PROTOCOL

Genetic Spectrum of Primary Ciliary Dyskinesia in Iranian patients: A Systematic Review Protocol

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Abstract

Background: Primary ciliary dyskinesia (PCD) is a rare inherited disorder caused by defects in the structure or function of motile cilia. More than 60 genes have been linked to PCD, but the genetic variants reported in affected individuals differ across populations. This systematic review aims to describe the genetic spectrum of PCD reported in Iran, examine parental consanguinity, and explore possible relationships between genetic findings and clinical features.

Methods: We will search PubMed/MEDLINE, Scopus, Web of Science, Embase, Google Scholar, and Iranian databases, including SID, Magiran, and IranMedex, from inception without date restrictions. Case reports, case series, and observational studies describing molecular genetic findings in Iranian patients with PCD will be eligible. Data will be collected on patient characteristics, parental consanguinity, diagnostic approaches, affected genes, reported variants, zygosity, and clinical manifestations. Variants will be reviewed using American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines. Study quality will be evaluated using appropriate Joanna Briggs Institute (JBI) tools and the Newcastle–Ottawa Scale (NOS).

Results: The review will summarize the genes and variants reported in Iranian patients, highlight recurrent and potential founder variants, describe reported consanguinity patterns, and examine available evidence on genotype–phenotype relationships. When individual patient data are available, genetic findings will be compared with clinical and demographic characteristics.

Conclusion: By bringing together the available evidence, this review will clarify the reported genetic landscape of PCD in Iran. The findings may help guide molecular testing, strengthen genetic counseling, and support the development of national PCD registries.

Keywords: Primary Ciliary Dyskinesia; Genetic Variation; Ciliopathies; Consanguinity; Iran

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Background

Primary ciliary dyskinesia (PCD) is a rare inherited disorder characterized by marked genetic heterogeneity, displaying predominantly autosomal recessive inheritance, alongside rare X-linked (e.g., *RPGR*, *OFD1*) and autosomal dominant (e.g., *FOXJ1*) transmissions [1, 2]. The underlying pathology involves structural or functional abnormalities of motile cilia, which compromise mucociliary clearance and disrupt embryonic left–right body axis determination [1] . Patients characteristically present with chronic upper and lower respiratory tract infections, unexplained neonatal respiratory distress, bronchiectasis, chronic rhino-sinusitis, recurrent otitis media, and subfertility or infertility [2]. Situs inversus totalis is present in approximately 40–50% of individuals with primary ciliary dyskinesia (PCD), while other laterality abnormalities, such as situs ambiguus and heterotaxy, have also been reported in affected individuals [1-4].

The global prevalence of PCD is estimated at 1 in 10,000 to 1 in 20,000 live births, although the true incidence is likely higher due to diagnostic delays and under-recognition [3, 5]. Notably, higher prevalence rates are documented in genetically isolated communities and in populations with elevated rates of consanguineous unions [2, 4]. In Iran, where consanguineous marriage is culturally prevalent-estimated at approximately 38% overall, with first-cousin unions predominating-the biological burden of autosomal recessive disorders is disproportionately elevated, frequently unmasking rare, homozygous, and population-specific genetic alleles [6] .

To date, disease-causing variants in more than 60 genes have been implicated in PCD pathogenesis [7]. The mutational spectrum varies significantly across geographic and ethnic groups [2, 8, 9]. While variants in *DNAH5*, *DNAH11*, and *DNAI1* predominate in Western European cohorts, distinct founder variants and mutational spectra have been described in East Asian and Middle Eastern populations [1, 10, 11]. Studies from neighboring Middle Eastern cohorts have characterized recurrent variants in genes such as *CCDC39*, *RSPH9*, *DNAAF11* (*LRRC6*), and *CCDC103*, demonstrating marked regional molecular diversity [12-15].

Advances in next-generation sequencing (NGS), including targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS), have transformed the molecular diagnostic pipeline for PCD [11, 16] . Despite broad international systematic syntheses describing global PCD epidemiology [3, 7, 10], population-specific genetic evidence for Iran remains fragmented across single-center case reports, pedigree evaluations, and small series. High consanguinity rates and distinct ethnic subpopulations (including Persian, Azeri, Kurd, Lur, Arab, Baluch, and Turkmen groups) suggest that Iranian patients may harbor private or recurrent founder variants under-represented in international registries. Standard diagnostic gene panels designed primarily from European cohorts may therefore demonstrate reduced clinical sensitivity in Iran.

