



Fundació Puigvert

ANTI-PLA2R

Nueva herramienta en el manejo de la
recidiva de GMN Membranosa

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IDIOPATIC MEMBRANOUS NEPHROPATHY



Is a major cause of the nephrotic syndrome in adults, affecting 10-12 cases per million population

Lead to end-stage renal disease in 40-50%

Post-transplant relapse 7-42 %

Strong negative effect on kidney graft survival



IDIOPATIC MEMBRANOUS NEPHROPATHY

- Considered to be an autoimmune disease
- In 2009:
 - Possible to detect circulating antibodies against phospholipases A2 receptor (PLA2R1)
 - This antibody is present in 70-75 %

IDIOPATHIC MEMBRANOUS NEPHROPATHY



Glomerular extracts from human kidneys (as a source of antigens) enabled the identification of a **protein band** that was detected in about 70% of patients with idiopathic MN

Beck M-type phospholipase A 2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009

IDIOPATIC MEMBRANOUS NEPHROPATHY



PLA 2 R was detected in podocytes of normal human glomeruli

PLA 2R and IgG4 were within the subepithelial immune deposits in patients with idiopathic MN.

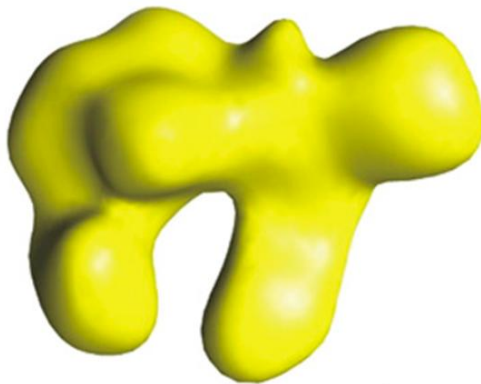
Beck M-type phospholipase A 2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009



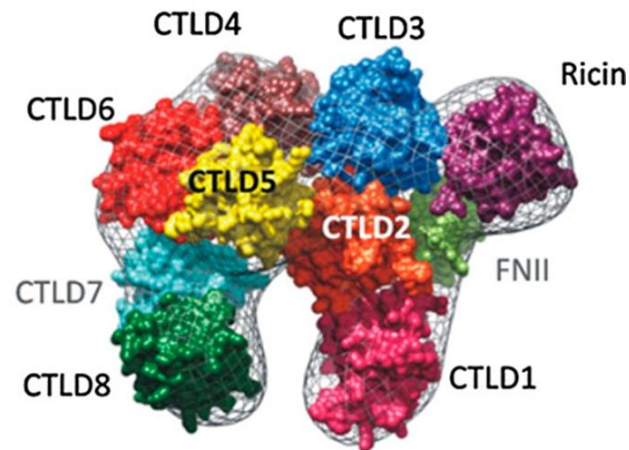
PLA2R1

PLA 2R is a transmembrane receptor for secretory phospholipase A 2, a member of the mannose receptor family

PLA2R structure



PLA2R domain fitting



IDIOPATIC MEMBRANOUS NEPHROPATHY



2011: Genetic susceptibility

- Chromosome 2q PLA2R1
- Chromosome 6p HLA complex class II DQA1

Some PLA2R1 alleles (3 variants)

HLA DQA1 (1 variant)

PLA2R1 Antibodies

clinically relevant



- **High levels of Anti PLA2R antibodies are associated to**
 - Active disease
 - Poor clinical outcome at 5 years
 - Less chance of spontaneous remission
- **Failure to render patients anti-PLA2R seronegative by immunosuppression therapy is associated with high risk of relapse**

PLA2R1 Antibodies

Diagnostic tests



Serological assays of circulating PLA 2R1 antibodies by indirect immunofluorescence and ELISA are now commercially available

High specificity (near 100%):

- elderly patients

- those with poor clinical condition

- those with life-threatening

kidney biopsy can be postponed or even not performed

PLA2R1 Antibodies

Clinical Application



Low prevalence of anti-PLA 2 R antibodies
in secondary forms of MN

Exceptions:

active sarcoidosis

replicating hepatitis B

Knehtl M, Ronco P: A case of phospholipase A 2 receptor-positive membranous nephropathy preceding sarcoid-associated granulomatous tubulointerstitial nephritis. Am J Kidney Dis 2011

