GENETICS

Mutant prolactin receptor—when lock and key no longer fit

Researchers led by Rajesh V. Thakker (University of Oxford, UK) have identified a new germline, loss-of-function mutation in the prolactin receptor gene *PRLR* that causes familial hyperprolactinaemia and occurs independently of pituitary tumours or hereditary multiple endocrine neoplasia syndromes.

Thakker and colleagues report data from three sisters with hyperprolactinaemia but variable manifestations of this disorder, including oligomenorrhoea and/or infertility. “We discussed two possibilities,” recalls Thakker. “Initially, we asked ourselves, is it the ‘key’? That is, might these individuals be secreting an abnormal or partially active form of prolactin?” However, DNA sequence analysis of the *PRL* gene did not reveal any abnormalities. “On the basis of other paradigms, for example, mutations in the growth hormone (GH) receptor that lead to GH insensitivity, we

then wondered whether the ‘lock’ was affected, that is, the prolactin receptor,” says Thakker.

Indeed, sequencing showed that the symptoms were caused by a heterozygous mutation in *PRLR*. The mutation leads to an amino acid change (His188Arg), which structural modelling showed disrupts the high-affinity ligand-binding interface of the prolactin receptor, leading to loss of downstream JAK–STAT signalling.

This finding raises a host of interesting new questions. For one, if MRI scans are normal in women with hyperprolactinaemia, should clinicians be screening for *PRLR* mutations instead of searching further for a pituitary tumour? Moreover, to date, commercial drug agonists or antagonists for the prolactin receptor are not available for clinical use. “Our findings open the door for devising molecules that inhibit prolactin from binding or, conversely, increase affinity to the receptor,” suggests Thakker.

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Furthermore, the fact that one mutation carrier had ovulatory cycles but infertility indicates that prolactin acts on the female reproductive tract directly.

Thakker hopes that his study will increase research interest in this area, help generate new ideas, and ultimately benefit the patients.

Linda Koch

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