 1 |
| Caso con fenotipo che non corrisponde a nessuna sindrome/malattia nota | 1 |

- Per considerare il peso del centro sommare il punteggio di tutti i suoi casi

- Riconoscere un contributo per il responsabile della stesura dei progetti

# Relative Role of Genetic Complement Abnormalities in Sporadic and Familial aHUS and Their Impact on Clinical Phenotype

Marina Noris,* Jessica Caprioli,* Elena Bresin,* Chiara Mossali,* Gaia Pianetti,* Sara Gamba,* Erica Daina,* Chiara Fenili,* Federica Castelletti,* Annalisa Sorosina,* Rossella Piras,* Roberta Donadelli,* Ramona Maranta,* Irene van der Meer,*† Edward M. Conway,‡ Peter F. Zipfel,§ Timothy H. Goodship,‖ and Giuseppe Remuzzi*¶

**Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases, Aldo e Cele Daccò, Villa Camozzi, Ranica, Bergamo, Italy; †Department of Internal Medicine, Division of Nephrology, University Hospital Maastricht, Maastricht, The Netherlands; ‡Centre for Blood Research, Life Sciences Centre, University of British Columbia, Vancouver, Canada; §Leibniz Institute for Natural Products Research and Infection Biology, Jena, Germany; ‖Institute of Human Genetics, Newcastle University, Newcastle upon Tyne, United Kingdom; and ¶Department of Nephrology and Dialysis, Azienda Ospedaliera, Ospedali Riuniti di Bergamo, Bergamo, Italy*

was achieved in the majority of plasma-treated episodes. On the other hand, results were less favorable for patients with *CFI* mutations, despite the fact that CFI is a plasma complement regulatory protein as well. Data on treatment of patients with C3 mutations are scarce (8). Plasma treatment could remove mutant hyperactive C3 and also provide regulatory plasma proteins to counteract complement activation induced by mutant C3. In fact, in our series, response to plasma treatment in patients with C3 mutations was comparable to that of patients with *CFH* mutations. In patients with *MCP* mutations, plasma therapy did not affect outcome, which is consistent with the fact that MCP is not a circulating protein (35).

Contrary to other reports (34,36), we found no difference in response to plasma infusion versus plasma exchange. The rationale behind using plasma exchange instead of infusion is that plasma exchange also removes mutant circulating molecules (37) and CFH autoantibodies and allows administration of higher volumes of plasma without the risk of fluid overload.

Of note, results of response to plasma in patient subgroups and the comparison between plasma infusion/exchange are limited by the retrospective nature of our analyses and by different approaches to plasma treatment in different centers (including volume of plasma, delay between diagnosis, and treatment). Recent expert opinion papers (23,34) recommended, as a practical point, empiric plasma exchange in episodes of aHUS, since genetic information is usually not available when the patient is presenting with aHUS.

These findings and previous data emphasize that kidney transplantation alone in aHUS is severely compromised by the risk of recurrence (27,38), especially in patients with *CFH* and *CFI* mutations and to a lesser degree in patients with C3 mutations. Because CFH, CFI, and C3 are plasma proteins synthesized predominantly by the liver, kidney transplantation alone does not correct the defect. As reported previously, simultaneous liver–kidney transplantation prevented recurrences in patients with *CFH* mutations but had a high mortality rate (23,24,39,40).

Kidney graft outcome was favorable in patients with MCP mutations, none of whom had disease recurrence in the graft, as expected, considering that MCP is a transmembrane protein highly expressed in the kidney.

Of note, two patients with *THBD* mutations developed HUS after kidney transplant (one *de novo* and one recurrence), which is unexpected, because thrombomodulin is an endothelial transmembrane protein like MCP. However, a soluble thrombomodulin form (sTM) circulates in plasma and possesses similar functional activities as membrane-bound thrombomodulin. Treatment with sTM attenuated ischemia–reperfusion renal injury in the rat (41). One could speculate that, because of dysfunctional sTM, in *THBD*-mutated recipients, the grafts were not sufficiently protected against complement activation and prothrombotic stimuli triggered by ischemia–reperfusion injury.

