

A novel mutation of *KISS1R* causing a normosmic isolated hypogonadotropic hypogonadism

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TAKE HOME MESSAGE

- ✓ A novel mutation c.953T>C (p.L318P) in *KISS1R* leads to normosmic isolated hypogonadotropic hypogonadism by impeding the intracellular trafficking of kisspeptin receptor.
- ✓ This patient is a novel candidate to a treatment by a chemical chaperone to rescue expression of the mutated receptor.

INTRODUCTION

Kisspeptin receptor (*KISS1R*), which is also known as GPR54 and encoded by *KISS1R*, is a G-protein-coupled receptor expressed in GnRH neurons. Its ligand kisspeptin is known as strong regulators of GnRH secretion through *KISS1R*. Inactivation mutation of *KISS1R* associated with normosmic isolated hypogonadotropic hypogonadism (nIHH), which was first described at 2002.

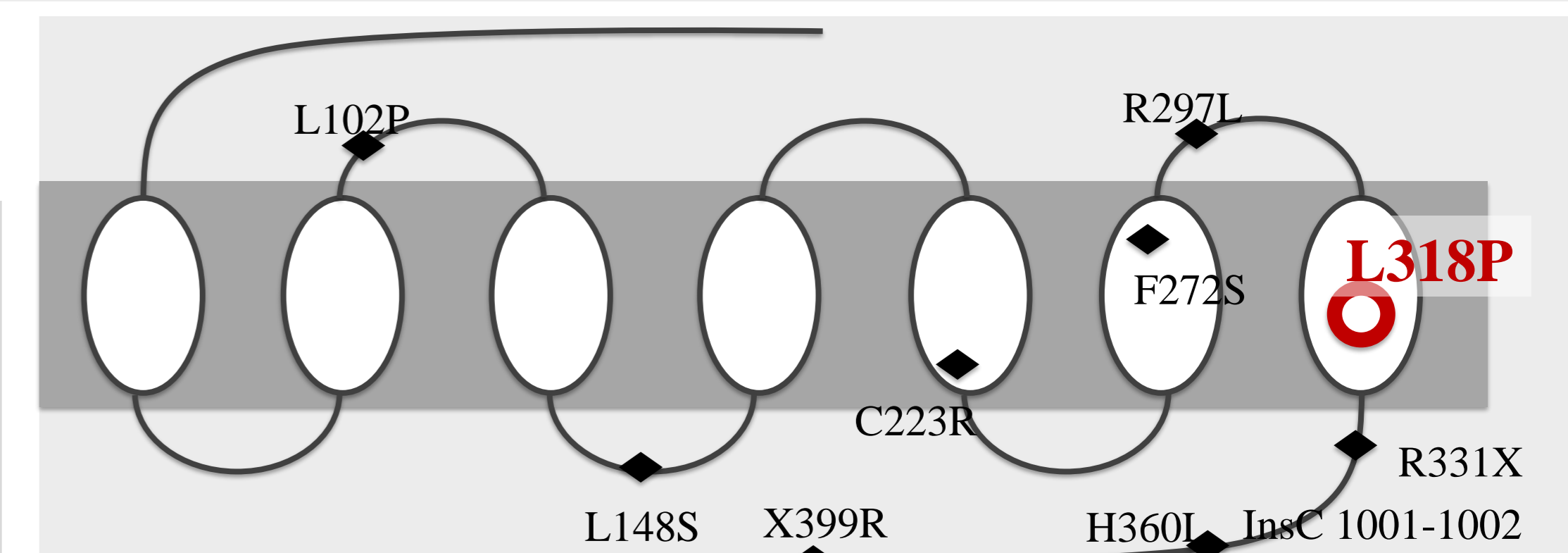


Figure 1 Localization of the L318P substitution and other published point of mutations of *KISS1R*.

CASE PRESENTATION

The patient was a Senegalese woman who was referred at 28 years old for primary amenorrhea. Family history revealed no delayed puberty or no fertility problem in the mother and 2 brothers. Breast development was scored Tanner stage 2, but pubic and axillary hair growth could not be evaluated because of depilation. She had a normal sense of smell on olfactory. The brain MRI showed normal findings. Pelvic sonography showed a small uterus and right small ovary with follicles, but left was not visualized. Her karyotype was 46,XX.

