european society for paediatric nephrology

ERKNet The European Rare Kidney Disease Reference Network

Membranous Nephropathy in Children

Dr. Julien Hogan
Dr. Claire Dossier
Hôpital Robert Debré, APHP, Paris
Université de Paris

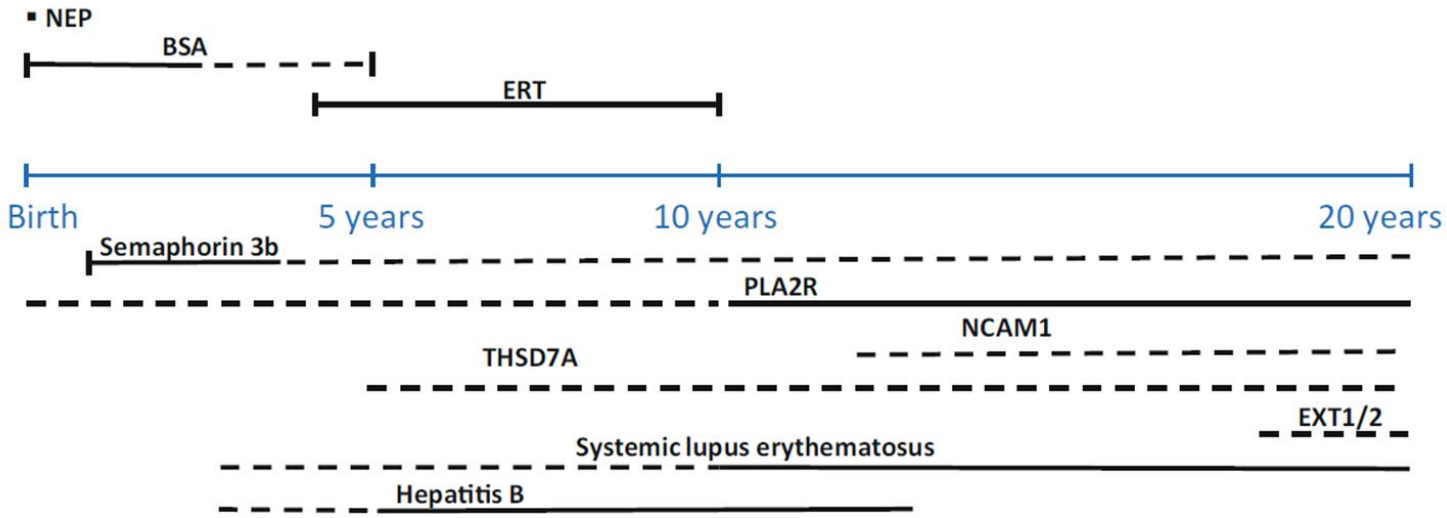
Dr. Marina Vivarelli
Ospedale Pediatrico Bambino Gesù, Roma

Pr. Pierre Ronco/Hanna Debiec, INSERM 1155
Sorbonne Université
Hôpital Tenon, Paris

Study rationale

- Membranous nephropathy is a rare condition in children
- Published data are mostly single center reports
- Lack of data on:
  - MN epidemiology in children
  - Treatment practicies and outcomes
  - Value of anti-PLA2R monitoring
- Need of large cohorts with clinical data and biopsy samples to assess the prevalence of recently discovered antigens and to discover new antigens.

Distribution of antigens according to age



Ronco P, Vivarelli M, Ayalon R & Debiec H Chapter 94.1 Pediatric Nephrology, 2021

Example: Discovery of Semaphorin 3B antigen

Flowchart of the discovery and validation cohorts

Discovery COHORT
70 biopsies of PLA2R-negative MN
MS/MS

↓

2 Sema3B-associated MN by MS/MS

↓

Both confirmed by IHC, + 1 additional case detected on screening 90 cases for Sema3B-associated MN and confirmed by MS/MS

