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REVIEWER'S REPORT

Manuscript No.: IJAR-53634 Date: 30/08/2025

Title: Genetic and Neuropeptide Aspects in Central Precocious Puberty (CPP)

Recommendation:
Accept as it is .....
Accept after minor revision.....
Accept after major revision **YES**.....
Do not accept (*Reasons below*) .....

Rating	Excel.	Good	Fair	Poor
Originality	YES			
Techn. Quality		YES		
Clarity	YES			
Significance	YES			

Reviewer Name: Emmanuel KUBANA **Date:** 30/08/2025

Reviewer's Comment

The manuscript provides a comprehensive and well-structured review of the genetic and neuropeptidergic mechanisms involved in central precocious puberty (CPP). The paper is timely, given the increasing recognition of genetic and neuroendocrine contributions to pubertal timing. The authors successfully synthesize evidence from genetic studies, neuropeptide biology, diagnostics, and therapeutic interventions. The review is clearly written, logically organized, and clinically relevant. However, several areas would benefit from refinement to strengthen the paper's impact and scientific rigor.

Detailed Reviewer's Report

Strengths:

1. The manuscript provides a clear and thorough background on the role of MKRN3, DLK1, KISS1, and KISS1R mutations in CPP.
2. The integration of both genetic and neuropeptide aspects into a single review is valuable and highlights the multidimensional nature of CPP.
3. Clinical relevance is well emphasized, particularly in the sections on diagnosis and management.
4. Future perspectives are well discussed, with attention to emerging biomarkers, neuropeptide therapies, and precision medicine.

Weaknesses / Areas for Improvement:

- **References:** Some statements are not adequately referenced (e.g., psychosocial outcomes, prevalence data, long-term metabolic risks). More recent primary studies (2022–2024) should be added.
- **Balance of Content:** The genetic aspects are described in much greater depth than the neuropeptidergic mechanisms. Expanding discussion on neurokinin B, dynorphin, and KNDy neuron physiology would strengthen balance.

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- **Clinical Application of Biomarkers:** The discussion on serum kisspeptin and DLK1 levels is promising but requires clarification regarding their clinical feasibility, cost, and availability.
- **Therapeutic Section:** While GnRHa therapy is well covered, the review could expand on potential side effects, adherence challenges, and newer delivery systems.
- **Psychosocial Outcomes:** The review mentions psychosocial distress but does not adequately expand on how treatment impacts psychological well-being or quality of life. A dedicated subsection would be valuable.
- **Language and Style:** Minor grammatical issues and redundancies appear throughout the text. A thorough language edit would improve readability.
- **Figures/Tables:** Inclusion of summary tables or diagrams (e.g., genetic mutations and their clinical features; diagnostic algorithm; comparison of therapies) would greatly enhance clarity and accessibility.

Recommendation:
Major Revision

The manuscript is scientifically sound and clinically important, but revisions are necessary to ensure balance between genetic and neuropeptide aspects, strengthen evidence with updated references, and improve clarity with tables/figures.