



Co-existing Prolactinoma and Primary Aldosteronism: is there a pathophysiological link?

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Background and Objectives

PROLACTINOMAS → Most frequent pituitary tumour
 ↳ Microprolactinomas (≤10 mm)
 ↳ Macroprolactinomas (>10 mm)

PRIMARY ALDOSTERONISM (PA) → Most frequent cause of secondary hypertension
 ↳ Bilateral Hyperplasia (BAH)
 ↳ Unilateral Adenoma (APA)

- ▶ 60-500 cases of prolactinoma per million in normal population
- ▶ Recurring number of prolactinoma cases in German Conn PA registry
- ▶ Co-existing prolactinoma-PA infrequently reported

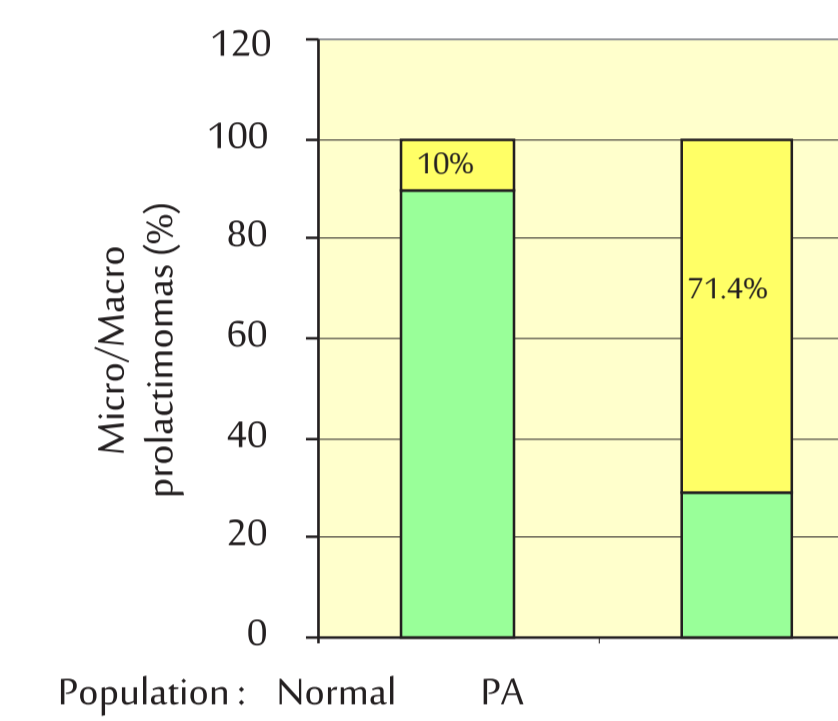
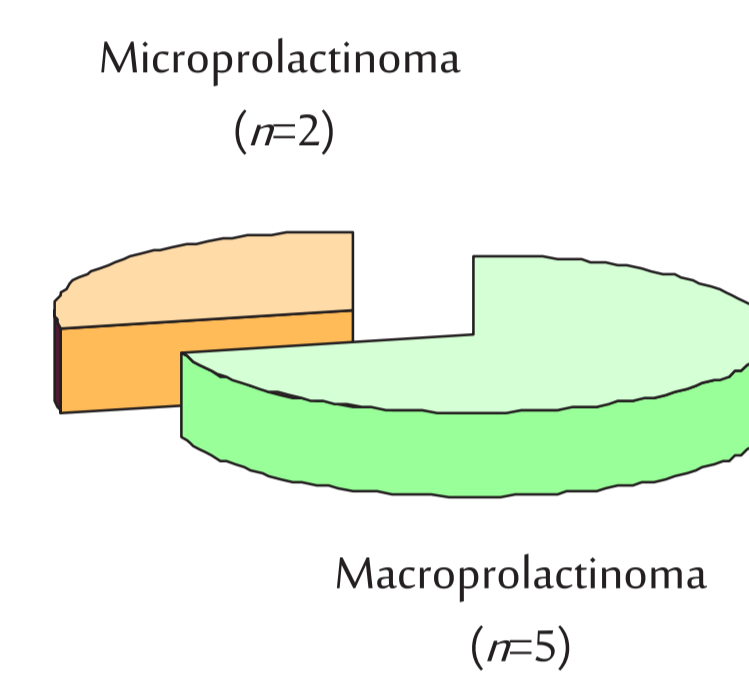
- ▶ Identify patients with co-existing prolactinoma-PA from PA patients recruited in two referral centres (Munich and Turin)
- ▶ Test hypothesis that elevated prolactin may play a role in pathogenesis of PA