Plasma prophylaxis has been proposed as a strategy to prevent disease recurrence (42,43). In our series, three patients with *CFH* mutations, one with a *CFI* mutation, and one with a C3 mutation received plasma prophylaxis after transplant and had no recurrence. However, these patients are plasma dependent, which calls for alternative, more specific strategies. In contrast, plasma was minimally effective in treating ongoing recurrences in transplanted patients with *CFH*, *CFI*, or C3 mutations, because remission was achieved in only 1 of 10 plasma-treated patients.

Screening for all genetic aHUS susceptibility factors is a time-consuming procedure; however, results of this study emphasize the clinical importance of such screening, because patients on dialysis with single mutations in *MCP* would safely benefit from a kidney transplant. Finally, showing the complement abnormalities underlying aHUS opens perspectives for specific treatment of the disease with complement inhibitors. Eculizumab, a human anti-C5 monoclonal antibody, induced remission of aHUS in recent case reports (44–48) and could represent the future for treatment of acute episodes and prevention of recurrences in the graft.

**Appendix**

*International Registry of Recurrent and Familial HUS/TTP*

Coordinators: G. Remuzzi, MD, P. Ruggenenti, MD (Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," Ranica, Bergamo, and Division of Nephrology and Dialysis, "Ospedali Riuniti" Azienda Ospedaliera, Bergamo), M. Noris, Chem. Pharm. D. (Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," Ranica, Bergamo).

Investigators—Italy: M. Garozzo, MD (Division of Nephrology and Dialysis, "S. Marta e S. Venera" Hospital, Acireale, Catania); F. Casucci, MD, F. Cazzato, MD (Division of Nephrology, "Miulli" Hospital, Acquaviva delle Fonti, Bari); A. Ortensia, MD (Division of Nephrology, "SS. Antonio e Biagio e C. Arrigo" Hospital, Alessandria); I. M. Ratsch, MD (Pediatric Clinic, "G. Salesi" Hospital, Ancona); S. Alloatti, MD, V. Pellu, MD (Division of Nephrology and Dialysis, Ospedale Regionale, Aosta); G. Cesano, MD (Division of Nephrology, Ospedale Civile, Asti); G. Claudiani, MD (Division of Hematology, "S. Liberatore" Hospital, Atri, Teramo); W. De Simone, MD (Division of Nephrology and Dialysis, "S. Giuseppe Moscati" Hospital, Avellino); P. Dattolo, MD, F. Pizzarelli, MD (Division of Nephrology and Dialysis, "S. M. Annunziata" Hospital, Bagno a Ripoli, Firenze); R. Bellantuono, MD, T. De Palo, MD (Division of Nephrology and Dialysis, "Giovanni XXIII" Pediatric Hospital, Bari); M. Schiavoni, MD (Assistenza Emofilici e Coagulopatici, Ospedale Policlinico Consorziale, Bari); M. R. Caruso, MD, E. Gotti, MD, S. Rota, MD, A. Schieppati, MD (Division of Nephrology and Dialysis, "Ospedali Riuniti" Azienda Ospedaliera, Bergamo); T. Barbui, MD, A. Falanga, MD (Division of Hematology, "Ospedali Riuniti" Azienda Ospedaliera, Bergamo); P. Comelli, MD, G. Toere, MD (Pediatric Department, "Ospedali Riuniti" Azienda Ospedaliera, Bergamo); R. Fumagalli, MD, I. Pelliccioli, MD (Pediatric Acute Care, "Ospedali Riuniti" Azienda Ospedaliera, Bergamo); I. M. Beno, MD (Division of Nephrology, "Ospedale degli Infermi", Biella); P. Riegler, MD (Division of Nephrology and Hematology Service, Hospital of Bolzano, Bolzano); J. Mahlknecht, MD, M. Neunhauserer, MD, (Division of Pediatrics, Hospital of Brunico, Bolzano); E. Ragazzoni, MD (Division of Nephrology and