PLA2R1 Antibodies Clinical Application



To increase sensitivity

Deteccion of PLA2R antibodies in kidney biopsy :
rapid clearance of circulating antibodies
not all antibodies to PLA2R1 are pathogenic

Kidney biopsies: IgG subclass: IgG4 is the
major deposited subclass in IMN

Debiec H, Ronco P: PLA 2 R autoantibodies and PLA 2R
glomerular deposits in membranous nephropathy. N Engl
J Med 2011

Genetic susceptibility



genomawide association

Table 1. Characteristics of Patients in the Three Study Cohorts.*

Characteristic	French Cohort	Dutch Cohort	British Cohort
No. of patients	75	146	335
Sex (no.)			
Male	58	109	231
Female	17	37	104
Sex ratio (M:F)	3.4:1	2.9:1	2.2:1
Age at diagnosis (yr)	49.8±15.3	51.8±14.2	52.5±13.3

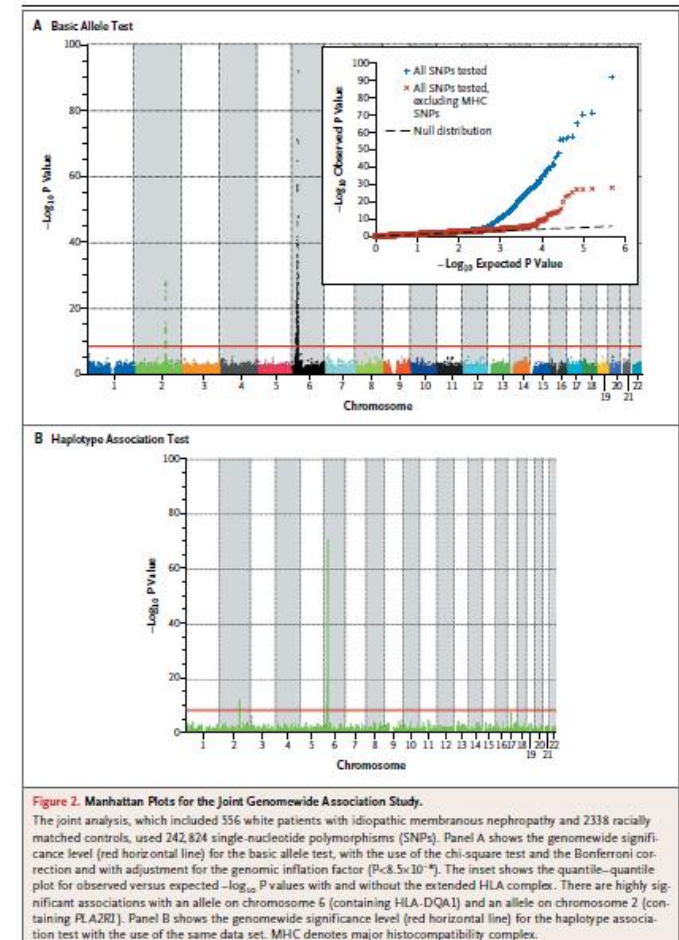
Stanescu, M.D., Risk HLA-DQA1 and PLA2R1 Alleles in Idiopathic Membranous Nephropathy N Engl J Med 2011;

Genomewide association study



There are highly significant associations with an allele on chromosome 6 (containing HLA DQA1) and an allele on chromosome 2 (containing PLA2R1)

Stanescu, M.D., Risk HLA-DQA1 and PLA2R1 Alleles in Idiopathic Membranous Nephropathy N Engl J Med 2011;



Genomawide association study



Table 3. Odds Ratios for Idiopathic Membranous Nephropathy, According to Single-Nucleotide Polymorphism (SNP) and Genotype Combinations.*

SNP rs2187668 (HLA-DQA1)	SNP rs4664308 (PLA2R1)		
	GG	GA	AA
GG			
No. of cases/total no. of subjects	14/354	79/944	97/659
Odds ratio (95% CI)	1.00	2.22 (1.24–3.97)	4.19 (2.36–7.46)
GA			
No. of cases/total no. of subjects	23/115	94/363	178/348
Odds ratio (95% CI)	6.07 (3.01–12.27)	8.49 (4.73–15.22)	25.43 (14.32–45.16)
AA			
No. of cases/total no. of subjects	5/11	23/41	42/55
Odds ratio (95% CI)	20.24 (5.51–74.38)	31.03 (13.72–70.19)	78.46 (34.55–178.17)