Results

1. Increased incidence of prolactinomas and notably macroprolactinomas in primary aldosteronism patients

Centre	PA patients	No. Prolactinomas
MUNICH	584	4
TURIN	442	3
TOTAL	1026	7

- ▶ 7 co-existing prolactinoma-PA is largest case-series reported to date
- ▶ 60-500 cases of prolactinoma per million in normal population
- ▶ 10-100-fold increased prevalence of prolactinoma compared to normal population in 2 independent PA cohorts



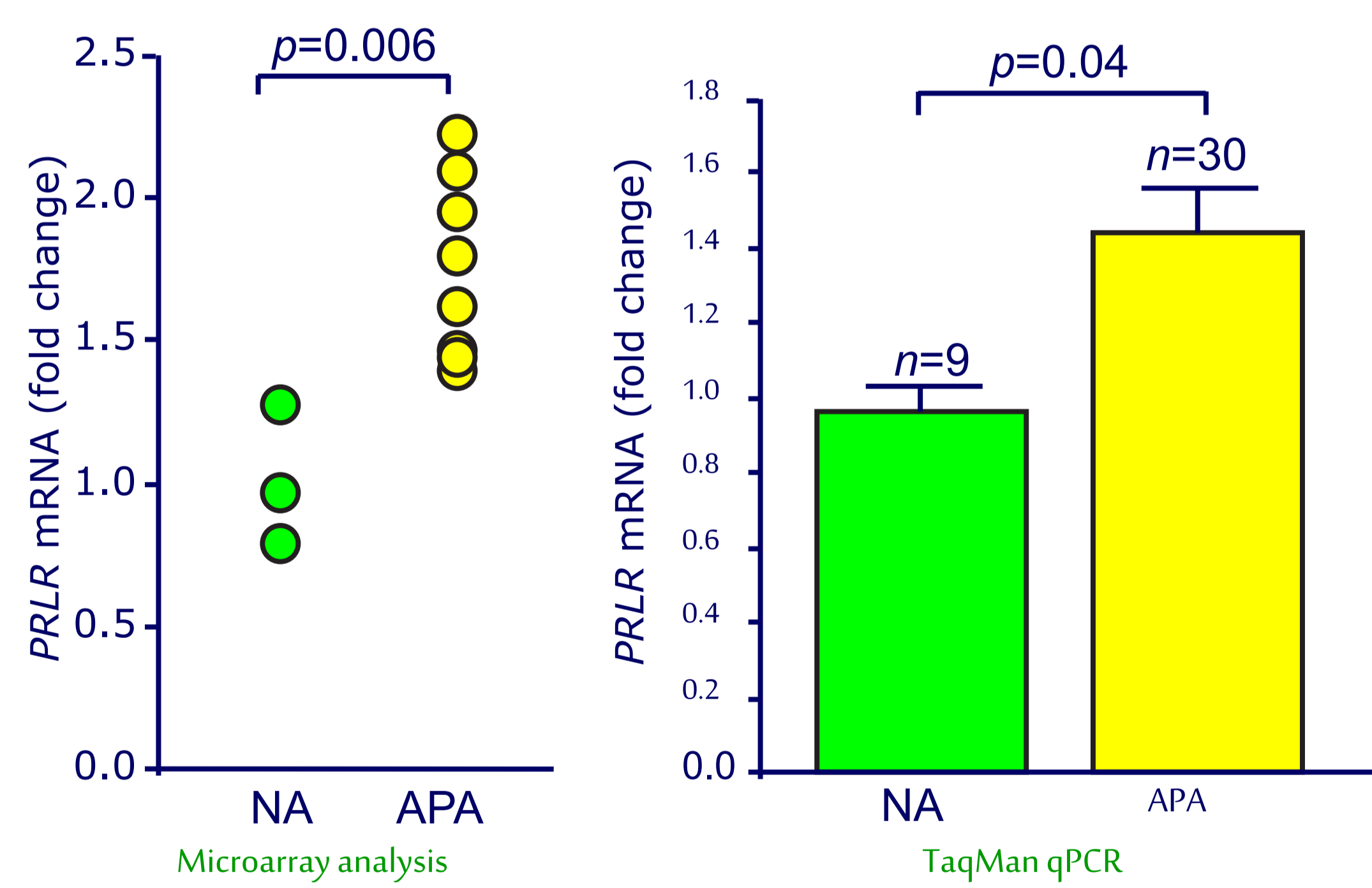
- ▶ Increased incidence of macroprolactinoma compared to normal population

