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Since publication of their article, the authors report no further potential conflict of interest.

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Mutant Prolactin Receptor and Familial Hyperprolactinemia

TO THE EDITOR: Newey et al. (Nov. 21 issue)¹ compare the mutant prolactin receptor with other mutant endocrine receptors (parathyroid hormone and growth hormone) characterized by loss of function (hypocalcemia and short stature, respectively). The authors attempt to explain the reproductive abnormalities in their pedigree as being the result of hyperprolactinemia and excessive signaling by the prolactin receptor. They point out the persistent postpartum galactorrhea of the proband is indicative of excess prolactin signaling. However, they report a loss of function in relation to this mutation in heterologous systems. Hyperprolactinemia in the presence of a loss-of-function mutation would not lead to increased signaling. One possibility is that the reproductive abnormalities are mediated by a second receptor, as is the case in syndromes of resistance to other hormones (thyroid hormone and glucocorticoids). Alternatively, the reproductive abnormalities seen could be due to loss of function. One way to resolve this question would be to determine the patients' clinical response to cabergoline: if oligomenorrhea and infertility were due to excess prolactin signaling, one would expect these conditions to resolve with the normalization of prolactin levels after treatment with a dopamine agonist, and if these conditions were due to a loss of function in prolactin-receptor signaling, then dopamine agonist treatment would have no effect, despite the normalization of prolactin levels.

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No potential conflict of interest relevant to this letter was reported.

1. Newey PJ, Gorvin CM, Cleland SJ, et al. Mutant prolactin

receptor and familial hyperprolactinemia. *N Engl J Med* 2013; 369:2012-20.

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TO THE EDITOR: Newey et al. identified a germline loss-of-function mutation affecting the prolactin receptor as a cause of familial hyperprolactinemia in three sisters, two of whom presented with oligomenorrhea and one with infertility. Aside from its essential role in lactation, prolactin has no established role in reproductive function in humans.¹ Therefore, it is unclear whether the inactivating mutation in the gene encoding the prolactin receptor (PRLR) explains the reproductive phenotypes in the three sisters. Newey et al. speculate that the hyperprolactinemia observed in the three sisters may have induced hypogonadism owing to the loss of hypothalamic pulsatile secretion of the gonadotropin-releasing hormone. However, this explanation does not seem logical to me because inhibition of the secretion of the gonadotropin-releasing hormone by means of increased circulating levels of prolactin presumes the presence of a functioning prolactin receptor.² Therefore, an alternative explanation may be that the increased prolactin levels in the sisters represent merely a compensation for reduced signaling by the prolactin receptor and that the reproductive abnormalities are coincidental.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Newey et al. report a mutant prolactin receptor as a cause of familial hyperprolactinemia. I don't understand why such a mutation in the proband would result in galactorrhea. A loss-of-function mutation would be more likely to prevent galactorrhea than to cause it.

Why should this mutation cause hyperprolactinemia? The authors make an analogy to the growth hormone insensitivity syndrome, but in this syndrome the target hormone, insulin-like growth factor I, cannot be stimulated by growth hormone, which diminishes negative feedback and thereby results in increased secretion of growth hormone. With the mutant prolactin receptor, what target hormone is absent, causing the loss of negative feedback? The authors do not provide evidence that negative, short-loop, autofeedback of prolactin exists in humans, and I am unaware of such information.¹

In the Discussion section, the authors state that this loss-of-function mutation results in "infertility." Yet the proband had four children — hardly a case of infertility. Furthermore, her obviously fertile father also harbored this mutation. Thus, further explanation is needed before we can accept that this mutation is a cause of familial hyperprolactinemia.