A dedicated systematic review is required to consolidate the Iranian molecular spectrum, map recurrent alleles, delineate genotype–phenotype correlations, quantify consanguinity rates, and inform the rational design of cost-effective diagnostic workflows tailored to the region [13, 16].

Primary Objective

To systematically identify and synthesize published evidence regarding the genetic spectrum of primary ciliary dyskinesia in Iranian patients.

Secondary Objectives

- To determine the most frequently reported PCD-associated genes and pathogenic variants in the Iranian population.
- To identify recurrent, private, or potential founder variants in Iranian kindred.
- To summarize parental consanguinity rates and degrees of kinship among reported patients.
- To evaluate documented genotype–phenotype correlations across structural and functional ciliary categories.

Review Questions

- What is the reported genetic spectrum of PCD among Iranian patients?
- What are the observed parental consanguinity patterns?
- What genotype–phenotype correlations have been documented?

Methods

Protocol Design and Registration

This protocol was designed following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines (checklist completed in Supplementary File 1). The review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261407192. Any subsequent amendments to the protocol will be documented transparently in the final systematic review report.

Eligibility Criteria

Study Designs. Peer-reviewed observational studies-including prospective and retrospective cohort, case-control, and cross-sectional studies-as well as case series and individual case reports reporting original molecular genetic findings will be included. Reviews, systematic reviews, meta-analyses, editorials, commentaries, animal models, in vitro experimental studies, and conference

abstracts lacking full methodological datasets will be excluded. Where multiple publications describe overlapping or identical patient cohorts, the article reporting the most comprehensive clinical and genetic dataset will be retained.

Participants. Patients of any age, biological sex, or ethnicity originating from or residing in Iran with a clinically or genetically verified diagnosis of PCD will be included. Diagnostic eligibility will require at least one of the following recognized criteria:

1. Identification of bi-allelic pathogenic or likely pathogenic variants (or hemizygous/heterozygous variants for X-linked and autosomal dominant forms) in established PCD-related genes;
2. Hallmark ciliary ultrastructural defects identified via transmission electron microscopy (TEM);
3. Abnormally low nasal nitric oxide (nNO) measurement accompanied by typical clinical features, compliant with European Respiratory Society (ERS) or American Thoracic Society (ATS) guidelines [17];
4. Demonstrable, persistent ciliary motility or beat frequency abnormalities evaluated by high-speed video microscopy analysis (HSVA);
5. Clinical diagnostic criteria established by published international consensus guidelines [17].

Studies analyzing multinational or mixed cohorts without separately extractable data for Iranian participants will be excluded.

Genetic Exposure. The exposure of interest is the identification of genetic variants in PCD-associated genes identified through molecular sequencing approaches, including Sanger sequencing, targeted gene panels, Whole Exome Sequencing (WES), and Whole Genome Sequencing (WGS).

Information Sources and Search Strategy

Electronic literature searches will be performed across international databases (PubMed/MEDLINE, Embase, Scopus, Web of Science, and Google Scholar) and Iranian national databases (Scientific Information Database [SID], Magiran, and IranMedex) from database inception to the search date, without language or publication date restrictions. The exact date of the final search will be documented and reported in the completed systematic review. Both English and Persian publications will be evaluated.

Supplementary search methods will include backward citation searching of eligible studies and relevant review articles, alongside manual screening of reference lists from included works.

The search syntax was developed by combining Medical Subject Headings (MeSH), Emtree terms, and free-text terms covering three core concepts: (1) Primary Ciliary Dyskinesia and related ciliopathies (e.g., "Kartagener Syndrome", "ciliary motility disorders"); (2) Genetic terminology (e.g., "mutation", "variant", "exome sequencing", "whole-genome sequencing", "NGS"); and (3) Geographic and demographic terms ("Iran", "Iranian", "Persian"). Complete, fully reproducible search syntaxes for PubMed/MEDLINE and SID are provided in Supplementary Appendix 1.

Study Selection

All retrieved citations will be imported into EndNote (Clarivate, Philadelphia, PA), and duplicate records will be removed electronically and manually. Study selection will be performed independently by two investigators using a two-tier screening process:

1. Title and Abstract Screening: Records will be evaluated against predefined eligibility criteria. Articles that clearly do not meet inclusion criteria will be excluded.
2. Full-Text Review: Potentially eligible articles or citations with ambiguous eligibility will undergo full-text assessment.