Patient	Sex	Diagnosis of prolactinoma (age, y)	Clinical onset of hyperprolactinemia (age, y) and symptoms	Prolactinoma size at diagnosis	Therapy for prolactinoma	PRL at diagnosis (μU/ml)	Diagnosis of PA (age, y)	Onset of HT (age, y)	Lowest serum potassium (mEq/L)	AVS	PA subtype	Aldo (ng/L) and renin (mU/L) or PRA (ng/mL/h)	Therapy for PA	Size of adrenals (imaging)
MU1	M	35	35, visual field defects	MACROADENOMA	transsphenoidal surgery 1979 and 1985 radiotherapy 1979	unknown	55	53	3.2	bilateral PA	BAH	PAC 249 PRA 0.08	spironolactone	normal
MU2	M	39	39, fatigue, infertility	MACROADENOMA, 12 mm	cabergoline, transsphenoid resection	6508	39	29	3.7	bilateral PA	BAH	PAC 143 PRC 3.2	spironolactone	normal
MU3	M	57	56, visual field defects	MACROADENOMA, 35 mm	quinagolid cabergoline	45289	64	53	3.5	not selective	BAH	PAC 341 PRC <1	left ADX + spironolactone (persisting PA)	left nodule 20 mm
MU4	M	63	61, hyposexuality	MACROADENOMA, 20 mm	cabergoline	23946	63	42	3.1	not performed	APA	PAC 444 PRC 1.2	left ADX	left nodule 46 mm
TO1	F	51	51, oligomenorrhoea	idiopathic hyperprolactinemia	bromocriptine	840	51	51	3.8	left PA	APA	PAC 450 PRA 0.1	left ADX	left nodule 10 mm
TO2	F	51	51, oligomenorrhoea, galactorrhea	microadenoma, 10 mm	bromocriptine	1200	51	44	3.4	left PA	APA	PAC 480 PRA 0.1	left ADX	left nodule 20 mm
TO3	M	63	61, hyposexuality	MACROADENOMA, 30 mm	cabergoline	3481	63	39	3.6	left PA	APA	PAC 162 PRA 0.2	refuses ADX	left nodule 5 mm