FRENCH VALIDATION COHORT #1*
59 biopsies of MN

↓

2 Sema3B-associated MN by IF

FRENCH VALIDATION COHORT #2*
16 biopsies of MN by IF

↓

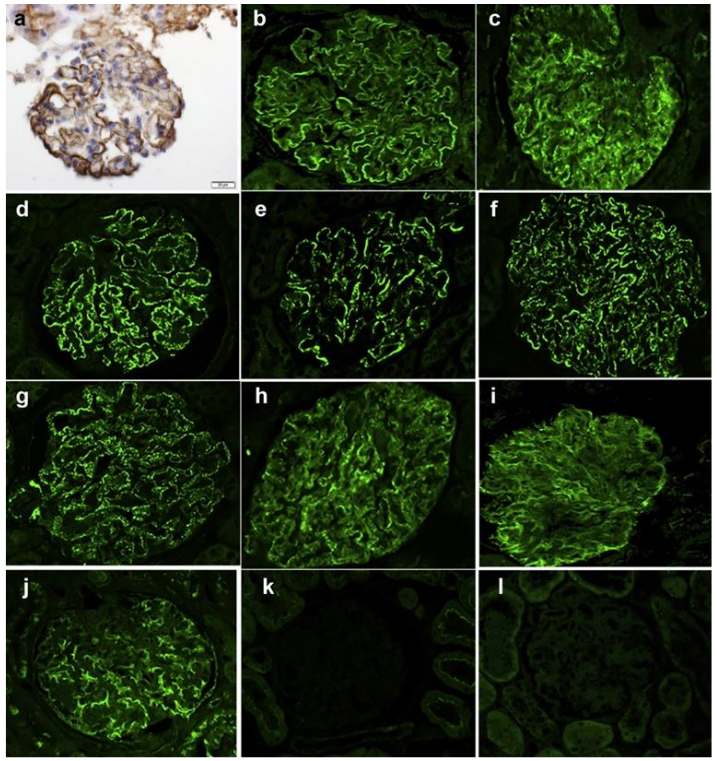
2 Sema3B-associated MN by IF

ITALIAN VALIDATION COHORT*
43 biopsies of MN by IF

↓

4 Sema3B-associated MN by IF

IHC and IF labeling of the paraffin biopsies from the European patients



c: Patient #5 at 1 year

d: Patient #5 at 19 years

e-j: All pediatric patients

Control cases:

k: PLA2R positive MN
i: PLA2R negative, Sema3b negative child

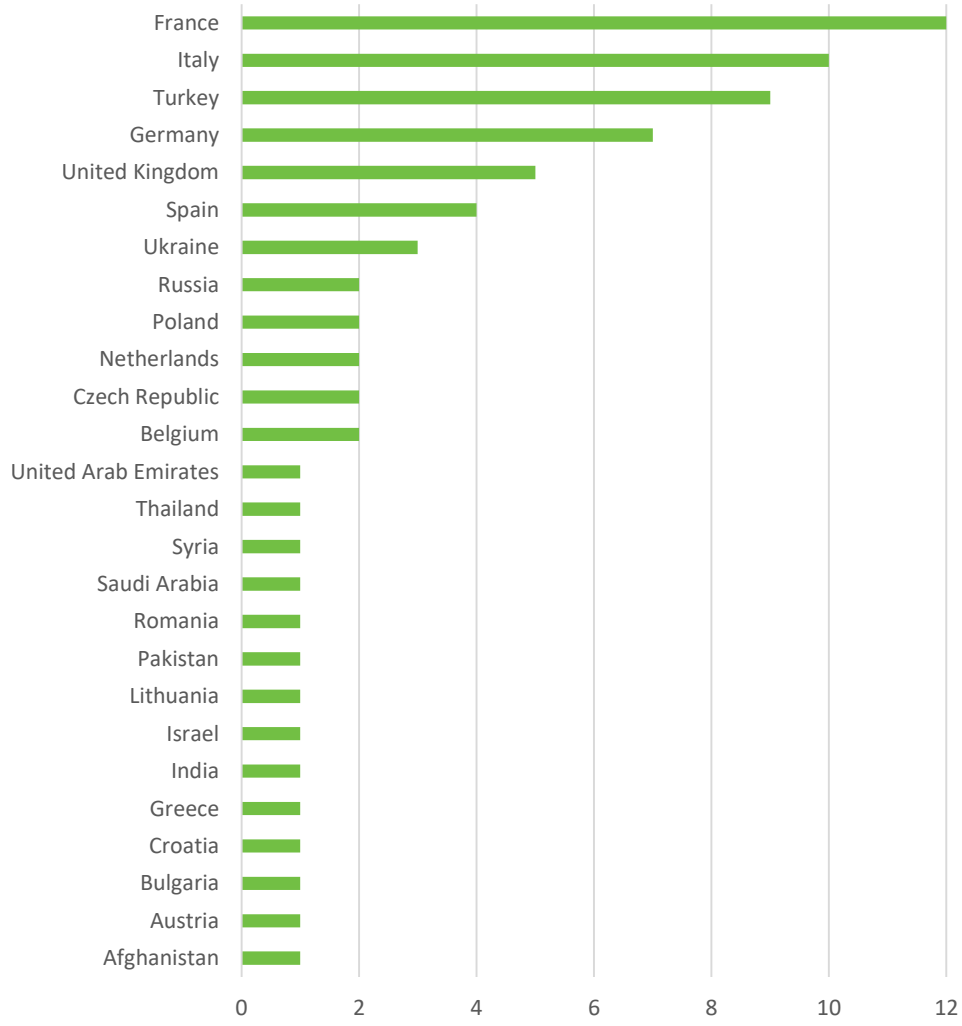
Kidney Int 2020, 98:1253

Study Objectives

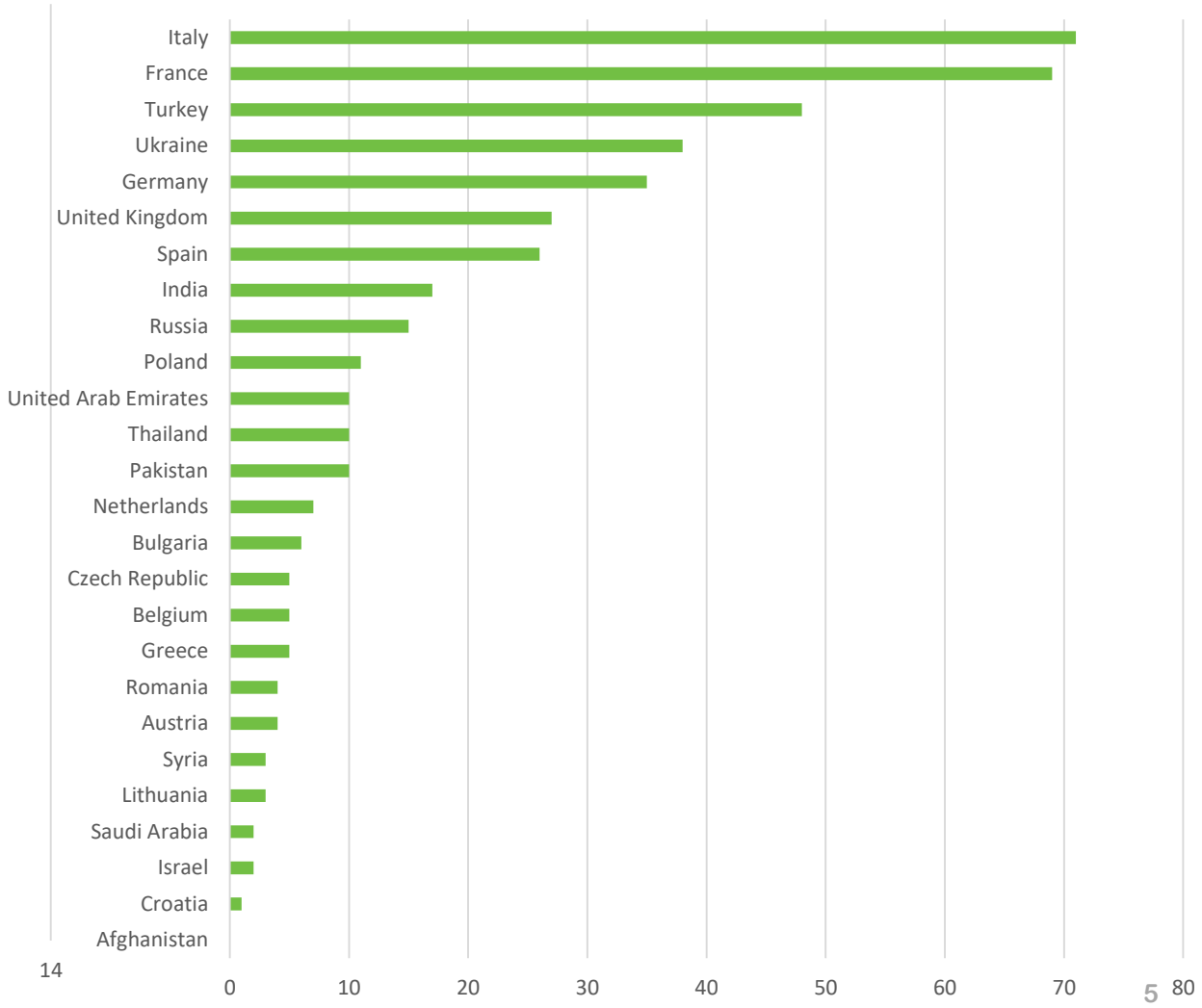
- **Objective 1:** To describe the epidemiology of membranous nephropathy in children in a large multinational cohort.
  - Population: All patients with MN (IMN and secondary MN)
  - Data collected: Demographics, clinical data, anti-PLA2R Ab at diagnosis
- **Objective 2:** To assess the oucomes of pediatric patients treated for IMN based on treatment regimen and immunological monitoring (anti-PLA2R Ab during follow-up).
  - Population: All patients with idiopathic MN
  - Additional data collected: Treatment regimen, outcomes (uPCR, serum albumin, eGFR, complications), immunological monitoring (anti-PLA2R Ab, B cell count if RTX…)
- **Objective 3:** Assess the prevalence of « new antigens » in children with IMN and create a tissue biobank of IMN without identified Ag for future discovery analysis.