Reasons for full-text exclusions will be formally recorded. Disagreements between reviewers at either stage will be resolved by discussion or through consultation with a third senior reviewer. The screening and selection workflow will be mapped using a standard PRISMA flow diagram.

Data Extraction and Phenotypic Framework

Data will be extracted independently by two reviewers using a standardized extraction template. Discrepancies will be reconciled by consensus or third-party adjudication. The following parameters will be systematically collected:

- **Study Characteristics:** First author, publication year, city/province, study design, and clinical setting.
- **Patient Demographics:** Sample size, age at symptom onset, age at definitive diagnosis, sex, and ethnicity/subpopulation (if reported).
- **Consanguinity Data:** Parental consanguinity status (positive, negative, or unreported), prevalence of consanguinity, and degree of biological relatedness, categorized as follows:
  - First cousins (inbreeding coefficient, F = 1/16);
  - More distant relatives, including first cousins once removed (F = 1/32) and second cousins (F = 1/64);
  - Consanguineous unions of unspecified degree;
  - Non-consanguineous unions.
- **Diagnostic Modalities:** Application and findings of TEM, nNO, HSVA, ciliary immunofluorescence, and chest/sinus CT imaging.
- **Phenotypic Domains:**
  1. *Laterality Profile:* Situs solitus, situs inversus totalis, heterotaxy (situs ambiguus), and congenital heart disease.

2. *Respiratory Manifestations:* Bronchiectasis, chronic productive cough, recurrent pneumonia, chronic rhinosinusitis, nasal polyposis, and recurrent/chronic otitis media.
3. *Fertility Status:* Male infertility (astheno-teratozoospermia, azoospermia), female subfertility, history of ectopic pregnancy, or verified fertility.
4. *Neonatal/Early-Life Indicators:* Unexplained neonatal respiratory distress in term infants, neonatal oxygen requirement, or early rhinorrhea.

- **Molecular Genetic Data:** Implicated gene name, transcript ID, cDNA change, protein change, variant type (missense, nonsense, frameshift, splice-site, copy-number variation), zygosity (homozygous, compound heterozygous, hemizygous, heterozygous), sequencing methodology, and inheritance pattern.

Variant Classification and Genomic Curation Framework

All reported genetic variants will be compiled and aligned with canonical human reference transcripts using Human Genome Variation Society (HGVS) nomenclature (v20.05). Standardized curation will follow this framework:

- Primary Variant Synthesis: The primary mutational spectrum will include variants classified as Pathogenic (Class 5) or Likely Pathogenic (Class 4) according to the 2015 American College of Medical Genetics and Genomics / Association for Molecular Pathology (ACMG/AMP) guidelines, or relevant ClinGen Sequence Variant Interpretation (SVI) expert criteria.
- Variants of Uncertain Significance (VUS): Variants designated as Class 3 (VUS) will be excluded from the primary pathogenic spectrum and summarized in a dedicated secondary descriptive analysis, noting computational predictions (e.g., REVEL, CADD), published functional assays, and familial co-segregation.
- Variant Re-evaluation Protocol: For variants published prior to 2015 or reported without formal classifications, two reviewers with genetic expertise will re-evaluate pathogenicity using ACMG/AMP criteria, referencing ClinVar, population allele frequencies (gnomAD Middle Eastern and global datasets), and curated functional literature.

Missing Data and Incomplete Reporting Strategy

1. Minimum Genetic Reporting Threshold: Studies must report, at minimum, the affected gene name and unambiguous variant notation (cDNA/protein change or genomic coordinates).
2. Author Query Protocol: When essential genetic variables (e.g., zygosity, transcript accession, or exact coordinate) or primary phenotypic domains are missing, the corresponding authors will be contacted via email. A structured follow-up reminder will be dispatched at 14 days. If no response is obtained within 28 days of the initial inquiry, the variable will be marked as "Not Reported" (NR).
3. Synthesis Handling: Studies lacking verified variant details will be retained for contextual discussion of clinical epidemiology if diagnostic criteria are fulfilled, but will be excluded from molecular frequency and recurrent-variant tabulations.

Outcomes

Outcomes were defined a priori as follows.

Primary outcomes:

(1) Distribution and relative frequency of pathogenic and likely pathogenic variants in known PCD-associated genes among Iranian patients;

(2) Prevalence and degree of parental consanguinity in reported pedigrees;

(3) Genotype–phenotype correlation patterns stratified by ciliary ultrastructural/functional groups.

Secondary outcomes:

Identification of recurrent or potential founder variants, utilization of diagnostic modalities, and frequency of neonatal respiratory distress.