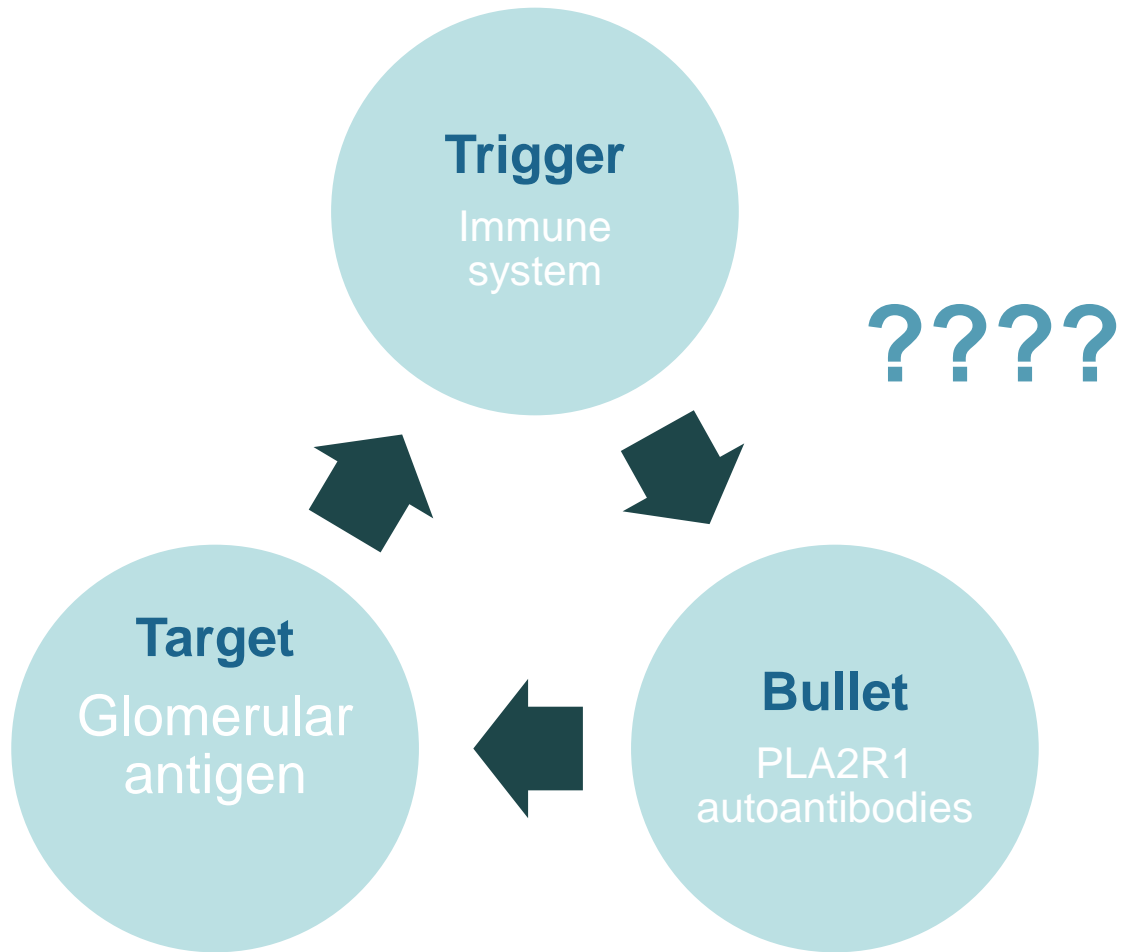
* Persons who were homozygous for the low-risk allele (GG) constituted the reference category. Numbers of cases and total numbers of subjects are from the joint analysis. OR denotes odds ratio.

IDIOPATHIC MEMBRANOUS NEPHROPATHY



- The association is stonger for HLA DQA1 than for PLA2 receptor 1
- HLA DQA1 allele might facilitate autoantibody development (also antiGBM disease)

IDIOPATIC MEMBRANOUS NEPHROPATHY



METHODS



Prospective unicenter study to determine the presence of anti PLA2R antibodies in biopsy proven IMN transplant recipients

The role of anti PLA2R antibodies in the post-transplant MN recurrence and response to immunosuppressant treatment

