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LABORATORY INVESTIGATION

Low levels of *PRB3* mRNA are associated with dopamine-agonist resistance and tumor recurrence in prolactinomas

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Abstract Prolactinomas, or prolactin-secreting adenomas, constitute the most common type of hyperfunctioning pituitary adenoma. Dopamine agonists are used as first-line medication for prolactinomas, but the tumors are resistant to the therapy in 5–18 % of patients. To explore potential mechanisms of resistance to bromocriptine (a dopamine agonist), we analyzed six responsive prolactinomas and six resistant prolactinomas by whole-exome sequencing. We identified ten genes with sequence variants that were differentially found in the two groups of tumors. The expression of these genes was then quantified by real-time reverse-transcription PCR (RT-qPCR) in the 12 prolactinomas and in six normal pituitary glands. The mRNA levels of one of the genes, *PRB3*, were about fourfold lower in resistant prolactinomas than in the responsive tumors ($p = 0.02$). Furthermore, low *PRB3* expression was also associated with tumor recurrence. Our results suggest that low levels of *PRB3* mRNA may have a role in dopamine-agonist resistance and tumor recurrence of prolactinomas.

Keywords Prolactinoma · Resistance · Recurrence · *PRB3* mRNA · Whole-exome sequencing

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Introduction

Prolactinomas account for ~40 % of all pituitary tumors [1], and dopamine agonists (DAs) are the first-line drugs of choice to treat them [1–3]. DAs selectively stimulate the dopamine D2 receptor (D2R), thus suppressing secretion of prolactin (PRL) and multiplication of normal and prolactinoma cells, leading to reduction of tumor size and serum PRL levels. Bromocriptine (BCR), the only commercially available DA in mainland China, is very effective in normalizing PRL levels and reducing tumor size. However, the tumors in 5–18 % of patients are resistant to BCR [1, 4].

The mechanisms underlying BCR resistance of prolactinomas are not fully understood, although reduced expression of D2R, or of one of its isoforms (D2S and D2L), may have a role in these processes [1, 5]. Here, we studied prolactinomas by whole-exome sequencing and identified ten genes containing sequence variants that were differentially found in BCR-responsive and BCR-resistant

Table 1 Patient classification according to their response to BRC

Patient number	Gender/age	Serum PRL levels (μg/ml)			Higher BRC dose (mg/day)	Months with higher BRC dose	Classification	Tumor size (cm)
		Before BRC	With BRC	Normal				
1	M/33	4,843	15	Yes	2.5	10	Responsive	2.5
2	M/48	928	3.9	Yes	5.0	6	Responsive	2.0
3	F/43	122.3	3.18	Yes	2.5	3	Responsive	1.8
4	M/63	899	7.6	Yes	7.5	6	Responsive	4.5
5	M/54	3,117	9.2	Yes	7.5	3	Responsive	2.5
6	F/20	3,830	15.5	Yes	5.0	8	Responsive	2.0
7	M/35	>6,000	268	No	15	5	Resistant	3.0
8	F/31	975	165	No	15	4	Resistant	3.5
9	M/25	182	83.2	No	15	5	Resistant	2.0
10	M/15	>6,000	68.2	No	15	6	Resistant	2.5
11	F/36	168	150	No	15	6	Resistant	0.8
12	M/46	2,899	128.6	No	15	24	Resistant	5.0

The PRL level the day after medical therapy (<20 ng/mL in women and <15 ng/mL in men is considered cure [20]

prolactinomas. We also found that mRNA levels of one of the genes, *PRB3*, were lower in BCR-resistant prolactinomas than in BCR-responsive prolactinomas. Furthermore, low levels of *PRB3* mRNA were associated with prolactinoma recurrence. Therefore, *PRB3* expression might have a role in BCR resistance and tumor recurrence of prolactinomas.

Materials and methods

Tissue specimens

Samples from six BCR-responsive prolactinomas (the patients had emergency operations because of vision and visual field disorders) and six BCR-resistant prolactinomas were obtained from patients who underwent endoscopic trans-sphenoidal surgery between December 2009 and January 2012 at the Tiantan Hospital, Beijing, China. In addition, six normal pituitary glands, used as controls, were collected within 12 h of death from three adult males who had died in car accidents. Clinical and pathological characteristics of the prolactinomas are described in Table 1. There was a near equal distribution of macro and microadenomas in each of the two groups in the study [6, 7]. All specimens were stained and showed no hemorrhage or necrosis, microscopically or at intraoperative inspection. Tested specimens were the same ones confirmed as prolactinomas by IHC (Supplementary Fig. S1). Portions of the surgical specimens were snap-frozen in liquid nitrogen and stored at −80 °C. Prolactinomas were characterized based on presurgical clinical and biochemical findings and on morphological and immunohistochemical analysis of removed tissue samples. Resistant tumors were defined as those from patients whose serum PRL levels remained abnormally high after at least 3 months of treatment with a daily dose of 15 mg BCR [1]. Informed consent was obtained from all patients, and the study was approved by the Ethics Committee of Beijing Tiantan Hospital.