Risk of Bias Assessment

The methodological quality of included studies will be independently evaluated by two reviewers using study-design-specific instruments:

- **Case Reports:** Appraised using the *Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports* (8 evaluation criteria covering demographic clarity, clinical history, diagnostic assessment, and adverse event reporting).
- **Case Series:** Appraised using the *JBI Critical Appraisal Checklist for Case Series* (10 criteria assessing inclusion criteria, consecutive enrollment, reporting completeness, and diagnostic standard reliability).
- **Comparative Observational Studies:** Appraised using the *Newcastle–Ottawa Scale (NOS)* for cohort and case-control studies across participant selection, comparability, and outcome/exposure ascertainment [18].

Studies will not be excluded based on appraisal scores alone; however, identified design limitations and risks of bias will be integrated into the narrative interpretation.

Data Synthesis and Analytic Framework

Given the anticipated clinical, diagnostic, and methodological heterogeneity across included studies, a narrative and descriptive synthesis will be conducted. The synthesis will be stratified a priori by study design: Case reports and case series will be used solely

to describe the genetic spectrum (genes, variants, zygosity, and individual phenotypes) and will not contribute to quantitative frequency estimates or pooled prevalence calculations; Observational studies (cohort and cross-sectional) will be prioritized for any quantitative summaries of variant frequencies or associations where data homogeneity permits. Quantitative pooling and meta-analyses will not be performed as the primary approach unless sufficiently homogeneous cohorts reporting comparable genetic frequencies are identified; if undertaken, a random-effects model (DerSimonian–Laird) will be applied.

Heterogeneity will be assessed qualitatively by examining differences in diagnostic criteria, sequencing platforms, patient ascertainment, and geographic origin; if quantitative synthesis occurs, statistical heterogeneity will be quantified using the I^2 statistic and Cochran's Q test ($I^2 > 50\%$ indicating substantial heterogeneity).

Extracted data will be synthesized across the following structures:

- **Gene and Variant Frequencies:** Tabular summaries of implicated genes, specific pathogenic variants, mutational mechanisms, and zygosity patterns.
- **Recurrent and Founder Variants:** Recurrent variants-defined as identical pathogenic variants documented in two or more unrelated pedigrees-will be evaluated for potential founder effects by mapping geographic distribution and homozygosity patterns.
- **Consanguinity Summary:** Descriptive synthesis of consanguinity percentages and degree-of-kinship distributions.
- **Genotype–Phenotype Relationships:** Synthesized using a two-tier framework:
  - *Tier 1 (Author-Reported Correlations):* Explicit genotype–phenotype associations and statistical findings documented by primary study authors.
  - *Tier 2 (Pattern-Based Synthesis):* Aggregation of individual patient data by structural ciliary functional groups (e.g., outer dynein arm components [*DNAH5*, *DNAI1*], inner dynein arm and regulatory complexes [*CCDC39*, *CCDC40*], radial spokes [*RSPH1*, *RSPH4A*, *RSPH9*], and cytoplasmic pre-assembly complexes [*DNAAF* family]) crossed with phenotypic features (situs abnormalities, bronchiectasis presence, and fertility).

Subgroup and Sensitivity Analyses

Where data permit, exploratory subgroup analyses will be conducted across:

- Parental consanguinity status (consanguineous vs. non-consanguineous kindreds);
- Diagnostic certainty (ATS/ERS-confirmed vs. clinically suspected cases);
- Sequencing technology (NGS panels/WES/WGS vs. targeted Sanger sequencing);
- Geographic/provincial distribution within Iran.

Methodological sensitivity analyses will examine the robustness of the synthesized findings by:

1. Excluding studies classified as high risk of bias on the JBI checklists or scoring low on the NOS;
2. Restricting the molecular spectrum strictly to ACMG/AMP Class 4 and 5 variants, excluding Class 3 (VUS);
3. Comparing findings between studies published prior to 2015 and those published during the modern NGS era (post-2015).

Assessment of Publication and Reporting Bias

Because this systematic review primarily synthesizes descriptive observational studies, case series, and case reports, conventional quantitative tests for publication bias (e.g., funnel plots, Egger's regression test) are methodologically unsuitable. Publication bias will be evaluated qualitatively across three domain-specific considerations:

1. ***Positive-Result and Novelty Bias:*** The tendency for case reports and small series to preferentially report novel mutations, severe presentations, or classic syndromic features (e.g., Kartagener triad), which may underestimate non-syndromic PCD phenotypes or variants of uncertain significance.
2. ***Diagnostic and Geographic Accessibility Bias:*** Disparities in access to advanced molecular testing across Iran, which may over-represent patients evaluated at tertiary referral centers in major metropolitan centers.
3. ***Non-reporting of Inconclusive Sequencing****:* The systematic underreporting of negative or non-diagnostic genetic analyses in patients with strong clinical PCD phenotypes.