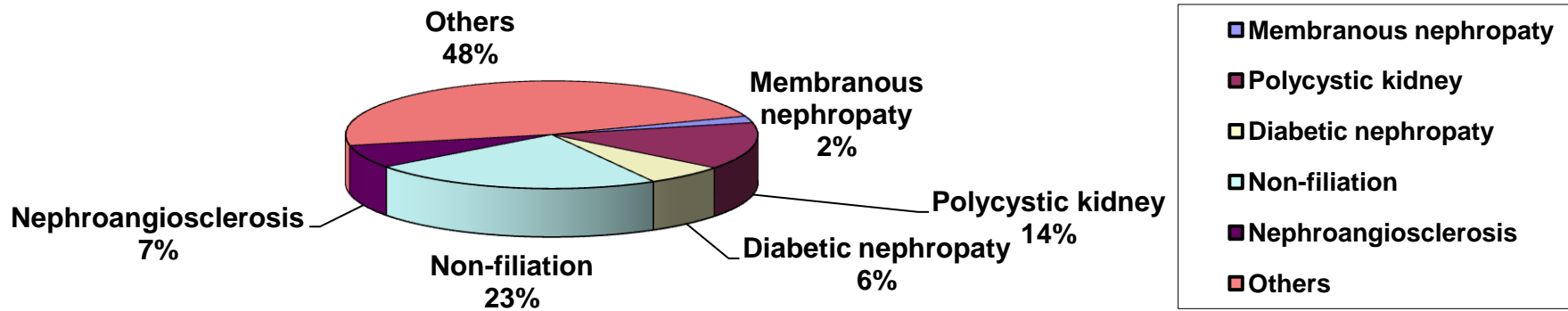


RESULTS

In our serie we identify 34 transplant recipients with a biopsy proven MN

IMN relapsed 23 %, time 31+/- 36 months after KT

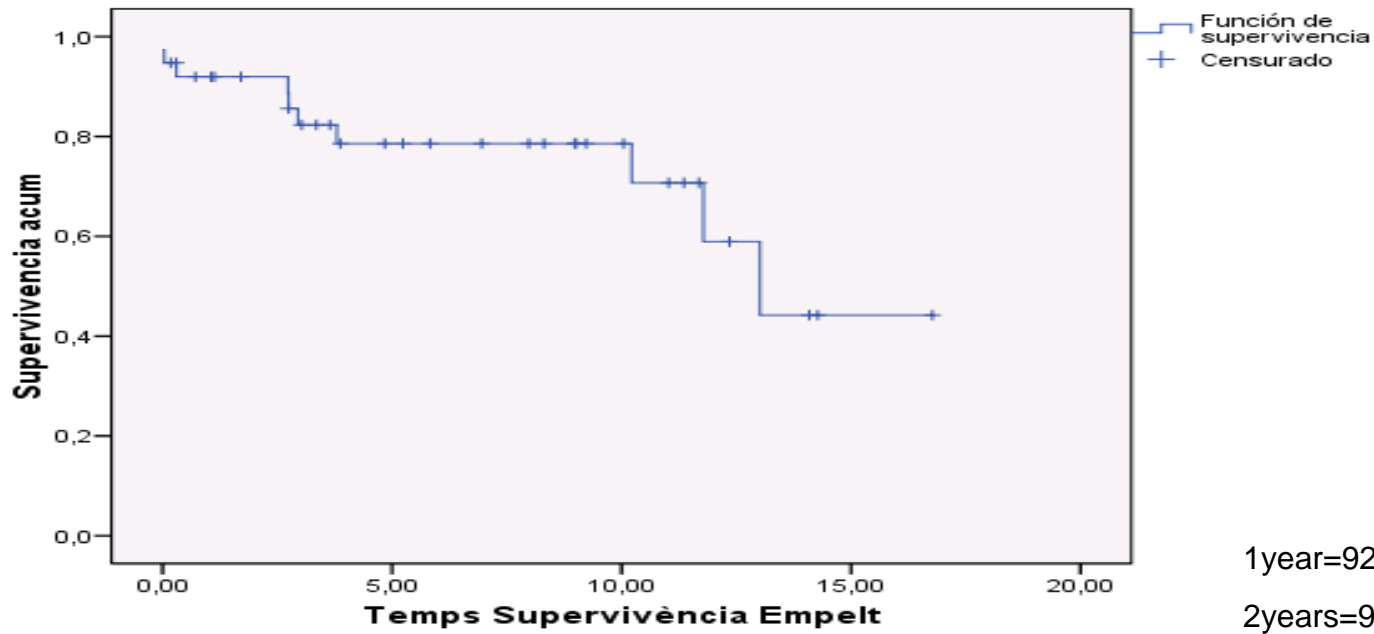
CAUSE OF RENAL KIDNEY DISEASE



GRAFT SURVIVAL(death-censored)