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THE AUTHORS REPLY: Harris proposes possibilities for reproductive abnormalities and requests details regarding responses to cabergoline. In the proband, cabergoline restored normoprolactinemia, but since she had a hysterectomy 3 months after treatment with cabergoline normalized her prolactin levels, its effects on the menstrual cycle could not be established. Another sister had regular ovulatory cycles before beginning quinagolide therapy, making it difficult to

assess responses. These small patient numbers and short follow-up periods do not yield mechanistic insights. The involvement of a second, hypothetical receptor mediating the peripheral effects of hyperprolactinemia is another possible explanation for the paradoxical occurrence of the loss-of-function mutation in *PRLR* with hyperprolactinemia and variable reproductive abnormalities (see Table S2 in the Supplementary Appendix of the article, available at NEJM.org). We proposed that such an occurrence could have resulted from differences in the numbers of functioning (non-mutant homodimers) and nonfunctioning (mutant homodimers and heterodimers) prolactin receptors (Fig. S2 in the Supplementary Appendix) within organs, in a process analogous to that of melanocortin 4 receptors in obesity.¹ The presence of some (albeit reduced in number) functioning nonmutant homodimeric prolactin receptors in breast cells may lead to postpartum galactorrhea, although other causes (Table S2 in the Supplementary Appendix) may also be involved, since the regulation and action of prolactin differ during and after pregnancy, and more than 85% of women with galactorrhea have normoprolactinemia.²

Grossmann states that "prolactin has no established role in reproductive function in humans." However, previous studies indicate that women with basal serum prolactin levels in the lower end of the normal range or with inadequate prolactin production in the endometrium when not pregnant are at increased risk for miscarriage and have poor fertilization rates,^{3,4} and it has also been reported that nonphysiological hyperprolactinemia is associated with menstrual disturbances and anovulation (Table S2 in the Supplementary Appendix).² We agree that hyperprolactinemia may be compensatory for reduced signaling by prolactin receptors, but there may be other explanations for these reproductive abnormalities. However, the suggested presence of hyperprolactinemia-induced hypogonadism in the three sisters is logical because gonadotropin-releasing hormone and kisspeptin neurons will have some functioning homodimeric, nonmutant prolactin receptors, even though the number of these receptors that will be activated by prolactin may be reduced.⁵

Molitch's remarks regarding galactorrhea and hyperprolactinemia are addressed in our response

to Harris and Grossmann. The autoregulation of prolactin secretion through a short negative feedback loop involving hypothalamic neurons expressing the prolactin receptor and the potential direct effects of prolactin on lactotrophs have been established in rodent studies (Table S2 in the Supplementary Appendix),⁵ since conducting such studies in humans is difficult. However, the phenotypic similarities between *Prlr*-null mice and patients with the *PRLR* mutation suggest that such prolactin effects may also occur in humans. Moreover, hyperprolactinemia in *Prlr*-null mice has an age-related penetrance with sex differences, which are also observed in patients with the *PRLR* mutation. This effect may explain both the proband's fertility before 35 years of age and the modest hyperprolactinemia and fertility of the proband's father. Our results show that the *PRLR* loss-of-function mutation cosegregates with familial hyperprolactinemia, with odds of more than 125 to 1 favoring linkage. The results also show that the *PRLR* loss-of-function mutation is associated with a phenotype that is similar to that in *Prlr*-null mice. We consider these findings to provide compelling

support for our proposal that this *PRLR* mutation plays a role in familial hyperprolactinemia.

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Bilirubin-Induced Neurologic Damage

TO THE EDITOR: Watchko and Tiribelli (Nov. 21 issue)¹ note that preterm infants have an increased risk of acute bilirubin encephalopathy. The clinical manifestations of bilirubin encephalopathy in preterm infants are more subtle than those in term infants, and evidence-based guidelines for the management of hyperbilirubinemia are not well defined. Increased intravenous lipid intake is required in preterm infants for adequate nutrition and optimal growth. Traditionally, intravenous lipid intake has been limited in preterm infants with indirect hyperbilirubinemia, irrespective of gestational age, given the potential for bilirubin displacement secondary to an elevated concentration of free fatty acid.^{2,3} Studies have shown that in extremely preterm infants, intravenous lipid intake may be associated with an increase in the level of unbound bilirubin, mediated by an increase in free fatty acids and a secondary decrease in binding affinity.^{4,5} In infants born at more than 28 weeks' gestation, higher intravenous lipid intake may be used be-

cause increases in levels of free fatty acids and unbound bilirubin do not occur.^{4,5} Large, randomized, controlled trials are warranted to further establish the role of intravenous lipids and the risk of bilirubin neurotoxicity among preterm infants.

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