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TGFBR3L IN NON-FUNCTIONING PITUITARY NEUROENDOCRINE TUMOURS

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Background: Transforming Growth Factor Beta Receptor 3 Like (TGFBR3L) is a pituitary enriched gene that is selectively expressed in gonadotroph cells (1). We have recently shown in a retrospective material that TGFBR3L is present both in gonadotroph tumours and in normal gonadotroph cells (2). The protein has been found to be a coreceptor for inhibin B, involved in regulation of FSH and fertility in mouse studies (3). This study aimed to validate previous findings of TGFBR3L in a well characterized cohort of non-functioning pituitary neuroendocrine tumours (NF-PitNETs).

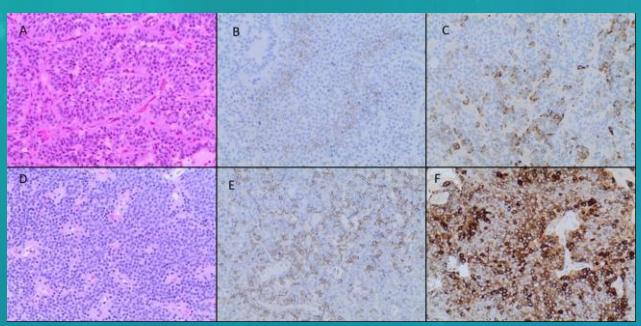

Figure 1: Hematoxylin and eosin, and immunohistochemical staining of two gonadotroph tumours. Each line represent one tumour . Hematoxylin and eosin staining (A and D); TGFBR3L staining low (1-10% positive cells) and high (≥30% positive cells) (B and E); and their corresponding LHβ IRS score 6 and 9 (C and F). All magnifications 200x.

Methods: 145 patients operated for clinically NF-PitNETs (116 gonadotroph) were included prospectively. All patients were operated at the department of neurosurgery, Oslo University Hospital. None of the tumours showed biochemical or clinical signs of hormone production prior to surgery. The tumours were immunohistochemically classified based on the presence of pituitary hormones and/or pituitary specific transcription factors. Immunohistochemical (IHC) staining for FSHβ and LHβ was scored using the immunoreactive score (IRS) (4). TGFBR3L was scored based on the percentage of positive staining cells (negative: no positive cells; low: ≤10% positive staining cells; moderate: 10-30% positive staining cells; high: ≥ 30% positive staining cells), and compared to clinical and radiological data. TGFBR3L staining was missing for one tumour.

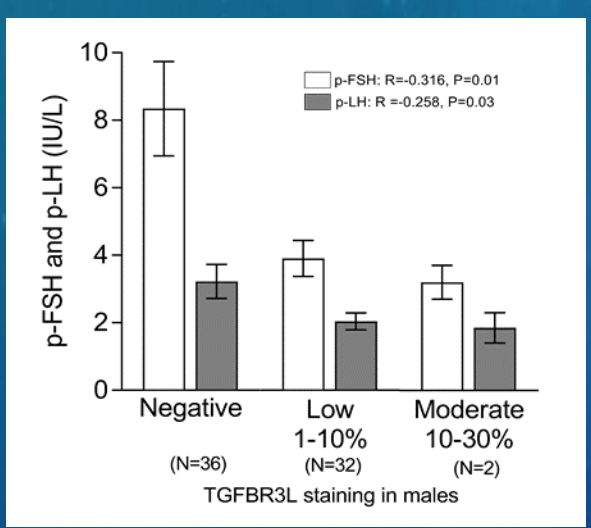

Figure 3: TGFBR3L is negatively associated to plasma gonadotropins in males. Data is presented as median +/- SEM. TGFBR3L score ≥30% is not shown, since this was not seen in samples from any male.

Limitations: This study was based on IHC, biochemical and radiological data. Therefore, the function of TGFBR3L and its downstream signalling could not be determined.

Baseline characteristics	
Gender	Female 42% (N=61)
Age	61 years (50-70) Females 61 (47-70) Males 61 (52-70)
Tumour volume (mm^3)	6126 (3870-9249)
Tumour invasiveness (Knosp≥3)	30.3% (N=44)
Indication for surgery	
Visual disturbances	87.6% (N=87)
Tumour growth	10.3% (N=15)
Headache	0.7% (N=1)
Apoplexy	1.4% (N=2)
PitNET subtype	
Gonadotroph	80.0% (N=116)
Corticotroph	13.8% (N=19)
Plurihormonal Pit-1 tumours	2.1% (N=3)
Somato-lactotroph	1.4% (N=2)
Plurihormonal (Sf-1 and Pit-1)	0.7% (N=1)
Double PitNET	0.7% (N=1)
Hormone and TF negative	2.1% (N=3)

Table 1: Numbers are given as percentages or median with interquartile range (IQR).

Results:

- Positive staining for TGFBR3L was exclusively present in gonadotroph tumours, and not in the remaining NF-PitNETs.
- Half of the gonadotroph tumours (52%, N=60), and in addition one double-PitNET (positive for FSH and SF-1 in some cells and for ACTH and T-pit in others) presented staining for TGFBR3L.
- Only four tumours showed positive staining for TGFBR3L in ≥10% of cells (Figure 2).
- The TGFBR3L positivity was not associated with gender, age at primary surgery, tumour invasiveness or age adjusted preoperative tumour volume (data not shown).
- TGFBR3L detection showed a positive correlation to the IRS of LHβ (ρ=0.56, p<0.001), but not to the IRS of FSHβ (ρ=0.15, p=0.15) (Figure 3).

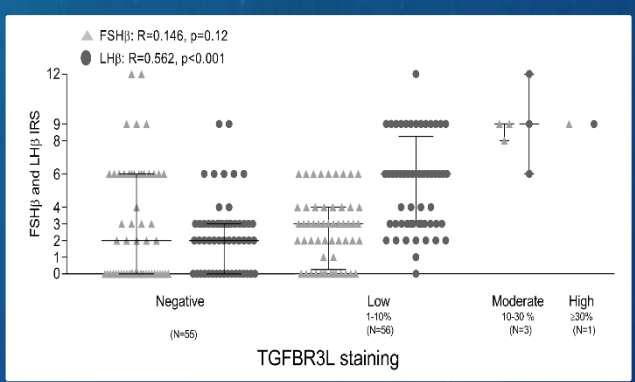

Figure 2: TGFBR3L was associated with IRS LHβ, but not IRS FSHβ. Data is presented as median and IQR (error bars). Only one tumour received a score >30% positive cells, thus no error bars shown for this group.

Conclusion: We have validated that TGFBR3L is selectively expressed in gonadotroph NF-PitNETs. Few tumors present TGFBR3L staining in more than 30% of the cells. Although it does not seem to be related to tumour aggressiveness,TGFBRL3 seems to be related to LHβ expression suggesting a role in gonadotropin regulation.

References: 1. Tissue expression of TGFBR3L- The Human Protein Atlas. Available at https://wwwproteinatlasorg/ENSG00000260001-TGFBR3L/tissue.Accessed June 2022; 2. Sjöstedt E et al. TGFBR3L-An Uncharacterised Pituitary Specific Membrane Protein Detected in the Gonadotroph Cells in Non-Neoplastic and Tumour Tissue. Cancers. 2020;13(1). 3. Brûlé E et al. TGFBR3L is an inhibin B co-receptor that regulates female fertility. Science advances. 2021;7(51):eabl4391. 4. Remmele W et al; Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue [in German]. Pathologe. 1987;8(3):138–140.