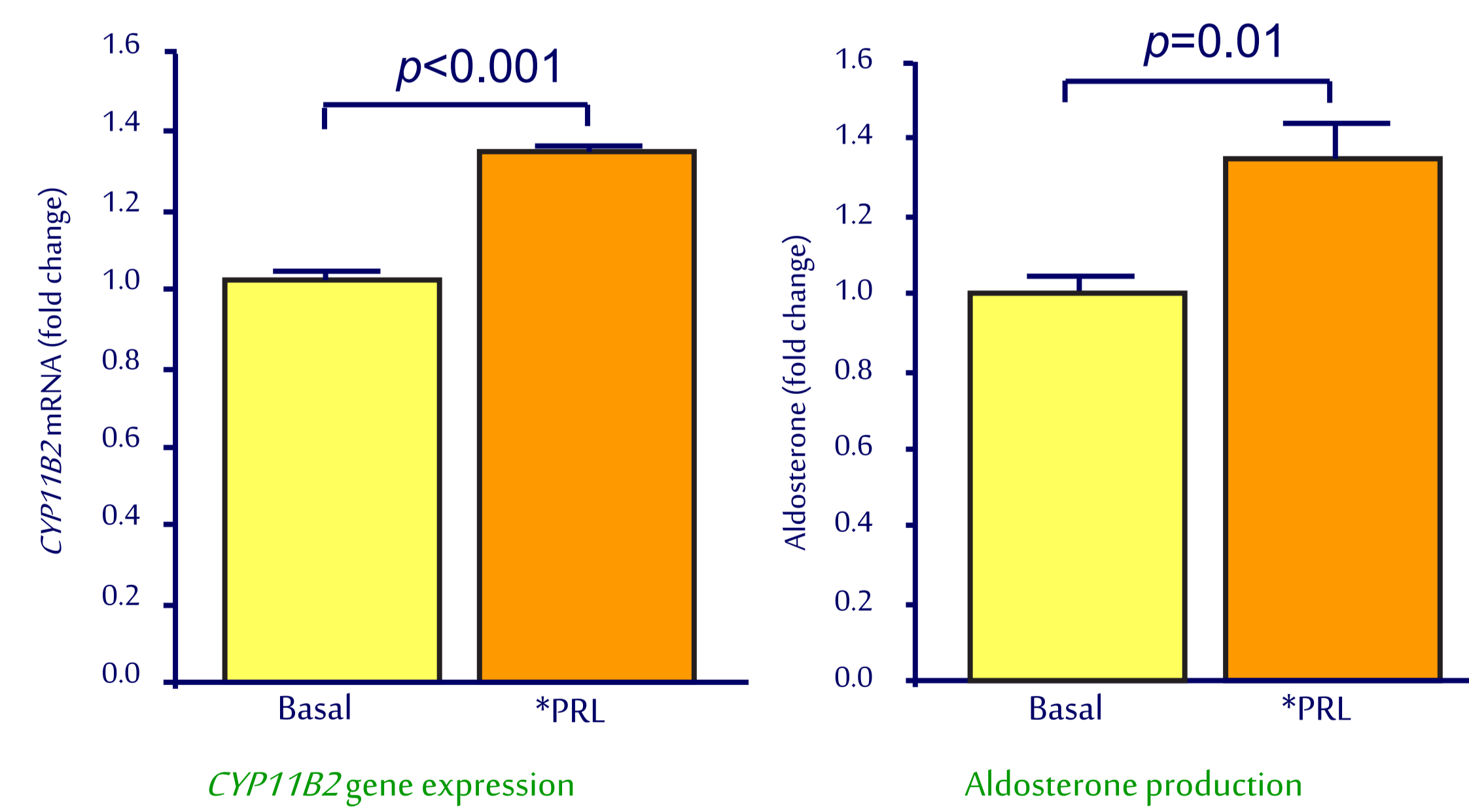
M, male; F, female; y, years; PRL, prolactin; PA, primary aldosteronism; HT, hypertension; AVS, adrenal venous sampling; Aldo, aldosterone; PRA, plasma renin activity; PAC, plasma aldosterone concentration; PRC, plasma renin concentration; BAH, bilateral adrenal hyperplasia; ADX, adrenalectomy.

- ▶ Predominance of macroprolactinomas over microprolactinomas co-existing with PA consistent with putative role for elevated prolactin levels in PA
- ▶ Increased expression of prolactin receptor could potentially increase sensitivity of zona glomerulosa to prolactin

2. The prolactin receptor gene is upregulated in APA compared to normal adrenals



3. High prolactin concentrations stimulate CYP11B2 gene expression and aldosterone production in NCI H295R adrenal cells



*PRL used for stimulations = 100 nM (equivalent to 53000 mU/ml) that is found in macroprolactinoma patients. 100 nM PRL is 12-fold and 22.5-fold higher than during the 3rd gestational period of pregnancy (4430 μU/ml) and the 4th-8th weeks of lactation (2343 μU/ml), respectively (Tay et al. Hum Reprod 1996;11:950-955).

Summary and Conclusions

- ▶ Increased incidence of prolactinoma in Munich-Turin PA cohort compared to normal population
- ▶ Increased incidence of macroprolactinomas in co-existing prolactinoma-PA:
- ▶ Increased expression of prolactin receptor gene expression in APA compared to normal adrenals
- ▶ Increased expression of CYP11B2 and aldosterone production in adrenal cell line

Evidence for a direct role of high levels of prolactin on aldosterone production and a putative pathophysiological link between hyperprolactinemia/prolactinoma and PA