**Appendix**

*International Registry of Recurrent and Familial HUS/TTP*

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Investigators—Italy: M. Garozzo, MD (Division of Nephrology and Dialysis, "S. Marta e S. Venera" Hospital, Acireale, Catania); F. Casucci, MD, F. Cazzato, MD (Division of Nephrology, "Miulli" Hospital, Acquaviva delle Fonti, Bari); A. Ortensia, MD (Division of Nephrology, "SS. Antonio e Biagio e C. Arrigo" Hospital, Alessandria); I. M. Ratsch, MD (Pediatric Clinic, "G. Salesi" Hospital, Ancona); S. Alloatti, MD, V. Pellu, MD (Division of Nephrology and Dialysis, Ospedale Regionale, Aosta); G. Cesano, MD (Division of Nephrology, Ospedale Civile, Asti); G. Claudiani, MD (Division of Hematology, "S. Liberatore" Hospital, Atri, Teramo); W. De Simone, MD (Division of Nephrology and Dialysis, "S. Giuseppe Moscati" Hospital, Avellino); P. Dattolo, MD, F. Pizzarelli, MD (Division of Nephrology and Dialysis, "S. M. Annunziata" Hospital, Bagno a Ripoli, Firenze); R. Bellantuono, MD, T. De Palo, MD (Division of Nephrology and Dialysis, "Giovanni XXIII" Pediatric Hospital, Bari); M. Schiavoni, MD (Assistenza Emofilici e Coagulopatici, Ospedale Policlinico Consorziale, Bari); M. R. Caruso, MD, E. Gotti, MD, S. Rota, MD, A. Schieppati, MD (Division of Nephrology and Dialysis, "Ospedali Riuniti"

# Putative Damaging variants in genes not associated with features of the patient's phenotype

| Gene | Aa change | Frequency in ExAC population | PS | CADD | Info/Known related disease |
|---|---|---|---|---|---|
| **GCC2** chr2:108469672 | p.D115H | 0.000008459 | PS=9/10 | 18 | **Code for**: GRIP AND COILED-COIL DOMAIN-CONTAINING PROTEIN 2 **Function:** vesicular transport between endosomes and the Golgi |
| **FCGBP** chr19:39906191 | p.V1190A | 0 | PS=3/7 | 10 | **Code for:** Fc FRAGMENT OF IgG-BINDING PROTEIN **Function:** may be involved in maintenance of the mucosal structure. |
| **ASB11** chrX:15297648 | p.V99L | 0.0000698 | PS=7/10 | 29 | **Code for:** ANKYRIN REPEAT- AND SOCS BOX-CONTAINING PROTEIN 11 **Function:** Neurodevelopment. **Disease:** misexpression of asb11 caused impaired neurogenesis |
| **STRA8** chr7:135240663 | p.F69V | 0 | PS=9/10 | 25 | **Code for:** Stimulated By Retinoic Acid 8 **Function**: Meiosis-Inducer **Disease:** Reproductive system disorder (spermatogenesis and oogenesis). |
| **CFAP47** chrX:36366986 | p.I3015T | 0 | PS=6/10 | 23 | **Code for:** cilia and flagella associated protein 47 **Function**: not available **Disease:** not described |

# TRGI168 –FAT1 R1953T

| Gene | Aa change | Frequency in ExAC population | Info/Known related disease |
|---|---|---|---|
| **FAT1**<br>chr4:187541882 | p.R1953T | 0 | **Code for**: FAT TUMOR SUPPRESSOR, DROSOPHILA, HOMOLOG OF, 1<br><br>**Function:** receptor for a signaling pathway that regulates growth, gene expression, and planar cell polarity<br><br>**Diseases:**<br>• Cancer: glioblastoma, colorectal cancer, head and neck cancer, pancreas cancer<br>• Kidney: Nephrotic syndrome - Hematuria<br>• Facioscapulohumeral muscular dystrophy-Like<br>- Autosomal dominant<br>- Muscle weakness (face, scapula, abdomen, axial and lower limbs)<br>- Variable age of onset |

