



Acquired Drivers of Disease
aHUS and autoantibodies: their role in disease
and their impact on patient management

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Disclosure of Interests

- Alexion : consultancy; member of the Registry SAB
- Achillion : Consultancy
- Novartis : consultancy

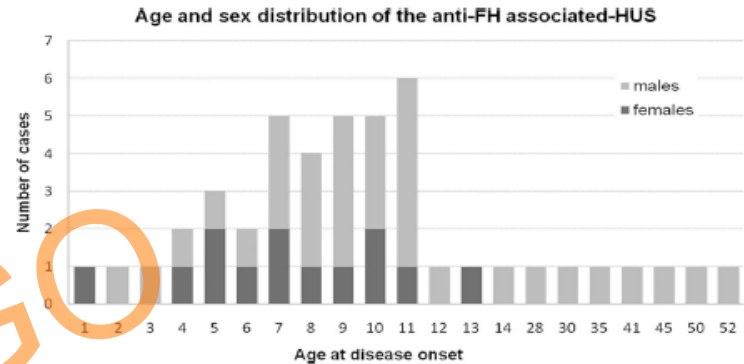
KDIGO



Anti -Factor H antibodies : epidemiology

- First report in 2005¹ ; Robust association with aHUS
- First cause of aHUS in children with aHUS onset between 5-11 years²
- In Children and Adult onset
- Identified in 5 -14% in European cohorts but more than 50% in south Asia³
- With FH-anti FH Immune Complexes in plasma

Determine triggers for production of anti FH Ab
Why this age specific occurrence



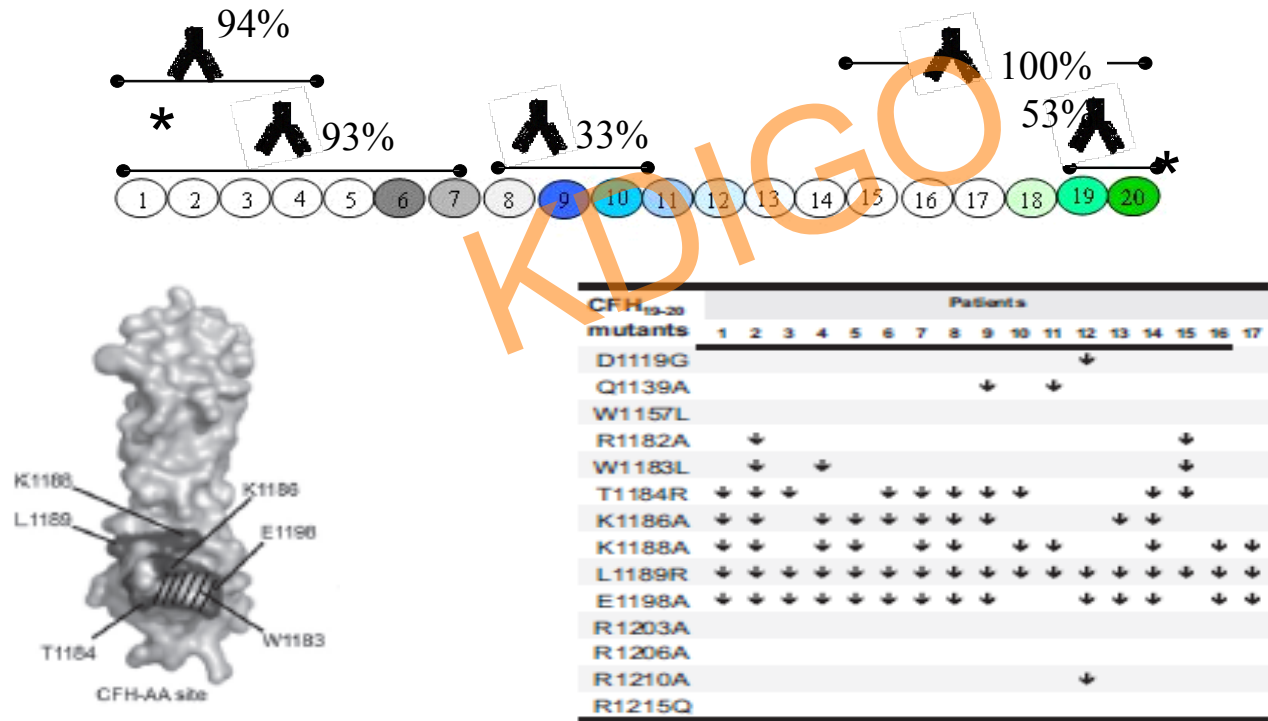
anti FH Ab		
Authors	Country of origin	Frequency (number of tested patients)
Children onset		
Noris et al, 2010	Italy	3.9 (152)
Fremaux-Bacchi et al, 2013	France	11 (89)
Geerdink et al, 2012	Belgium, Netherlands	13 (45)
Hofer et al, 2013	Austria, central Europe	25 (100)
Lee et al, 2014	Korea	29 (51)
Sinha et al, 2014	India	56 (216)
Adult onset		
Noris et al, 2010	Italy	1.9 (104)
Fremaux-Bacchi et al, 2013	France	3.2 (129)