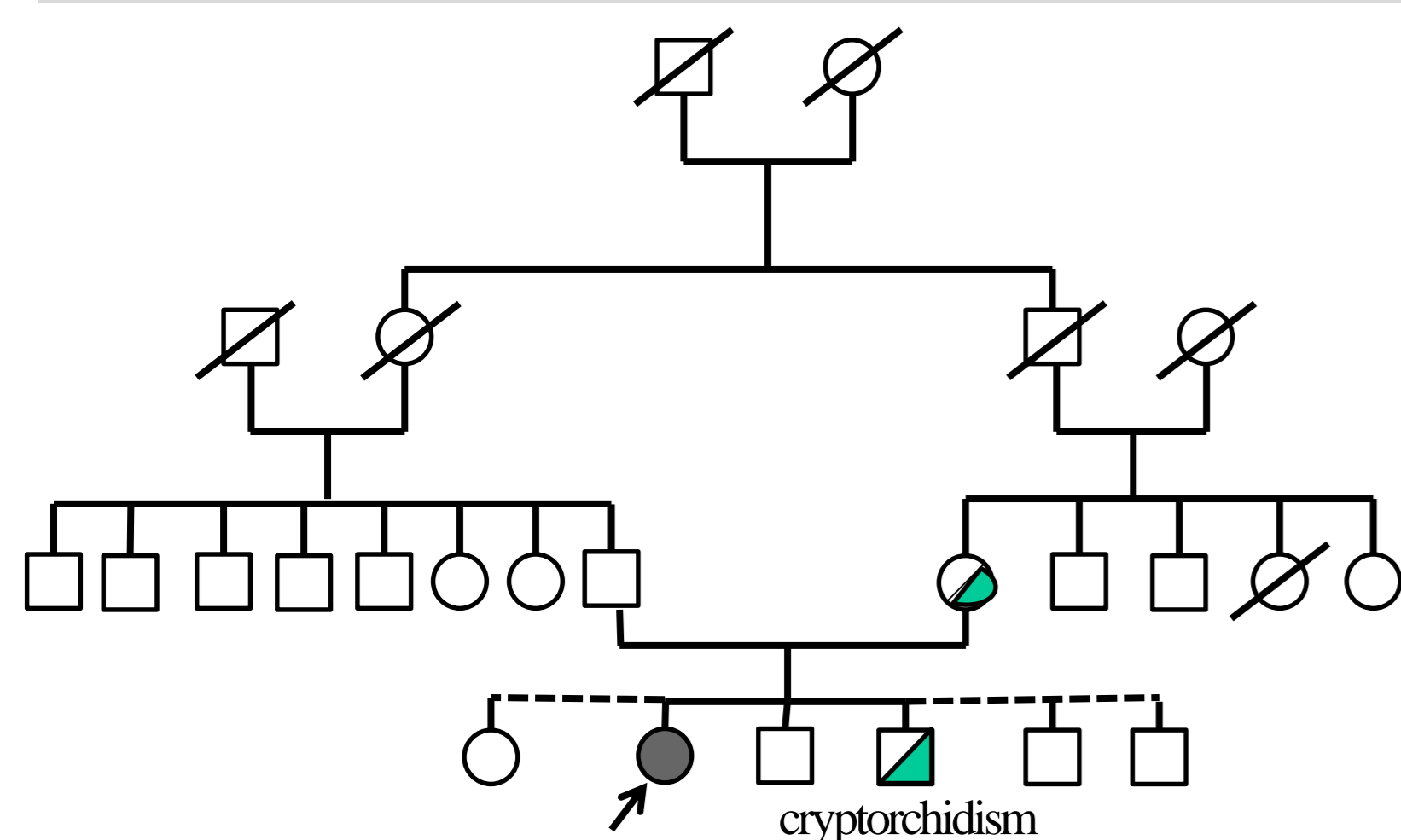


Figure 2 Pedigree of the family. Arrow indicate the proband. Half shaded indicate heterozygous. The father didn't consent to genetic analysis.

Estradiol	11.8 pg/ml
FSH	6.6 IU/L
LH	4.5 IU/L
Peak LH by GnRH test	35.9 IU/L
Peak FSH by GnRH test	20.1 IU/L
Prolactin	104 mUI/L
AMH	1.18 ng/ml

DISCUSSION

Loss of function mutations in *KISS1R* is a rare cause of congenital nIHH. 9 homozygous mutations including five point mutations, one splice site mutation, one deletion, one insertion, one insertion/deletion and 3 compound heterozygous mutations are already known to date. A novel loss-of-function mutation (c.953T>C) in the *KISS1R* gene is associated with nIHH due to a defect of trafficking of proteins to the cell membrane.