MARIO NEGRI
ISTITUTO DI RICERCHE FARMACOLOGICHE

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This site complies to the HONcode standard for trustworthy health information

# Clinical Trials Register

FOUND 16 RESULTS

**Drug:** no drug **Department:** Rare Diseases Documentation and Research
**Disease:** Haemolytic-uraemic syndrome

EX VIVO STUDY DESIGN TO INVESTIGATE WHETHER MUBODINA, AN ANTI-C5 MINIBODY, INHIBITS COMPLEMENT DEPOSITION AND THROMBUS FORMATION ON ACTIVATED ENDOTHELIAL CELLS EXPOSED TO SERUM FROM PATIENTS WITH STEC-HUS

ONGOING

**Drug:** no drug **Department:** Rare Diseases Documentation and Research
**Disease:** Diffuse mesangiocapillary glomerulonephritis

COMPLEMENT ABNORMALITIES IN PRIMARY MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

ONGOING

**Drug:** no drug **Department:** Rare Diseases Documentation and Research
**Disease:** Thrombotic microangiopathy

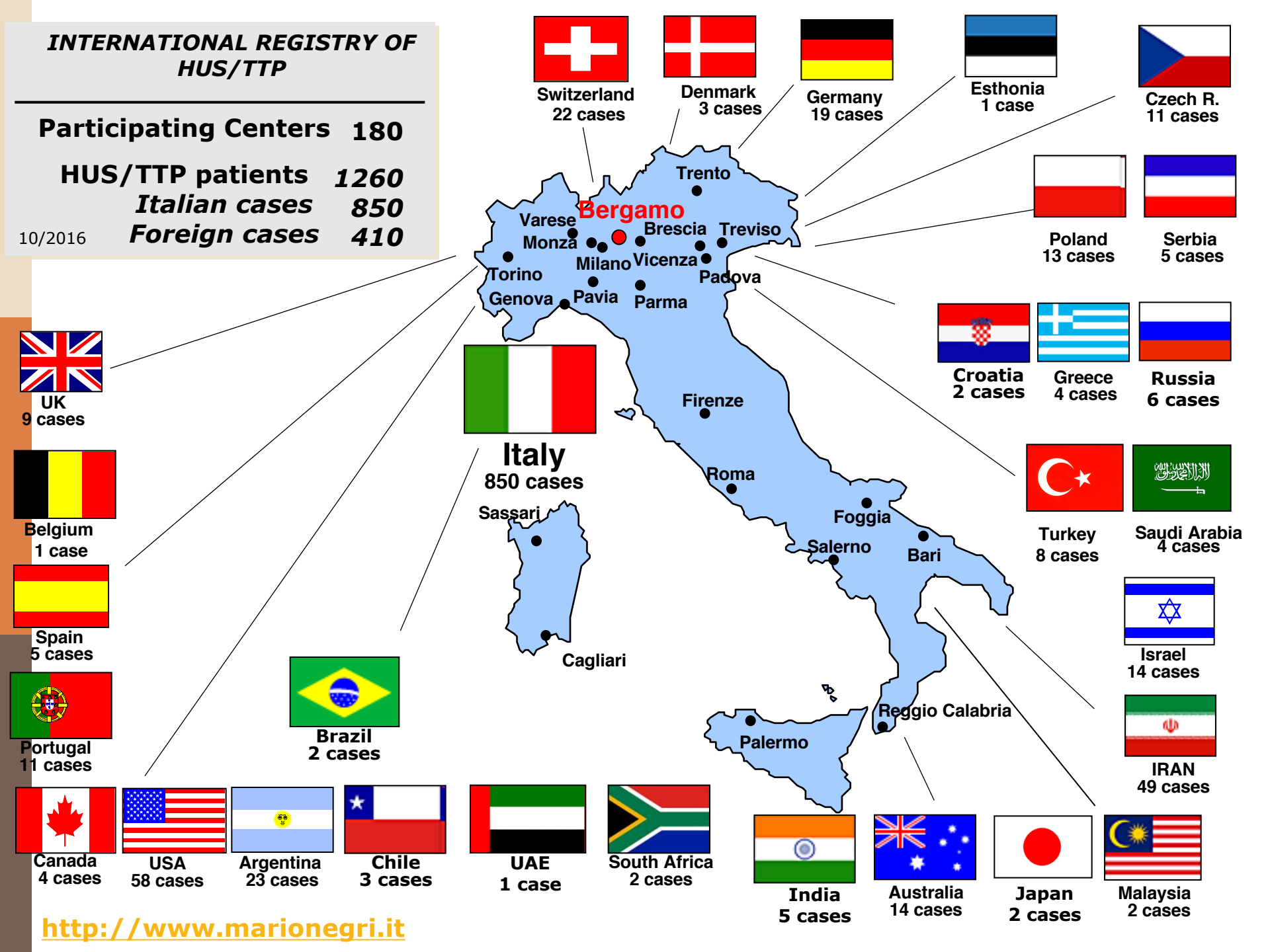
GENETIC AND BIOCHEMICAL ABNORMALITIES IN HEMOLYTIC UREMIC SYNDROME AND THROMBOTIC THROMBOCYTOPENIC PURPURA