1. Dragon-Durey et al. JASN, 2005; 2. Dragon-Durey et al. JASN, 2010 3. Sinha et al. Kidney, 2013

Anti -Factor H antibodies : epitope mapping

More frequently IgG (IgG3); Polyclonal (cases of monoclonal)

Bind preferentially within the C-terminal domains of the proteins



1. Blanc *et al.* JASN, 2012; 2 .Bhattacharjee *et al.* JASN, 2015 3. Jozsi *et al.*, 2007

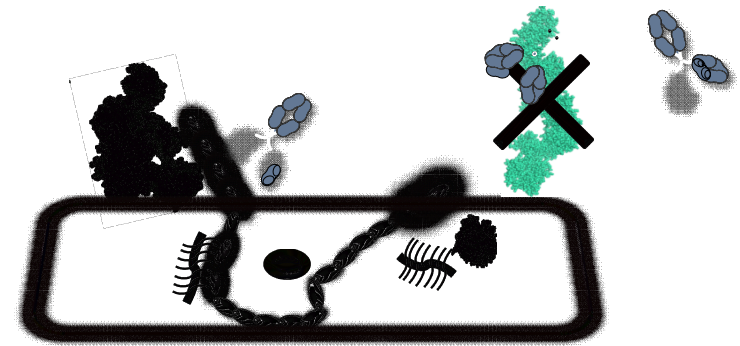
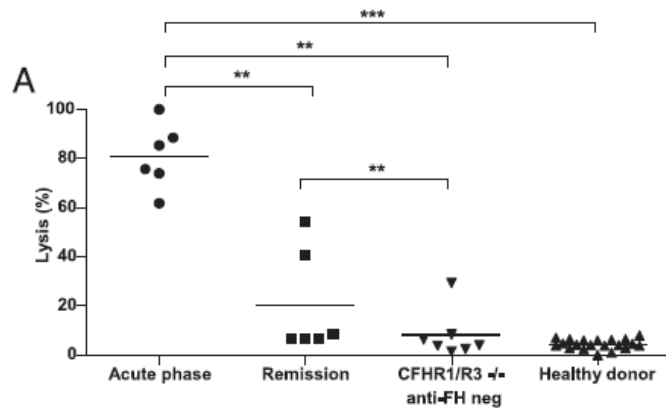
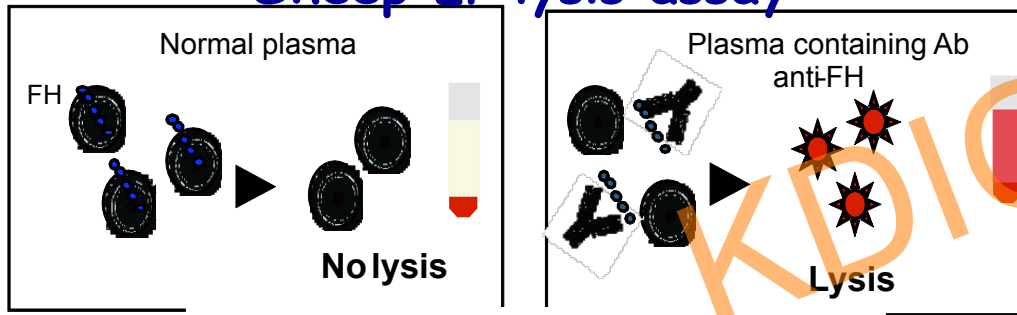


