Key to regulation of puberty discovered

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A team of scientists from the University of Cambridge and the University of Cukurova in Turkey have taken a major step to understanding how the brain controls the onset of puberty.

The research, published in this week's *Nature Genetics*, identified the hormone Neurokinin B as a critical part of the control system that switches on the master regulator of human puberty. Although Neurokinin B was previously known to be present in the hypothalamus, the part of the brain that controls puberty, its key role was not previously appreciated.

The identification of Neurokin B could lead to new treatments for sex hormone dependent diseases like prostate cancer, new approaches to contraception, and its manipulation could result in new treatments for children with delayed or abnormal puberty.

It has long been known that a specific hormonal signal from the hypothalamus is essential to switch on the system that controls the production of sex hormones from the ovaries and testis. Turning on the system is essential to enter puberty and maintain sexual function in adults.

Control over this system is governed by the brain through the release of the hormone GnRH (gonadotroopin releasing hormone) which starts a series of processes that ultimately leads to the production of sex hormones. However how GnRH secretion is turned off after birth, and how it reactivates at puberty, has been unclear.

In order to identify new signals involved in regulating this process, the researchers used a strategy of searching for genetic defects in families in Turkey in which more than one member did not go through puberty, making an inherited defect likely. They discovered mutation in two genes: TAC3 (one family) and TACR3 (three families).

Mutations in these genes severely affect the function of Neurokinin B. The TAC3 gene codes for Neurokinin B while TACR3 produces its receptor. These mutations were only found in members with the condition, severe congenital gonadotropin deficiency, and not their siblings. Affected individuals were all homozygous (they have two identical copies of the gene) for these mutations.

A small number of studies using mice and rats had previously linked Neurokinin B to puberty, but the wider view was that its main role was instead in water balance, cognitive function or a number of other processes. This research clears this uncertainty and establishes the central role for Neurokin B and its receptor in puberty and the regulation of sexual and reproductive function.

Commenting on the research Dr Robert Semple, from the University of Cambridge and one of the authors of the study said: "As a practicing doctor I am excited by this discovery because it immediately helps to understand the underlying problem in rare patients with inherited defects in sexual maturation, and suggests a potential target for their specific treatment. However identifying single genetic defects in patients with rare disorders also has implications for understanding normal regulation of key bodily functions, and is one of the most powerful ways of proving the genes concerned.

"The neurokinin B/neurokinin 3 receptor system is highly amenable in principle to targeting as a treatment, and I expect that this genetic discovery will lead to intense efforts to understand neurokin B's role in

puberty in more detail, and to try to develop clinically valuable drugs."

Professor Steve O'Rahilly, from the University of Cambridge said: "This unexpected finding puts one more important piece in the unfinished jigsaw puzzle that is our understanding of puberty. It could also open up new ways of treating certain sex hormone related diseases."

Article: The article 'TAC3 and TACR3 Mutations in Familial Hypogonadotropic Hypogonadism Reveal a Key Role for Neurokinin B in the Central Control of Reproduction' will appear in the online edition of Nature Genetics on 12 December.

Source: University of Cambridge