

Relevance of astrocytic signals for GnRH neuronal function

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Background

Gonadotropin releasing hormone (GnRH) secretion is not only regulated by neuronal factors but also by astroglia cells via growth factors [neuregulin (NRG) e.g.], prostaglandin E2 (PGE2) and the erbB receptor family. NRG stimulates the erbB4 receptor. This results in an increased PGE2 concentration which stimulates the GnRH release. Alterations in the erbB receptor system result in an impaired reproductive capacity. Mice carrying mutations show a typical skin phenotype with wavy hair and curly whiskers. The rat strain SPRD-Cu3 (curly) shows a similar phenotype. Whether there is a dysfunction in the astrocytic receptor system is elucidated in the following.

Study design

Pubertal development and reproductive capacity of SPRD-Cu3 (Cu3) rats were compared to two control strains: outbred Crl:CD(SD) (WT) and inbred Lewis (Lew) rats. Primary astrocytic hypothalamic cell cultures from 0-2 days old rats were stimulated with NRG. Activity of the stimulated erbB4 receptor was determined by ELISA. *ErbB4* expression was detected by qPCR. Sequencing analysis of *ErbB4* receptor gene.

Results

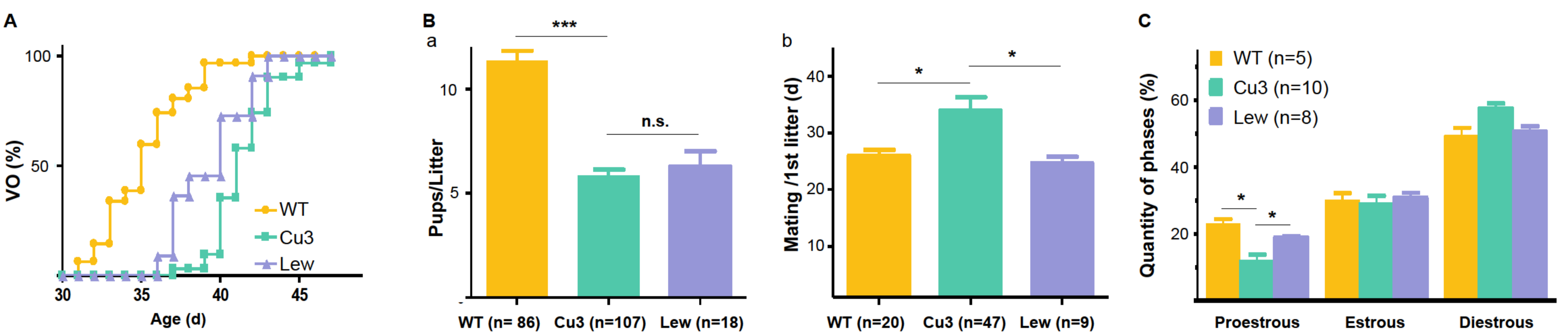


Fig.1: Puberty and reproductive capacity is impaired in Cu3 rats

A: Age of vaginal opening
WT (n=59) vs. Cu3 (n=31) p < 0.0001
WT v.s Lew (n=11) p < 0.0001

B: Reproductive capacity
a number of pups/litter is reduced in Cu3, n.s.
b they need longer time to become pregnant (days between mating and first litter)

C: Estrous cycle
Cu3 experience less phases of proestrous corresponding to less ovulations