Anti -Factor H antibodies : pathogenesis

Alternative pathway consumption in 30% of the cases

Induce FH deficiency with disruption cell protection

Sheep Er lysis assay



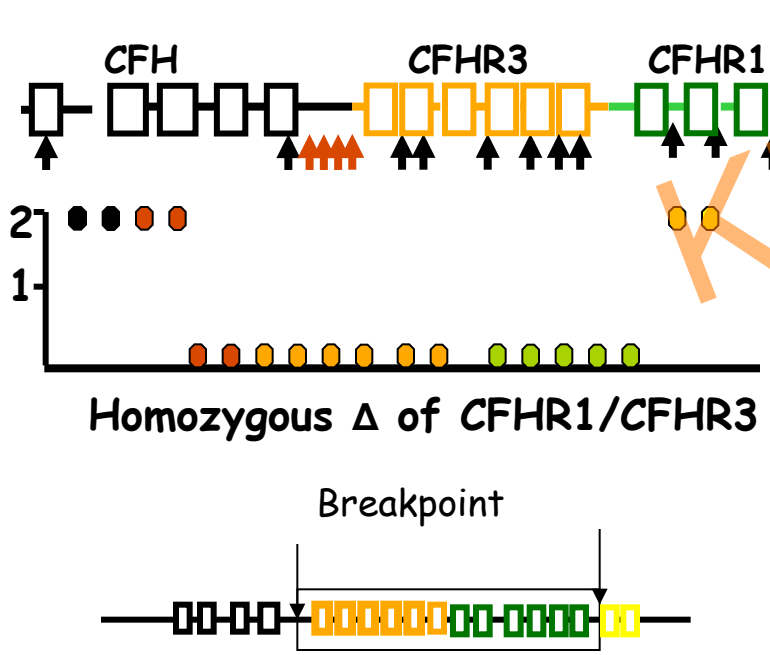
Determine whether functional assays identify patients with increased risk of relapse

1. Blanc *et al.* JASN, 2012; Blanc *et al.* 2015;

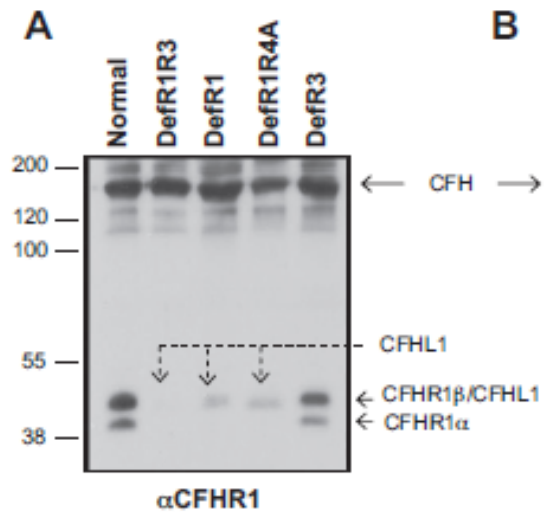
KDIGO Controversies Conference on Complement-Mediated Kidney Diseases
November 19-21, 2015 | Barcelona, Spain

Anti -Factor H antibodies : genetic background

- In association with CFHR1 deficiency in 85% (2 to 10% in healthy controls)
- Screening strategy : Multiplex ligation dependant amplification and western blott



CFHR1/CFHR3 or CFHR1/CFHR4 deletion
Link between CFHR1 deletion and haplotype FH 3 CAG