This patient has been treated by pulsatile GnRH (subcutaneous, 20ug/pulse every 90 min) to become pregnant. The quality of the ovarian response has been heterogeneous. Three cycles led to an ovulation associated to high levels of estradiol whereas four other cycles were unsuccessful. In addition, the endometrial maturation was of poor quality in the induced ovulation. A recent paper also reported that kisspeptin promotes endometrial gland development and function in mice. We speculate that female patients with *KISS1R* mutations might show atypical laboratory data to GnRH test, and a poor response to GnRH pulsatile treatment due to a defective kisspeptin signaling in the endometria and ovaries. This patient might benefit of a chemical chaperone treatment to rescue the mutated receptor at the cell surface.

CONFLICT OF INTEREST

We have no financial relationships to disclose.

MUTATION & FUNCTIONAL ANALYSIS

We identified a homozygous transition c.953T>C in exon 5 of *KISS1R*, leading to the amino acid substitution of leucine 318 by proline (p.L318P). Sequence analysis of other candidate genes didn't reveal any pathogenic variant. Sequencing of the mother and one brother showed a heterozygous c.953T>C, but the other brother wasn't a carrier of this transition.

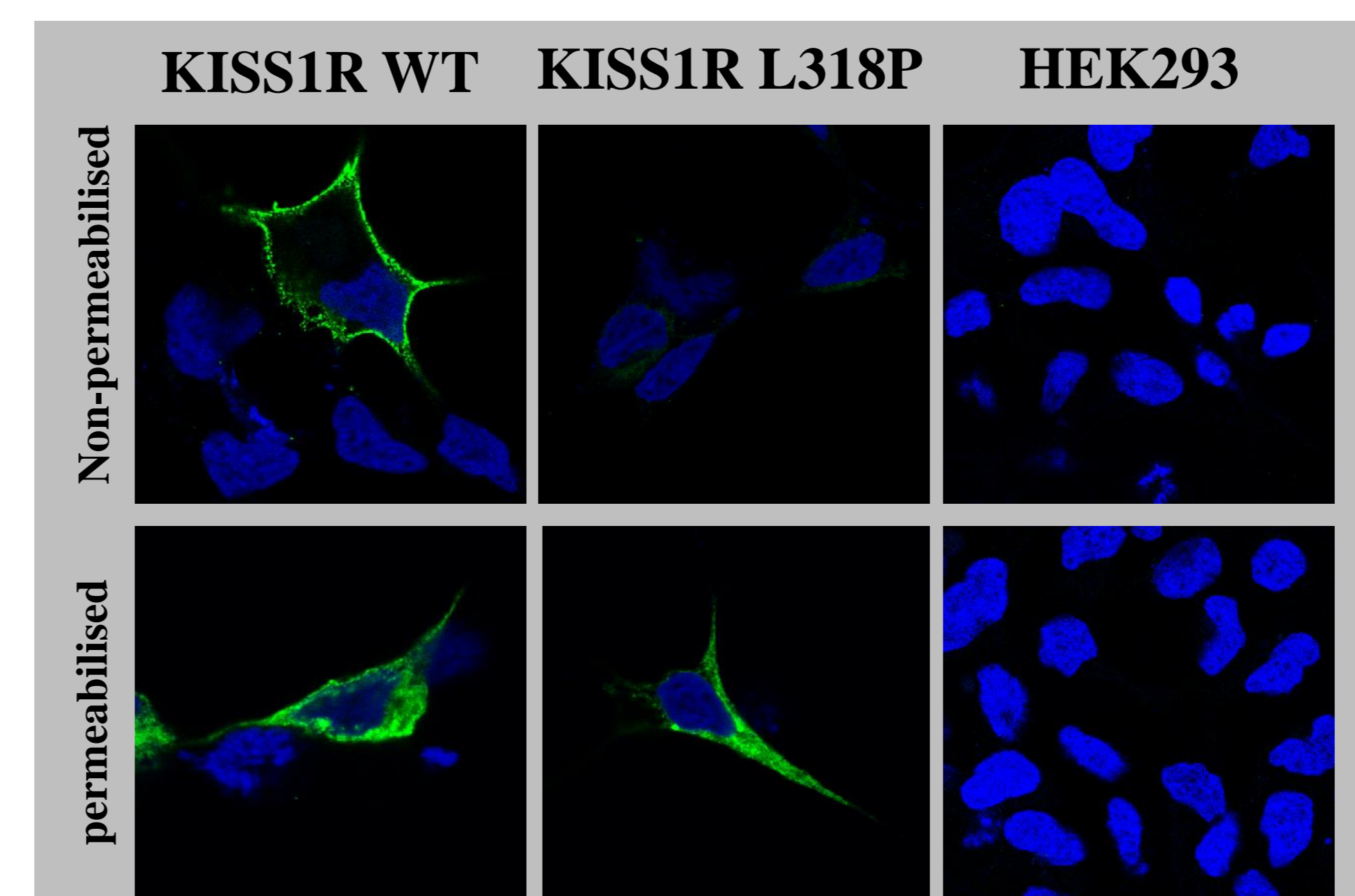


Figure 3

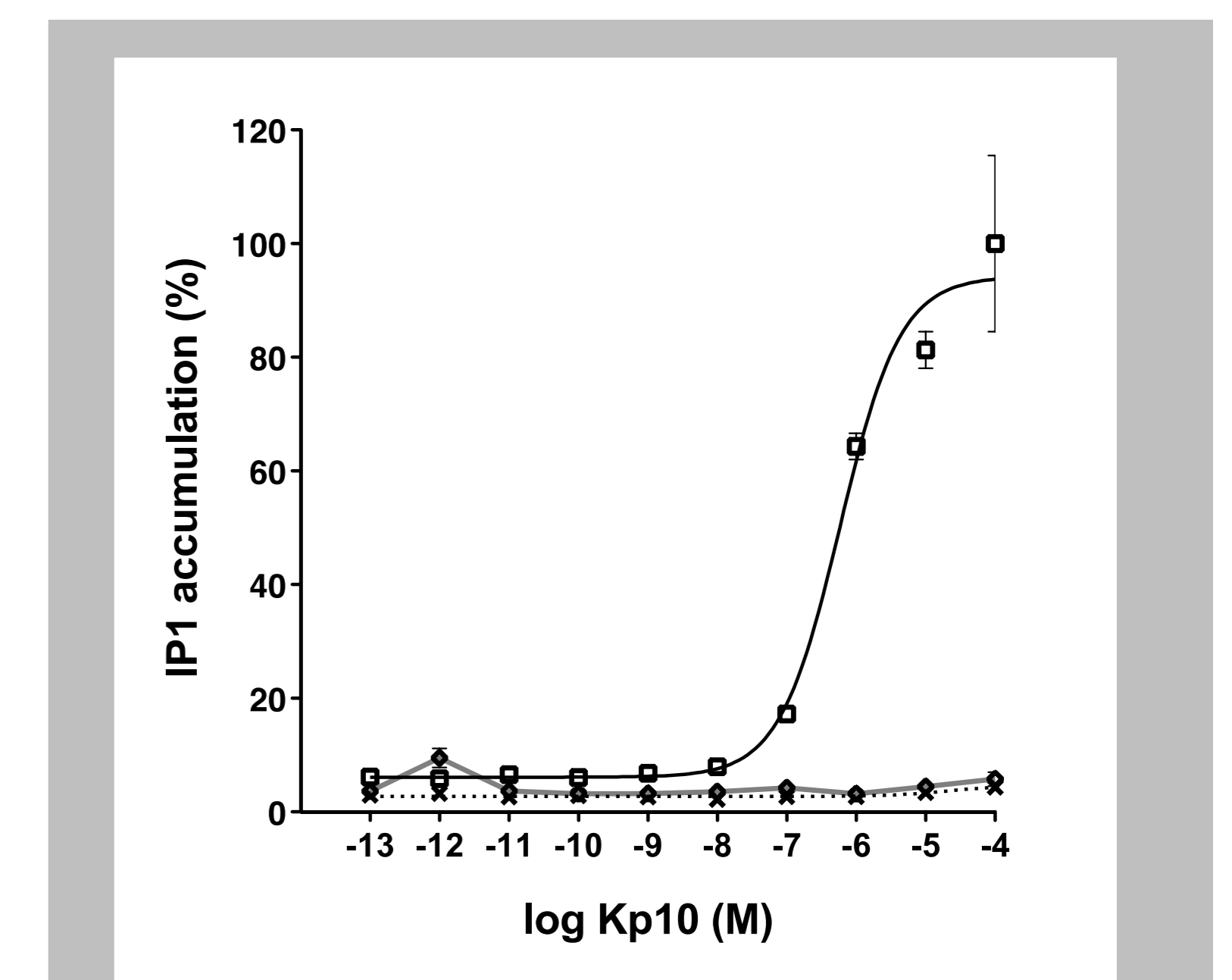


Figure 4

Figure 3: Membrane staining was observed in non-permeabilised HEK293 cells expressing the wild type receptor. No signals was detected in non-permeabilised cells transfected expressing the P318P mutated receptor. Strong intracellular staining was observed in permeabilised cells for both of them.

Figure 4: In cells expressing wild type, Kp-10 increased intracellular IPs. In mutated receptor-expressing cells, Kp-10 did not induce an intracellular increase of IPs.