Author’s response to reviews

Title: Familial early puberty: presentation and inheritance pattern in 139 families

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Author’s response to reviews:

Familial early puberty shows predominantly maternal inheritance

Changed in

Familial early puberty: presentation and inheritance pattern in 139 families

Reviewer #1:

Thank you for reviewing our manuscript.

Specific comments:

-Methods: A limitation is the difficulty in determining the precise age at onset of puberty in the boys and in their fathers [7]. Thus, as in our previous publication in boys with central precocious puberty [15], we included the patients with testicular enlargement (testicular volume index > 4 cm2) before 9-10 years. We added the definition of the testicular volume index and this limitation.

-Results section (and Abstract) has been rewritten and the Figure 1 has been modified. The pedigrees are now classified according to the mode of inheritance. We would like to not separate the precocious and advanced puberty as they probably represent a clinical spectrum of the same trait of early activation of the GnRH pulse generator. Their individual characteristics are on Tables 1 and 2.

The families with one parent affected have similar characteristics of those with both parents affected (added).
Discussion section has also improved. The recent references on MKRN3 have been added.

English language has been revised.

Reviewer #2:

Thank you for reviewing our manuscript.

The Results and the Discussion, as well as the Figures, have been changed.

Major points

1. The inheritance mode has been clarified according to the suggestions of the Reviewer. The pedigrees are now presented according to the mode of inheritance. We found no differences in presentation or severity according to the type of inheritance and to the fact that one or both parents are affected (added).

2. We have chosen not to report our non-familial forms (reported in Giabicani et al, ref 6) and to focus the article on the familial forms. We would like to maintain their comparisons in the Discussion.

3. Difficulty in obtaining timing of puberty in male

As suggested by the other Reviewer, a limitation exists in the difficulty in determining the precise age at onset of puberty in the boys and in their fathers [7]. Thus, as in our previous publication in boys with central precocious puberty [15], we included the patients with testicular enlargement (testicular volume index > 4 cm2) before 9-10 years. This is now included in the text.

We have not considered the isolated pubic hair development as sign of central precocious puberty. We reported it as sign at initial evaluation. All the boys had increased testicular volume before 9-10 years and all girls had breast development before 8 years. This has been clarified in the Results.

4. Ethnicity is generally not recorded in the French medical records.

Minor points

1. Line 28: The crude penetrance rate was determined by analyzing all obligate or potential carriers in each informative pedigree.

2. Line 140: described in 3.

3. Statistical methods are now detailed in the method section.