Discussion

Primary ciliary dyskinesia remains challenging to diagnose due to its phenotypic variability and the specialized infra-structure required for definitive testing, including high-speed video microscopy, transmission electron microscopy, and next-generation sequencing panels [3, 17]. In resource-constrained settings, clinical under-recognition and diagnostic delays are common, often resulting in advanced bronchiectasis and irreversible pulmonary impairment prior to formal identification[19] .

Although molecular genetic testing has emerged as a cornerstone of PCD diagnosis, the genetic landscape in Middle Eastern populations exhibits marked differences from that in Western cohorts [8, 12]. High rates of endogamy and consanguinity in Iran amplify the expression of homozygous pathogenic alleles, increasing the likelihood of identifying novel disease-associated genes and population-specific founder variants [6]. However, the existing literature on Iranian PCD genetics consists primarily of isolated case descriptions, small family pedigrees, and heterogeneous clinical series.

This systematic review will synthesize the existing molecular evidence in Iranian patients, catalog recurrent variants, assess consanguinity associations, and map genotype–phenotype patterns. Identifying recurrent regional variants has practical clinical relevance: it can inform the rational development of localized, tiered diagnostic gene panels, reduce testing turnaround times and costs, and enhance the precision of reproductive genetic counseling and pre-implantation diagnosis in affected families.

Strengths and Limitations

Key strengths of this systematic review protocol include prospective registration with PROSPERO, adherence to PRISMA-P reporting standards, comprehensive indexing across both international and Persian-language databases, and the implementation of standardized ACMG/AMP variant reclassification.

Anticipated limitations relate to the nature of the primary evidence base, which is expected to consist largely of case reports and small series characterized by variable diagnostic depth, historical shifts in genetic testing methods, and incomplete phenotypic reporting. These methodological and reporting variations will be addressed through explicit risk-of-bias frameworks, defined missing-data protocols, and qualitative reporting bias appraisals.

Conclusion

The available evidence regarding the molecular genetics of PCD in Iranian patients is dispersed across fragmented clinical reports. By applying a systematic search, standardized variant curation, and structured phenotypic extraction, this review will delineate the reported genetic spectrum, clarify genotype–phenotype associations, and quantify consanguinity rates in Iranian PCD cohorts. These findings will clarify current diagnostic gaps and help establish evidence-based priorities for molecular diagnostic panels and rare-disease registries in Iran.

Abbreviations

ACMG/AMP	American College of Medical Genetics and Genomics / Association for Molecular Pathology
ATS	American Thoracic Society
ERS	European Respiratory Society
HGVS	Human Genome Variation Society
HSVA	High-Speed Video Microscopy Analysis
JBI	Joanna Briggs Institute
NGS	Next-Generation Sequencing
nNO	Nasal Nitric Oxide
NOS	Newcastle–Ottawa Scale
PCD	Primary Ciliary Dyskinesia
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO	International Prospective Register of Systematic Reviews
TEM	Transmission Electron Microscopy
VUS	Variant of Uncertain Significance
WES	Whole-Exome Sequencing
WGS	Whole-Genome Sequencing

Declarations

Conflict of Interest: The authors declare that they have no competing financial or personal interests.

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Consent for publication: Not applicable.

Ethics Approval and Consent to Participate: As this systematic review protocol synthesizes data derived exclusively from previously published literature, direct human participant involvement and primary data collection are absent. Formal institutional ethical approval and individual informed consent are not required.

AI Disclosure: Artificial intelligence-assisted tools were utilized solely for language editing, stylistic improvements, and grammatical polishing. All conceptual frameworks, methodological designs, search strategies, and evidence interpretation were independently developed and approved by the authors.

Author Contributions: All authors contributed to the conceptualization and methodological design of the study. SZM and ZA developed the systematic review protocol, formulated the search parameters, and established the eligibility criteria. Both authors contributed to drafting the manuscript, developing data extraction frameworks, and critically revising the final protocol manuscript. Both authors approved the final version.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.18502/jimpc.v9il.22986

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