

Defining surveillance of extra-renal manifestations in MAPKBP1-related Nephronophthisis: a systematic review PROTOCOL

Working Title: *(the title may change for publication; this will be notified)*

Defining surveillance of extra-renal manifestations in MAPKBP1-related Nephronophthisis: a systematic review

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Review Questions:

- Do patients with biallelic germline pathogenic variants in the *MAPKBP1* gene manifest only nephrological diseases?
- Is there enough evidence to support a broader follow-up and surveillance?

Search Strategies

Since the MAPKBP1-nephronophthisis is a rare disease, the main source of information will come from case reports and case series.

Data will be sought from:

- MEDLINE (through PubMed)
- Google Scholar
- Scopus and Web of Science
- ClinVar database
- Unpublished/preprint (e.g. MedRxiv, direct contact)

No date restrictions will be applied. Searches will include all relevant studies published in English or Italian from inception to June 2026.

The core term for searches is “MAPKBP1”: we don’t expect too many results, so there is no need of adding more keywords.

All retrieved citations will be exported to a reference management software. Duplicates will be removed, and the final list will be prepared for title and abstract screening. All search activity will be documented in a shared folder.

Condition being studied

Biallelic pathogenic variants in MAPKBP1 have been recently associated with “NEPHRONOPHTHISIS 20” (NPHP20; MIM #617271), a rare autosomal recessive condition

characterized by a fast progression to End Stage Renal Disease already in young adulthood. It is generally considered a non-syndromic nephronophthisis affecting only the kidney; the OMIM Clinical Synopsis states that “Patients do not have extra-renal manifestations”. However, some recent case reports showed the presence of skeletal features, mainly scoliosis and long fingers, and vascular abnormalities. Our clinical experience reflects this impression, so we decided to gather clinical and molecular data of patients with MAPKBP1 biallelic variants AND extra-renal manifestations. This will improve follow-up strategy and surveillance for these patients.

Study Population

Studies involving human participants of any age or gender will be included, with no restrictions based on health status or clinical indication. Eventual basic science studies on cells and animal models will be used only for the introduction and to support possible clinical outcomes.

Intervention / Exposure

All studies in which one or more patient underwent a comprehensive genetic testing (for diagnostic or research purpose) that lead to the identification of a biallelic variant in the MAPKBP1 gene.

Comparator / Control

This review does not have any comparator(s) or control(s).

Main outcomes and measures of effect

The review will assess the presence and evolution of extra-renal features in patients with a biallelic alteration of the MAPKBP1 gene.

The main expected outcomes are:

- 1) A comprehensive list of all the causative genetic variants described in literature and in public databases. This will improve variant classification, the individuation of hot spots or relevant domain and possible recurring variants
- 2) Objective clinical outcomes, such as lab values, recognized clinical scores (e.g. Beighton score for joint laxity) or dysmorphological terms (HPO)
- 3) Patient-reported symptoms - such as pain, myasthenia, headache...etc.

The outcomes will be reported in a descriptive manner and the frequency will be studied through descriptive statistics. The final aim is to define the probability of extra-renal features in this syndrome and thus identify a possible follow-up and surveillance strategy.

Data extraction

The following data will be extracted from each included study:

- Study characteristics: authors, publication year, country, study design, setting
- Population details (for case series): sample size, age, sex, health status
- Genetic testing details: targeted panel VS whole exome/genome sequencing
- Imaging details: application of ultrasound, TC or MRI in studied patients
- Primary outcomes: pathogenic variants, objective and subjective signs and symptoms
- Results and descriptive statistics (frequencies, contingency tables...)
- Funding source and conflict of interest declarations
- Risk of bias assessments per study design

All data will be managed using a standardized data extraction form.

Risk of bias/ Quality assessment

The review will be based on case reports and case series, thus a simplified tool adapted from the JBI critical appraisal checklist will be used.

The focus will be on Clarity of reporting and Completeness of data reporting. The main source of bias will likely reside in the absence of specific clinical and imaging investigation for extra-renal features in the reported patients. For example, pediatric patients who were tested for nephronophthisis may hide a skeletal or cardiovascular feature that was missed or not reported. Missing data will be addressed and the clear absence of a symptom will be certified only if the specific diagnostic exam has been executed.

On the genetic side, a secondary genetic diagnosis may be missed, especially if a target multigenic panel have been used. When retrieving data from articles, a focus on possible other genetic explanation of extra-renal features will be guaranteed.

Two reviewers will independently assess the risk of bias. Disagreements will be resolved through discussion or third-party input. Risk of bias scores will be used to inform interpretation of results, while no studies will be excluded solely based on quality rating.

Data synthesis plan

A narrative synthesis approach will be used due to the expected heterogeneity in study designs, interventions, and outcomes. The synthesis plan includes descriptive summaries, tabulation and thematic analysis (e.g. focus on skeletal disorders, cardiovascular...).

No metanalysis is applicable.

Analysis of subgroups/subsets

Where data allow, subgroup and subset analyses will be conducted to explore potential differences in outcomes based on:

- Age at diagnosis (pediatric VS adult)
- Type of variant (truncating VS non-truncating)
- Protein domain involved (if applicable).

Funding

No dedicated funding is expected for this study. The review process will be performed on researcher's own time.