

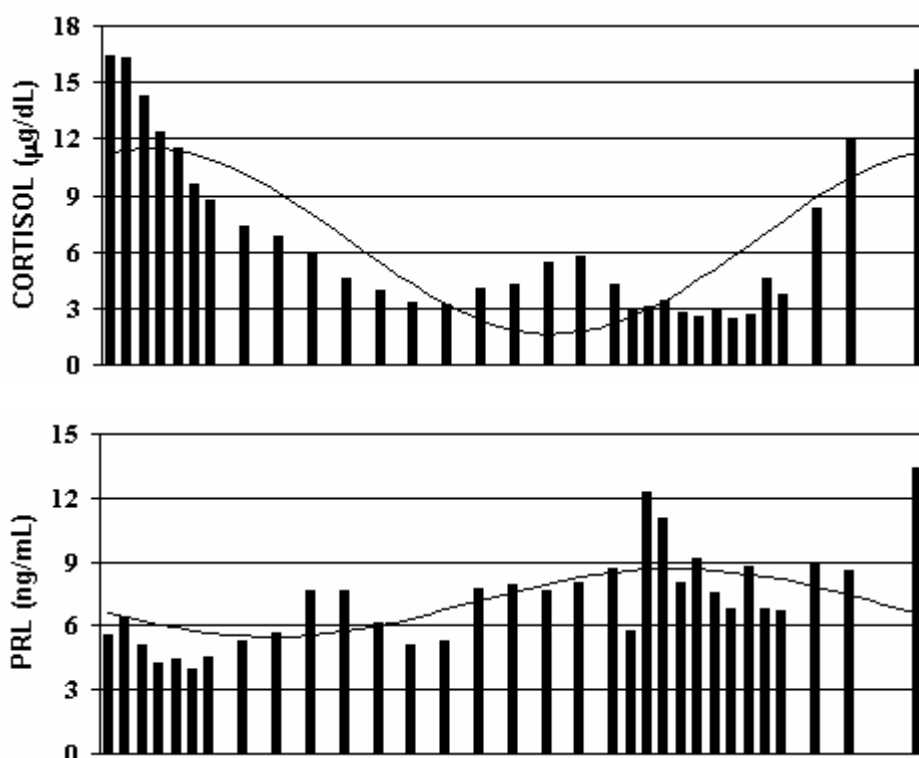
Supplementary Appendix

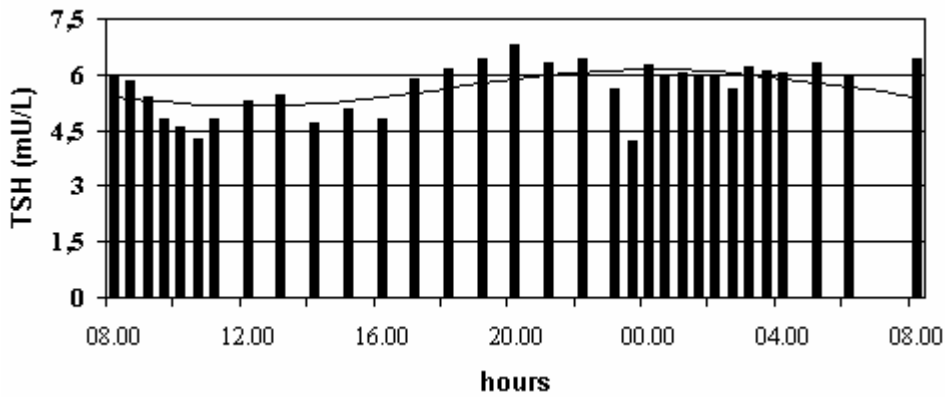
This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Bonomi M, Busnelli M, Beck-Peccoz P, et al. A family with complete resistance to thyrotropin-releasing hormone. *N Engl J Med* 2009;360:731-4.

Supplemental Appendix: Hormone circadian rhythms

Graphical representations of the secretion circadian pattern for Cortisol, PRL and TSH in the proband. In each graph, the cosine function that best fits the data is drawn. Chronobiological analyses reveal the presence of a statistically significant circadian rhythm for all the examined hormones. Cortisol and PRL oscillations were normal. TSH oscillation was significant, with a normal acrophase around midnight, but with a reduced amplitude compared to the control subjects. In panel D the following rhythmometric parameters are reported: MESOR, rhythm determined average; amplitude, difference between the MESOR and the peak of the best fitting cosine function; acrophase, time of the crest of the best fitting function; percent rhythm (PR), the percent variability in the data that is accounted for by the best fitting function. The rhythm is statistically validated when the amplitude zero hypothesis is rejected at the $p < 0.05$ level; if so, the 95% CL (Confidence Limits) for MESOR, amplitude, and acrophase are specified. The data series were also analyzed by one-way analysis of variance that confirmed that the variance between time points is significantly greater than the random variation within them (data not shown).





Hormone		<i>p</i>	PR %	MESOR (95% CL)	ACROPHASE (hours) (95% CL)	AMPLITUDE (% MESOR) (95% CL)
Cortisol (µg/dL) *	TRHR mut	<0.001	65	6.56 (5.56/7.56)	09.11 (07.50/10.41)	75.2 (53.6/96.8)
	Controls	<0.01	68	9.19 (8.06/10.32)	09.13 (07.39/10.47)	63.0 (52.4/73.6)
PRL (ng/mL) §	TRHR mut	<0.01	29	7.09 (6.37/7.80)	00.49 (21.13/04.07)	22.6 (9.2/35.9)
	Controls	<0.02	40	12.5 (9.8/15.2)	01.22 (22.02/04.42)	47.8 (28.4/67.2)
TSH (mIU/L)	TRHR mut	<0.01	29	5.65 (5.43/5.87)	00.07 (20.32/03.34)	8.7 (3.5/13.9)
	Controls	<0.04	48	1.4 (1.05/1.95)	02.20 (00.31/4.09)	21.8 (14.7/28.9)

* To convert the values for cortisol to nanomoles per liter multiply by 27.59;

§ to convert the values for prolactin to milliunit per liter multiply by 21.2.