ONGOING

**Drug:** no drug **Department:** Rare Diseases Documentation and Research
**Disease:** Nephrotic syndrome

IDENTIFICATION OF NEW GENES ASSOCIATED TO STEROID RESISTANT NEPHROTIC SYNDROME

ONGOING


INTERNATIONAL REGISTRY OF HUS/TTP
Participating Centers 180
HUS/TTP patients 1260
Italian cases 850
Foreign cases 410
10/2016
Switzerland 22 cases
Denmark 3 cases
Germany 19 cases
Esthonia 1 case
Czech R. 11 cases
Poland 13 cases
Serbia 5 cases
Croatia 2 cases
Greece 4 cases
Russia 6 cases
Turkey 8 cases
Saudi Arabia 4 cases
Israel 14 cases
IRAN 49 cases
Trento
Bergamo
Varese
Monza
Brescia
Treviso
Milano
Vicenza
Padova
Torino
Genova
Pavia
Parma
Firenze
Roma
Foggia
Salerno
Bari
Sassari
Cagliari
Reggio Calabria
Palermo
Italy
850 cases
UK 9 cases
Belgium 1 case
Spain 5 cases
Portugal 11 cases
Brazil 2 cases
Canada 4 cases
USA 58 cases
Argentina 23 cases
Chile 3 cases
UAE 1 case
South Africa 2 cases
India 5 cases
Australia 14 cases
Japan 2 cases
Malaysia 2 cases
http://www.marionegri.it

# IDENTIFICATION OF aHUS ASSOCIATED GENES

**aHUS genes**

*CFH*
***MCP***
*CFB*
*CFI*
*C3*
***THBD***
*DGKE*

THE LANCET • Vol 362 • November 8, 2003 • www.thelancet.com

## Familial haemolytic uraemic syndrome and an *MCP* mutation

*Marina Noris, Simona Brioschi, Jessica Caprioli, Marta Todeschini, Elena Bresin, Francesca Porrati, Sara Gamba, Giuseppe Remuzzi for the International Registry of Recurrent and Familial HUS/TTP**

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 361;4 NEJM.ORG JULY 23, 2009

## Thrombomodulin Mutations in Atypical Hemolytic–Uremic Syndrome

Mieke Delvaeye, Ph.D., Marina Noris, Ph.D., Astrid De Vriese, M.Sc., Charles T. Esmon, Ph.D., Naomi L. Esmon, Ph.D., Gary Ferrell, M.Sc., ...