Feasibility Survey

74 centers from 26 countries

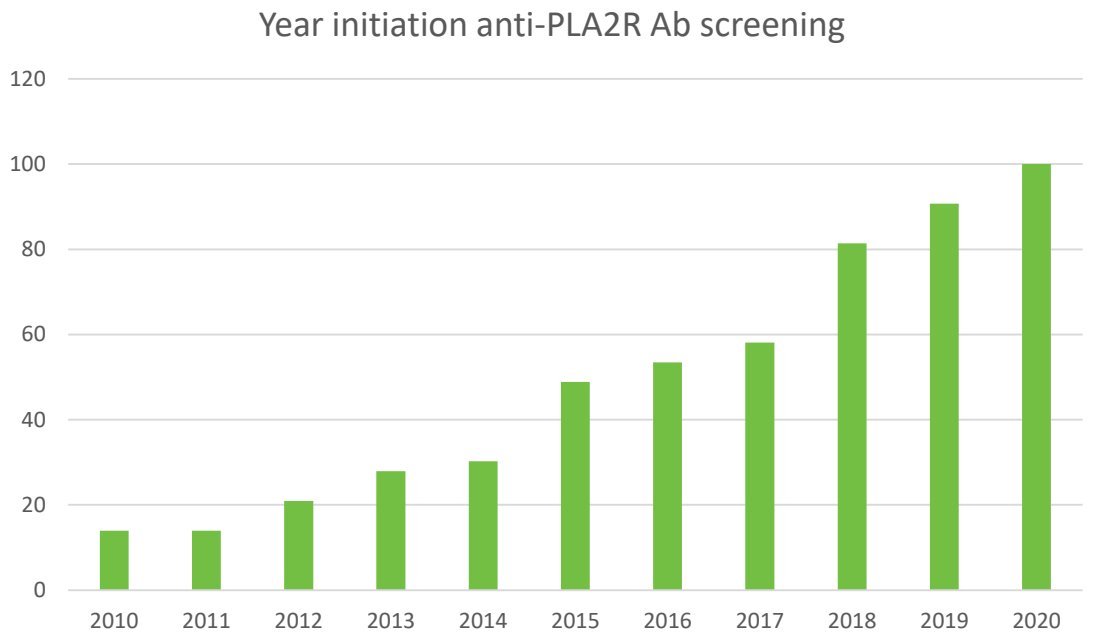


434 patients



PLA2R Ab testing

19/74 centers (24%) do not screen for anti-PLA2R Ab at diagnosis



47/55 centers (85%) monitor anti-PLA2R Ab titers during follow-up

Next steps: Objectives 1 and 2

- IRB approved in France (centers from countries requesting a local IRB approval will be provided with study documents for submission)
- Based on the answers to the survey, centers will be contacted to participate in the various objectives of the study.
- RedCap access will be provided to enter data for Objectives 1 and 2
- Data collection deadline *(December 30th 2021)*

Next steps: Objective 3

Samples required for antigen determination & serology

- Only patients with unknown antigen are included in the immunopathological study
  - Patients with positive PLA2R/THSD7A serology are excluded
  - For patients with negative PLA2R serology, the biopsy should be stained for PLA2R antigen
  - *For centers without access to PLA2R Ab and staining, we are working on identifying "local" labs to perform this first line screening.*
- Please provide slides , 3uM, from the paraffin-embedded biopsies with 2 sections per slide (ideally 4, one per antigen)
- Serum, ideally 1 ml, sampled at the time of biopsy or during active disease (heavy proteinuria); if positive (circulating antibodies), repeated sampling would be of interest for patients monitoring

List of centers

Afghanistan	Kabul
Austria	Vienna
Bulgaria	Sofia
Croatia	Zagreb
Greece	Thessaloniki
India	Kolkata
Israel	Tel Aviv
Lithuania	Vilnius
Pakistan	Karachi
Romania	Bucharest
Saudi Arabia	Alkhobar
Syria	Aleppo
Thailand	Bangkok
United Arab Emirates	Dubai
Belgium	Leuven, Gent
Czech Republic	Prague
Netherlands	Amsterdam, Groningen
Poland	Warsaw, Wrocław
Russia	Moscow
Ukraine	Lviv, Dnipro
Spain	Madrid, Barcelona, Barakaldo
United Kingdom	Southampton, Birmingham, Manchester, London, Nottingham
Germany	Frankfurt, Rostock, Stuttgart, Ulm, Münster, Hannover, Hamburg
Turkey	Istanbul, Ankara, Adana, Antalya
Italy	Milan, Bari, Naples, Florence, Bologna, Padua, Padova, Genova, Roma
France	Tours, Toulouse, Rouen, Nantes, Marseille, St Denis, Paris, Lille, Bron, Reims, Montpellier.