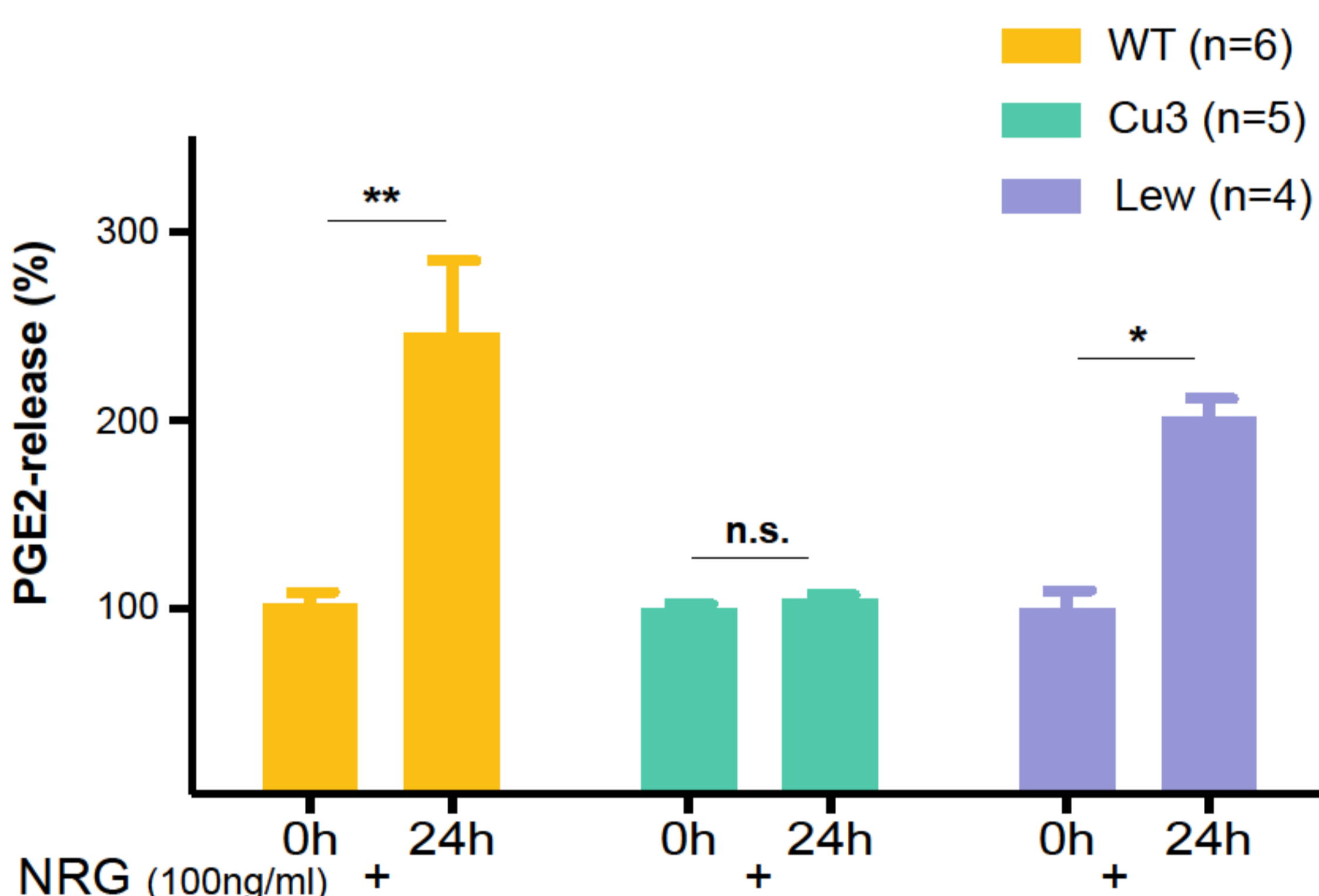


Fig.2: NRG fails to induce PGE2 secretion in Cu3 rats

Mean ± SEM, ***p<0.001, **p<0.01, *p<0.05

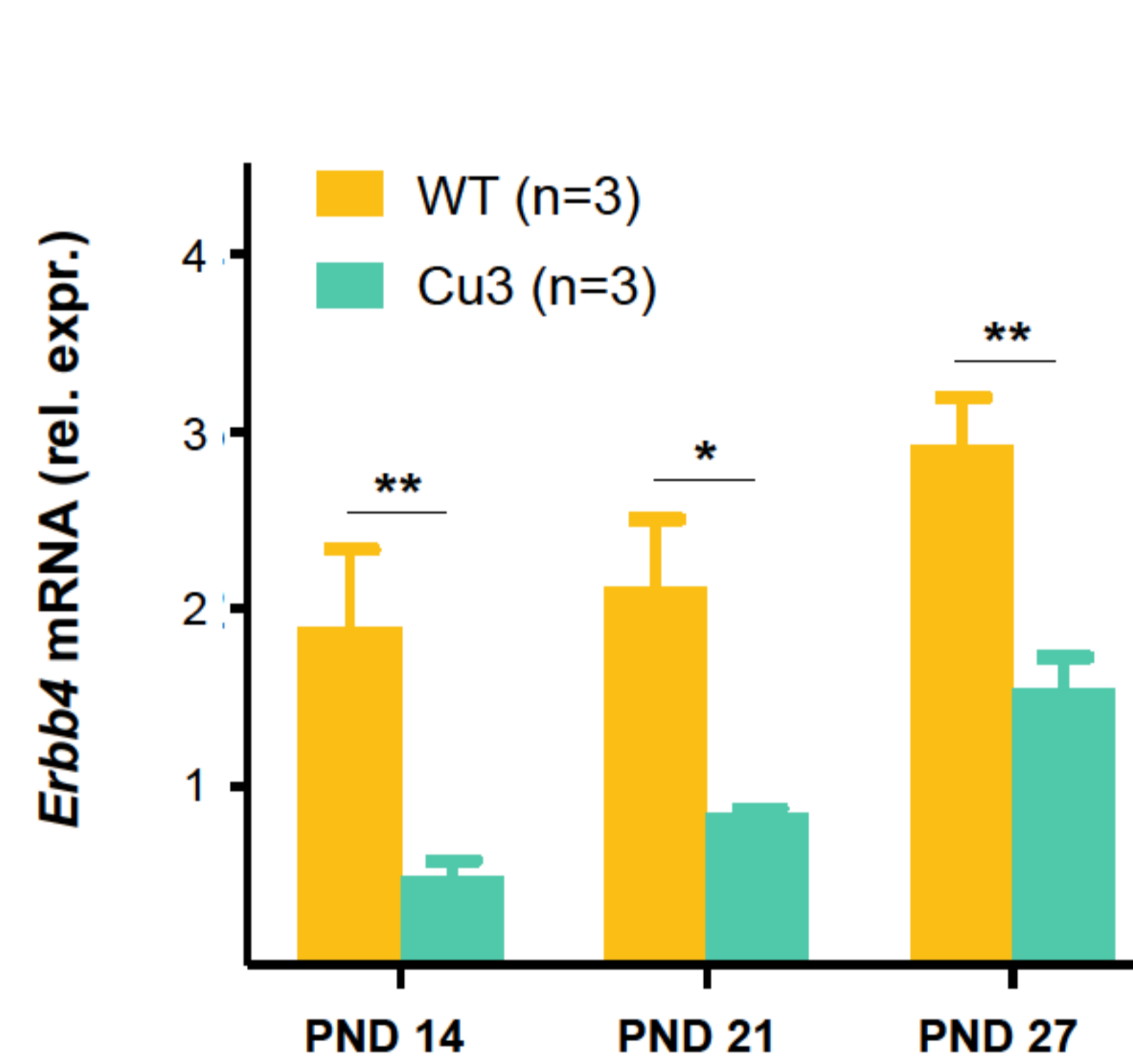


Fig.3: Expression of ErbB4 is impaired in the hypothalamus of Cu3 rats

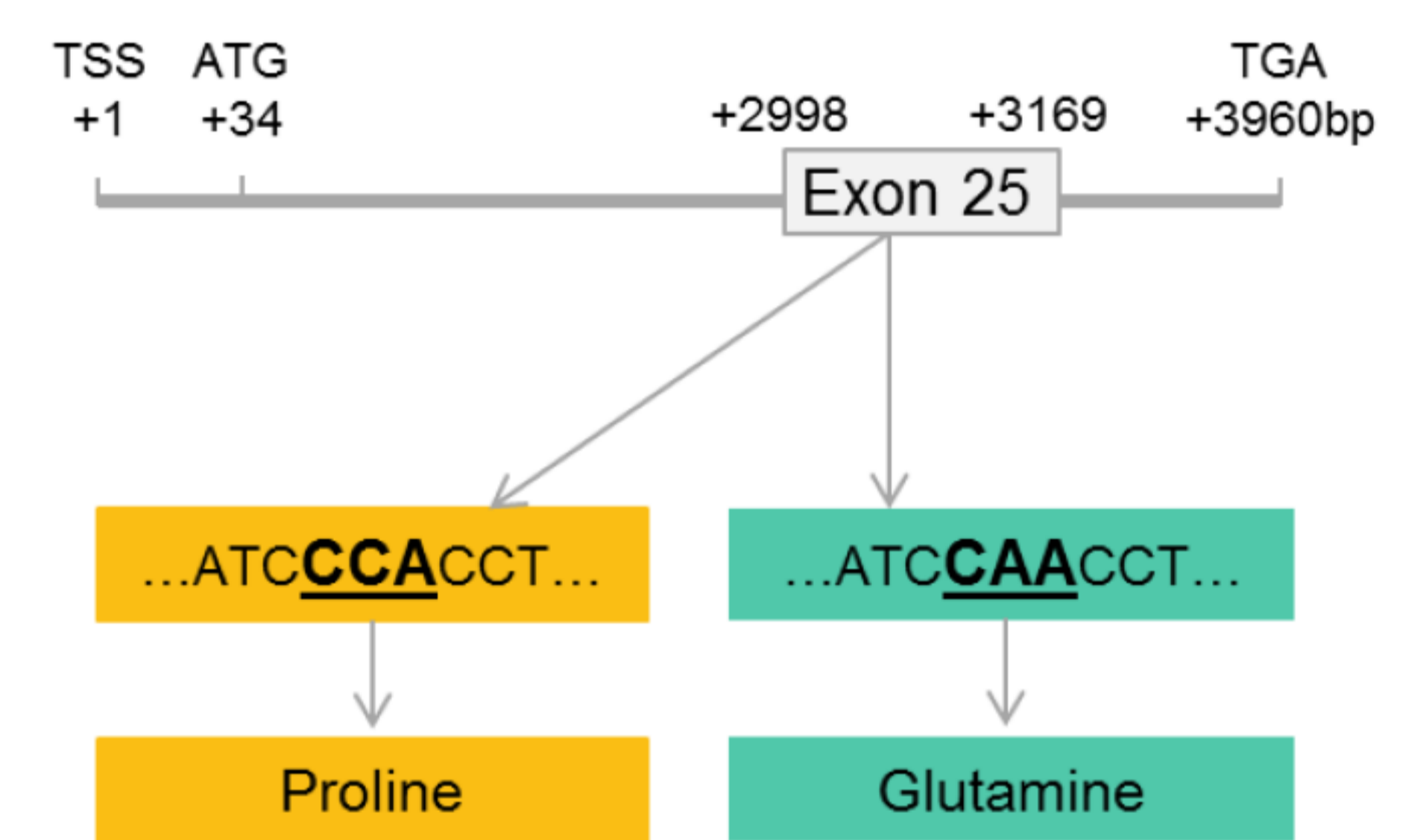


Fig.4: ErbB4 gene (NM_021687.1)
Exon 25: SNP at bp 3125 [C/A] Pro -> Glu

Summary

1. Puberty is delayed and reproductive capacity is impaired in both inbred strains (Lewis and Cu3 rats) compared to WT animals.
2. Cu3 rats experience less ovulations, illustrated by less proestrous phases.
3. NRG fails to induce PGE2 secretion only in Cu3 rats.
4. Expression of *ErbB4* is impaired in Cu3 rats compared to wild-type animals.
5. Sequence analysis of *ErbB4* reveals a SNP at bp 3125 [C/A] proline to glutamine in Cu3 rats.

Conclusion

Impaired puberty and reproductive capacity in Cu3 rats is due to a disrupted erbB2/erbB4 receptor signaling pathway. The underlying cause might be the SNP at bp 3125 [C/A] Pro-> Glu. Preliminary data suggest that the tertiary structure of the protein configuration might be affected resulting in an impaired signal transduction of the erbB2/erbB4 heterodimer.

