Effect of paternal loss-of-function mutations of GNAS on growth during the childhood: a role for *XL*

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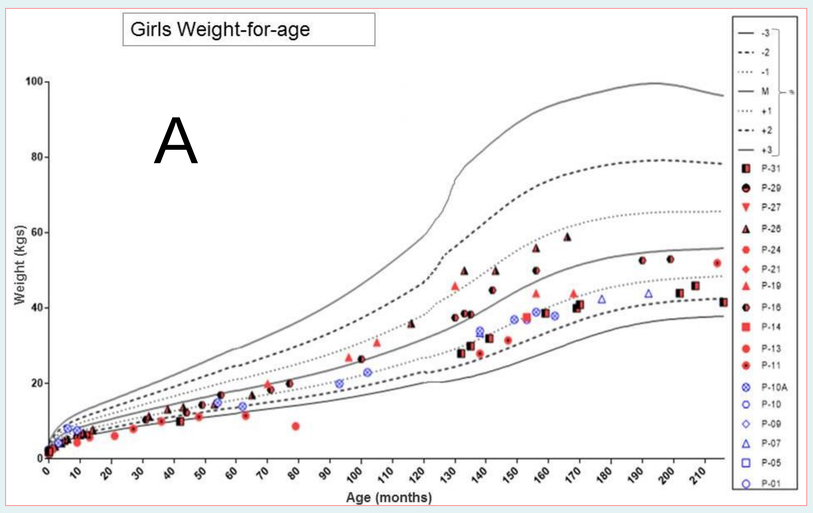
OBJECTIVES

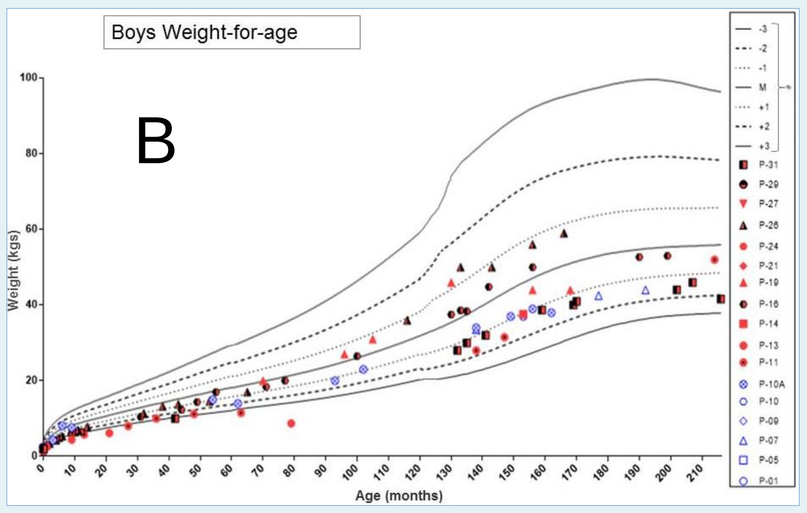
GNAS is a complex imprinted locus which leads to different transcripts characterized by one specific exon 1 and shared exons 2-13, with monoallelic (*XL*, *NESP55*) or biallelic ($G_s\alpha$) expression. Recent studies suggested that human birth weights were lower with paternal *GNAS* mutations affecting exons 2–13 (including *XL* and $G_\alpha s$) than with exon 1/intron 1 (specific to $G_\alpha s$) mutations, suggesting a role for *XL* in fetal growth (1).

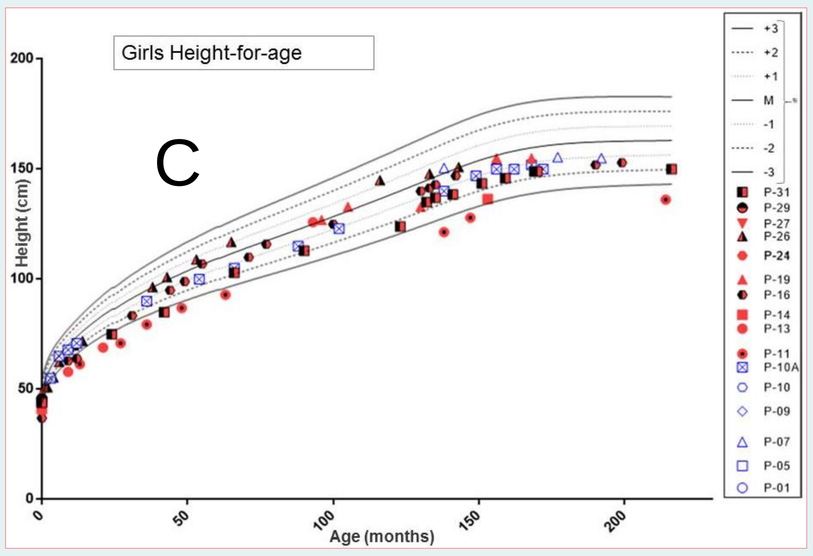
Our aim was to assess the growth, from early childhood to late adolescence, according to the location of the loss-of-function *GNAS* mutation (exon/intron 1 *versus* exons 2-13).