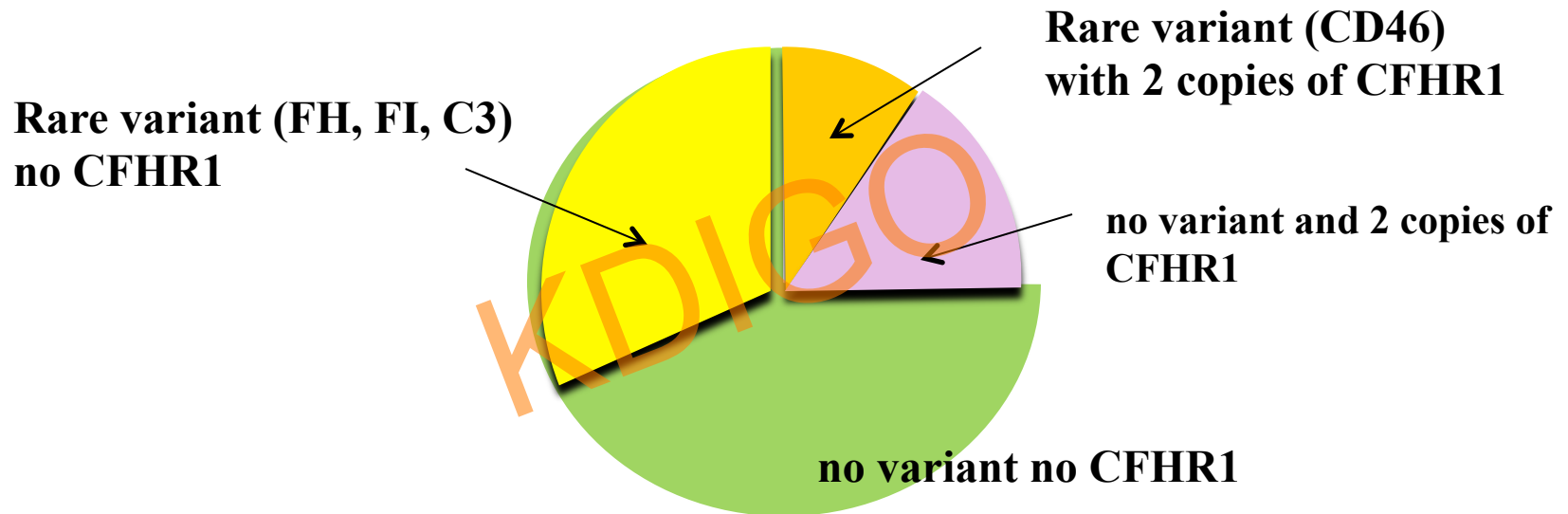


1. Jozsi *et al.* Blood, 2008; 2. Dragon-Durey *et al.* J Med Genet, 2009; 3. Moore *et al.* Blood, 2009; 4. Abarregui-Garrido *et al.* Blood, 2009;



Anti -Factor H antibodies : genetic background

Study of genetic background for 13 patients with anti FH Ab from the UK cohort



Why patients with auto Ab lack CFHR1 protein?
What is the role of the associated rare variant?

1. Moore *et al.* Blood, 2013;

Anti –Factor H antibodies: clinical features

- In Children and Adult onset
- Severe Illness with extrarenal manifestation (liver, pancreas, digital gangrene)
- Long-term evolution of the disease (death, renal sequel, cardiac insufficiency, non _auto immune diabetes)
- Risk of post transplantation recurrence is determined by the titre of anti FH Ab

Prodromes (n = 32)

gastrointestinal symptoms	84% (diarrhea: 53%) (2 cases with Mallory-Weiss syndrome)
infection	4 (1 varicella, 1 upper respiratory tract infection, 1 STEC, 1 norovirus)
other	2 urticaria and face edema

Clinical symptoms at onset (n = 32)

hypertension	68%
hematuria	27%
oligo-anuria	28%
seizures	23.5%
pancreatitis	23.1%
hepatitis	50%

1. Loirat *et al.* Pediatric Nephrol, 2015; 2. Sinha *et al.* Kidney Int 2013;



Anti –Factor H antibodies: diagnosis

Screening by ELISA (publication of the assay standardization, no commercial CQE)

Dose dependent binding to Factor H, results in UA /ml

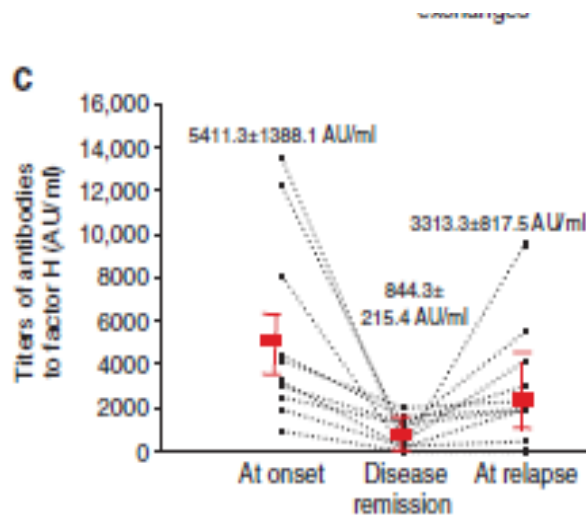
One standard provided by Marie Agnes Dragon Durey (24 laboratories worldwide)

