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Interferonopathy associated with ISG15 gene mutation: a systematic review

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Maria Eduarda Barreto de Siervi[1], Paula Dantas Meireles Silva[1,2], Christine Carvalho Almeida[1], Leila Vieira Borges Trancoso Neves[2], José arlson Santos de Oliveira[2]

[1]Hospital Martagão Gesteira, Salvador, Bahia, Brasil.; [2]Universidade Federal da Bahia, Salvador, Bahia, Brasil.

Maria Eduarda Siervi
Hospital Martagao Gesteira

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Disclaimer

No conflits of interest to disclose.

Abstract

In infectious diseases, type I interferons (IFN-1) play a central role in the regulation of the response to pathogens, which is a process induced by interferon-stimulated genes (ISGs). In infectious diseases, type I interferons (IFN-1) play a central role in regulating the response to pathogens, a process induced by interferon-stimulated genes (ISGs). The ISG15 gene regulates cellular trafficking, acting on the cell cycle and immunomodulation, primarily in response to viral and mycobacterial infections. Individuals with ISG15 loss-of-function (LoF) typically present with Mendelian Susceptibility to Mycobacterial Diseases (MSMD) and basal ganglia calcifications, but recent evidence has demonstrated phenotypic variability, ranging from susceptibility to mycobacterial infection to autoinflammation. This study aims to report a case of interferonopathy associated with an ISG15 mutation with an unusual presentation and perform a systematic review of the literature on this condition.

Before start

1. Study Types: Case-report studies, case-series studies.
2. Participant Age: Patients of all ages will be included.
3. Exposure: Not applicable
4. Outcome: Not applicable

Exclusion Criteria

1 Reviews, meta-analyses, letters to the editor are excluded.

2 Studies examining exclusively the pathophysiological and/or genetic aspects of ISG15 are excluded.

3 Studies focused on in vitro experiments or in non-human populations are excluded.

4 Studies that addressed the ISG15 mutation in contexts other than interferonopathy are excluded.

5 Studies that addressed MSMD not associated with the ISG15 mutation are excluded.

Search strategy

6 PubMed: (ISG15 OR interferon-stimulated genes 15 OR ISG15 protein, human OR ISG15 deficiency) AND (interferon type I OR type I Interferonopathies OR Interferonopathies OR Interferonopathy OR Type I Interferonopathy OR Interferonopath* OR mycobacterial disease OR Mendelian susceptibility to mycobacterial infections OR MSMD OR inflammatory cutaneous lesions).

7 Scopus: TITLE-ABS-KEY ("ISG15" OR "interferon-stimulated genes 15" OR "ISG15 protein, human" OR "ISG15 deficiency") AND TITLE-ABS-KEY ("interferon type I" OR "type I Interferonopathies" OR "Interferonopathies" OR "Interferonopathy" OR "Type I Interferonopathy" OR "Interferonopath*" OR "mycobacterial disease" OR "Mendelian susceptibility to mycobacterial infections" OR "MSMD" OR "inflammatory cutaneous lesions").

8 Cochrane: ("ISG15" OR "interferon-stimulated genes 15" OR "ISG15 protein, human" OR "ISG15 deficiency") AND ("interferon type I" OR "type I Interferonopathies" OR "Interferonopathies" OR "Interferonopathy" OR "Type I Interferonopathy" OR "Interferonopath*" OR "mycobacterial disease" OR "Mendelian susceptibility to mycobacterial infections" OR "MSMD" OR "inflammatory cutaneous lesions").

Data extraction

9 The search file will be exported to Zotero to delete duplicates and organize the studies for triage. Two reviewers will independently select the studies based on title and abstract, and in a second moment, read them in full to get to the final number of studies included. After the selection, the data of the first author, year of publication, population, and participant characteristics will be collected, such as the primary clinical characteristics. Data will be extracted and recorded on an Excel template by two authors.

Dissemination Plan

10 The review's results are planned to be published in a peer-reviewed scientific journal and presented at relevant scientific conferences.

Acknowledgements

Funding/Sponsors: There is no funding for this review.
Conflict of Interest: The authors declare no conflict of interest.
Project Dates: Start Date: 28th of October 2025
Current Stage of Review: Search and screening of titles and abstracts.

Search strategy:

PubMed: (ISG15 OR interferon-stimulated genes 15 OR ISG15 protein, human OR ISG15 deficiency) AND (interferon type I OR type I Interferonopathies OR Interferonopathies OR Interferonopathy OR Type I Interferonopathy OR Interferonopath* OR mycobacterial disease OR Mendelian susceptibility to mycobacterial infections OR MSMD OR inflammatory cutaneous lesions).

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Cochrane: ("ISG15" OR "interferon-stimulated genes 15" OR "ISG15 protein, human" OR "ISG15 deficiency") AND ("interferon type I" OR "type I Interferonopathies" OR "Interferonopathies" OR "Interferonopathy" OR "Type I Interferonopathy" OR "Interferonopath*" OR "mycobacterial disease" OR "Mendelian susceptibility to mycobacterial infections" OR "MSMD" OR "inflammatory cutaneous lesions").

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