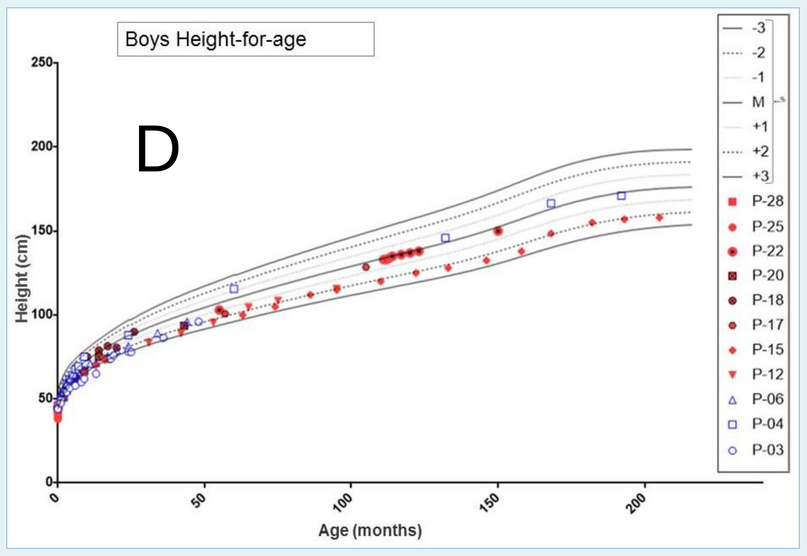
METHODS

This retrospective study was conducted on patients with paternal mutations on either **exon 1** (group 1: n= 9) or **exons 2-13** (group 2: n= 19). Weight (W) and height (H) were compared to sex-specific WHO reference charts, which curves have been created using GraphPad®. Data were gathered into three age groups, with birth data being excluded. Median values of Z-score between the two groups were statistically compared using Mann-Whitney test.









A, B: Weight-for-age charts for girls and boys, respectively. C, D: Height-for-age charts for girls and boys, respectively. Group 1 and Group 2 data are represented in blue (empty) and red/ red-black (full) symbols, respectively. The asterisk corresponds to standard deviations (SD) values associated with WHO growth charts.

E

Age range (months)	Group 1 (n=9) : Median weight Z-score (number of data, [1st quartile; 3rd quartile])	Group 2 (n=19) : Median weight Z-score (number of data, [1st quartile; 3rd quartile])	*P*-value
]0-24]	-1,2 (34, [-3,3;-0,6])	-3,3 (27, [-3,1;-1,2])	NS
]24-120]	-0,5 (11, [-1,2;-0,3])	-1,2 (45, [-1,9;-0,6])	NS
>120	-1,1 (10, [-1,3;-0,9])	-0,4 (38, [-1,9;-0,3])	NS

F

Age range (months)	Group 1 (n=9) : Median height Z-score (number of data, [1st quartile; 3rd quartile])	Group 2 (n=19) : Median height Z-score (number of data, [1st quartile; 3rd quartile])	*P*-value
]0-24]	-2,0 (32, [-3,1;-1,2])	-3,1 (26, [-3,7;-2,1])	NS
]24-120]	-1,4 (10, [-1,5;-1,3])	-1,0 (41, [-2,1;-0,1])	NS
>120	-1,0 (12, [-1,2;-0,1])	-1,5 (29, [-2,3;-0,6])	**< 0,05**

E, F: Comparison of median Z-scores of weight and height, respectively, between groups 1 and 2, according to the age range

RESULTS

Weight: The difference between groups 1 and 2 disappeared after birth. Despite being born with a severe intrauterine growth retardation, patients displayed a catch-up growth with weight-for-age values within the normal range (from -2 to +2 SD) after 10 years.

Height: Patients from both groups are smaller compared to the WHO normal references. Interestingly patients from group 2 remained significantly smaller than patients from group 1.

CONCLUSIONS

Our results confirm a role for *XL* in the regulation of fetal growth. After birth, the patients recovered a normal weight during the first few years, despite they were globally smaller than the median references in both groups. Our data implicate a role for the paternal imprinting in the height in these patients.

(1) Richard et al. JCEM 2013 Sep;98(9):E1549–56. The authors did not have any conflict of interest and have not been funded.

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