Usefull for monitoring disaese activity

Screening at onset, at day 7, 14 and 28 after diagnosis, then monthly and 1/year

Monitoring for relapses and peri transplantation management with the anti FH titers

Lack of quality controls

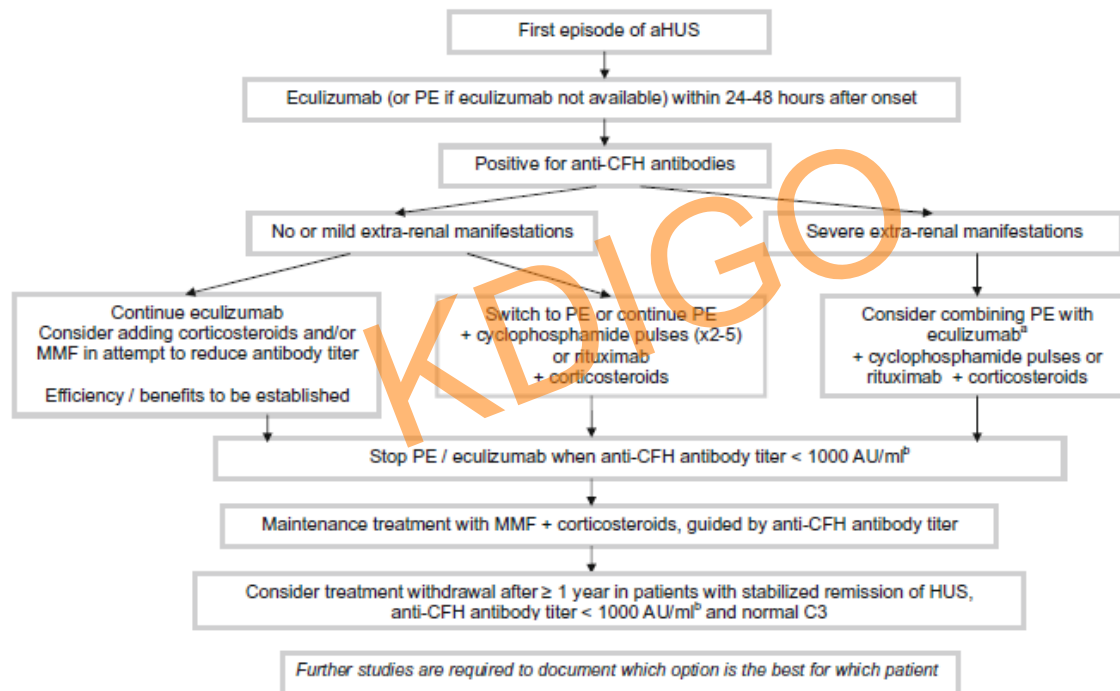


1. Dragon-Durey *et al.* JASN, 2005; 2. Dragon-Durey *et al.* JASN, 2010 3. Sinha *et al.* Kidney, 2013; 4. Loirat *et al.* Pediatric Nephrol, 2015; Watson *et al.*, Immunobiology, 2014



Anti –Factor H antibodies: Treatment

- Plasma Exchanges and IS are recommended ⁴



Determine the safety and the efficacy of the therapeutic options

1. Loirat *et al.* Pediatric Nephrol, 2015



Others acquired forms

- Anti FH Ab with/without MGUS (IgA isotype)
- Three reported cases of anti FI Ab without identified functional consequences
- Autoantibodies to CD59, CD55, CD46 or CD35 are not associated with Ahus
- Others : anti C3b

1. Blanc *et al.* JI, 2015; 2. Rigotherier *et al.* AJKD 2015 ; 3. Kavanagh *et al.* CJASN, 2012; 4. Watson *et al.* Mol Immunol, 2015;