# IDENTIFICATION OF NEPHROTIC SYNDROME ASSOCIATED GENES

Aut. Dominant steroid-resistant nephrotic syndrome

*INF2*
*WT1*
*ACTN4*
*CD2AP*
*TRPC6*
*ARHGAP24*
*PAX2*
*LMX1B*
*APOL1*

Recessive steroid-resistant nephrotic syndrome

*NPHS1*
*NPHS2*
*PLCE1*
***MYO1E***
***PTPRO***
*ARHGDIA*
*ADCK4*
*EMP2*

Syndromic forms with steroid-resistant nephrotic syndrome

*LAMB2*
*COQ6*
*COQ2*
*PDSS2*
*SCARB2*
*SMARCAL1*
*ITGA3*
*CD151*
*WT1*
*PAX2*
*LMX1B*
*MYH9*

Glomerulopathy with fibronectin deposits

***FN1***

2538–2543 | PNAS | February 19, 2008 | vol. 105 | no. 7

**Mutations in *FN1* cause glomerulopathy with fibronectin deposits**

Federica Castelletti*, Roberta Donadelli*, Federica Banterla*, Friedhelm Hildebrandt†, Peter F. Zipfel‡, Elena Bresin*, Edgar Otto†, Christine Skerka‡, Alessandra Renieri§, Marta Todeschini*, Jessica Caprioli*, Maria Rosa Caruso¶, Rosangela Artuso§, Giuseppe Remuzzi*¶‖, and Marina Noris*

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 365;4 NEJM.ORG JULY 28, 2011

*MYO1E* Mutations and Childhood Familial Focal Segmental Glomerulosclerosis

Caterina Mele, Biol.Sci.D., Paraskevas Iatropoulos, M.D., Roberta Donadelli, Biol.Sci.D., Andrea Calabria, Eng.D.,

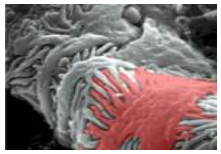
The American Journal of Human Genetics *89*, 139–147, July 15, 2011 REPORT

Disruption of *PTPRO* Causes Childhood-Onset Nephrotic Syndrome

Fatih Ozaltin,[1,2,*] Tulin Ibsirlioglu,[2] Ekim Z. Taskiran,[3] Dilek Ertoy Baydar,[4] Figen Kaymaz,[5] Mithat Buyukcelik,[6] Beltinge Demircioglu Kilic,[6] Ayse Balat,[6] Paraskevas Iatropoulos,[7] Esin Asan,[5] Nurten A. Akarsu,[8] Franz Schaefer,[9] Engin Yilmaz,[3] Ayşin Bakkaloglu,[1] and the PodoNet Consortium[10]

# International Network

- **PodoNet Consortium**



**PodoNet**
**Clinical, Genetic and Experimental Research into Hereditary Diseases of the Podocyte**

The Bergamo group is a confounder of PodoNet and organized the adult component of the Registry

- **EURenOmics**

EURenOmics

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

- **ERKNet**

ERN on kidney diseases (ERKNet)

| Features present in the case | FAT1 | POC1B | HSD17B10 | TTN |
|---|---|---|---|---|
| **Urinary Tract Abnormalities** | Resolved ? | - | - | - |
| - Proteinuria | Resolved ? | - | - | - |
| - Hematuria | Resolved ? | - | - | - |
| - Chronic kidney disease | Resolved ? | - | - | - |
| - Tubular abnormalities | Resolved ? | - | - | - |
| - Renal cyst | - | - | - | - |
| **Neoplastic disorders** | Resolved ? | - | - | - |
| - Papillary thyroid carcinoma | - | - | - | - |
| **Central Nervous System Abnormalities** | - | - | - | - |
| - Chronic subdural hematoma | - | - | - | - |
| **Ocular Abnormalities** | - | Resolved | Resolved | - |
| - Optic nerve atrophy | - | | Resolved | - |
| - Retinal cone-rod degeneration | - | Resolved | - | - |
| - Blindness | - | Resolved | Resolved | - |
| - Colorblindness | - | Resolved | - | - |
| **Muscular abnormalities** | - | - | - | Resolved |
| - Fasciculation / muscle hyper-irritability | - | - | - | - |
| - High blood CK levels | - | - | - | Resolved |
| **Miscellaneous** | - | - | - | - |
| - Linear morphea (face) | - | - | - | - |
| - Primary hyperparathyroidism | - | - | - | - |
| - Nonalcoholic steatohepatitis | - | - | - | - |