Función de supervivencia

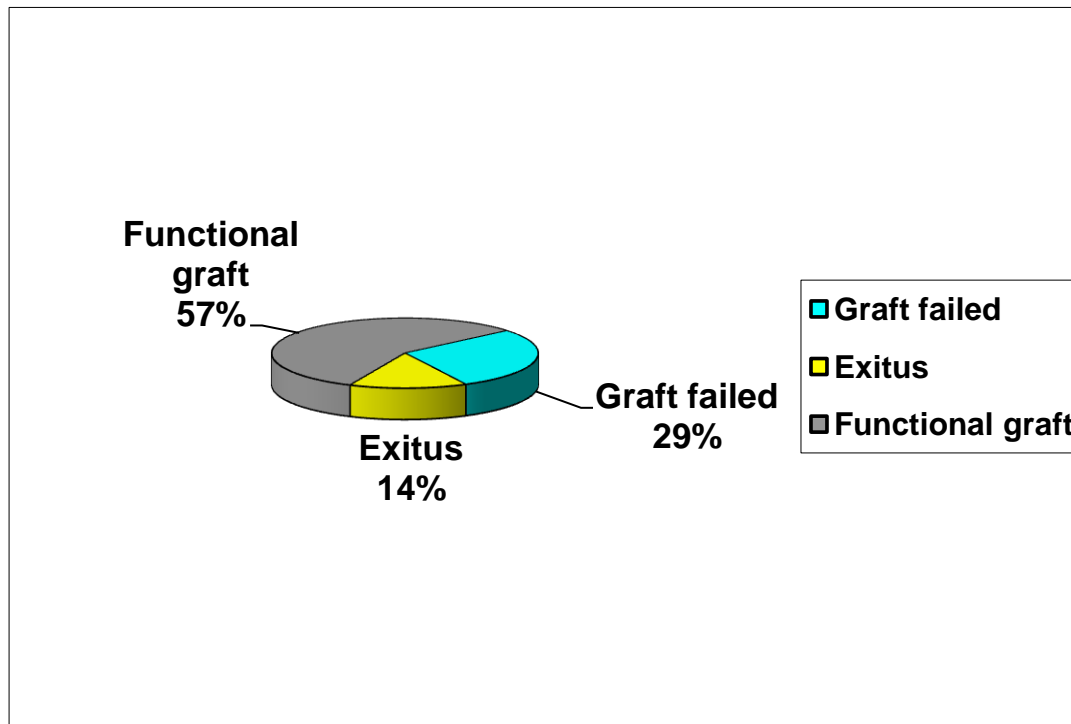


1year=92%
2years=92%
3years=82.3%
5years=78.6%



RECURRENCE OF IMN

8/34: 23% recurrence



Recurrence of membranous nephropathy (months)



Medium time from transplant to IMN relapse 58.6 ± 55.8 months.

Patient	Months	Serum creatinine($\mu\text{mol/L}$)	Proteinuria(g/24h)
1	140	146	4,4
2	49	215	2.1
3	16	245	2.8
4	102	116	1,7
5	23	175	2,2
6	2,4	162	1,8
7	4,2	116	1,93
8	122,5	178	3,06

RESULTS



- We detect anti PLA2R antibodies since 2012
 - Immunofluorescence
 - ELISA since 2013
- We treat all the recurrences with Rituximab

PLA2R1 antibodies



PLA2R1	Initial diagnosis	Transplant	Relapse	Post-Treatment
ND (?)	50% (4)	50% (4)	-----	
NEGATIVE	25% (2)	25% (2)	25% (2)	100 % (8)
POSITIVE	25 % (2)	25% (2)	75 % (6)	



Decreased of proteinuria

CONCLUSIONS



- Our incidence of relapsed MN is similar to others series
- Positive PLA2R1 antibodies at the moment of kidney transplant relapsed 100% in patients previously positive
- No difference in Negative or Positive PLA2R1 antibodies related to relapse

CONCLUSIONS



- In our study, the presence of anti-PLA2R1 is associated with:
 - Disease recurrence
 - Good Response to treatment (Rituximab)
- Patients with no PLA2R1 Antibodies did similar
- However, more studies are required to confirm these results



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Gràcies