Whole-exome sequencing

Total DNA was extracted from prolactinomas using the QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany). We purified and quantified 3 μg of genomic DNA from each specimen. For exome enrichment, we used an ABI SOLiD optimized SureSelect Human All Exon kit (Agilent, Santa Clara, CA, USA), which included exonic sequences of ~18,000 genes, covering a total of 37 Mb of genomic sequences. The enriched exome libraries were then amplified by emulsion PCR, according to the manufacturer's instructions (Life Technologies, Carlsbad, CA, USA), based on a library concentration of 0.5 pM. The PCR products were then sequenced on a SOLiD 4 sequencer (Life Technologies); one quad of a SOLiD sequencing slide was required for each sample.

Color-space reads were mapped to the hg19 reference human genome with the SOLiD BioScope software (Life Technologies), which is suitable for a repetitive mapping approach. Then we called single-nucleotide polymorphisms (SNPs) using the diBayes algorithm with a conservative default call stringency [8]. We excluded known SNPs available from the Single Nucleotide Polymorphism Database (dbSNP) v130, maintained by the National Center for Biotechnology Information (NCBI).

Table 2 Primers used for RT-qPCR analysis of the expression of 10 variant genes

Gene	Forward primer	Reverse primer
C1orf170	5′-CACCCTGCGTTTCTTCTGG-3′	5′-TGCCCATCCCCTCTTTG-3′
DPCR1	5′-AGTGCTGCCTCCTCTTCCTTCTA-3′	5′-GGGAGCTCTGGAGGTCTTTGTC-3′
DSPP	5′-GCATTTGGGCAGTAGCATGG-3′	5′-CTGACACATTTGATCTTGCTAGGAG-3′
KRTAP10-3	5′-AGCCAGCTTGCTGCACAT-3′	5′-TGAAGAGGAAGCCCCAGAG-3′
MUC4	5′-GCCAACTTCACGCTCAGAGAC-3′	5′-TCTCCAGAGTGAATGGCTCCAG-3′
MX2	5′-GCCAGGTGGAGAAAGAGATACACAA-3′	5′-AGGTCAATGATGGTCAGGTCTGG-3′
POTEF	5′-CTGCATGTGGCGTGACTCTG-3′	5′-CGGCATGGAATCAACCTCAA-3′
PRB3	5′-CCTCCAGCAAGATGCTACTGATT-3′	5′-GGGAGATTCTTCCTGGCTGA-3′
PRG4	5′-GGCAGCGCTTTCAACAGCTAA-3′	5′-CCAGGGCACTTCTGTACAGGTTC-3′
RP1L1	5′-AGAAGCGAGGCTGAAACTTTATCTG-3′	5′-TCACACTCGGCTTGGTCTTTG-3′

Table 3 Genes potentially related to BCR resistance in prolactinomas

Gene	GenBank ID	Encoded protein
C1orf170	BC006300	Uncharacterized protein, chromosome 1 ORF 170
DPCR1	NM_080870	Diffuse panbronchiolitis critical region protein 1
DSPP	NM_014208	Dentin sialophosphoprotein
KRTAP10-3	NM_198696	Keratin associated protein 10-3
MGAM	NM_004668	Maltase-glucoamylase (alpha-glucosidase)
MUC4	NM_138297.4	Mucin 4, cell surface associated
MX2	NM_002463	Myxovirus (influenza virus) resistance protein 2
PRB3	NM_006249	Proline-rich protein BstNI subfamily 3
PRG4	NM_005807	Proteoglycan 4 (PRG4), transcript variant A
RP1L1	NM_178857	Retinitis pigmentosa 1-like 1 protein

RNA extraction and real-time reverse-transcription PCR (RT-qPCR)

We measured the expression levels of 10 variant genes in a blinded fashion. Total RNA was extracted from frozen prolactinomas (~50 mg) using TRIzol Reagent (Life Technologies). The primers used in real-time reverse-transcription PCR (RT-qPCR) are listed in Table 2. RT-qPCR was performed as described previously [9], using Applied Biosystems 7500 Fast System (Life Technologies). The fold-change in differential expression for each gene was calculated using the comparative C_T method (also known as the $2^{-\Delta\Delta CT}$ method) as previously described [9].

Statistical analysis

All the statistical analyses were performed using SPSS version 20.0. For comparisons, one-way analyses of variance (LSD was used during multiple comparisons), Chi squared tests and two-tailed Student's *t* tests, were carried out as appropriate. Binary logistic regression was performed to identify independent factors related to prolactinoma recurrence.

Results

Identification of variant genes by whole-exome sequencing

We analyzed six BCR-responsive prolactinomas and six BCR-resistant prolactinomas by whole-exome sequencing. About 5 gigabases of mappable sequence data were generated for each individual, and 70 % of bases were mapped to the targeted exome. In total, 80 % of the exome was covered at least tenfold, and about 20,000 genetic variants were identified for each individual. Several prioritization steps were taken to lessen the number of genetic variants and to find the potentially pathogenic variants [8]. A comparison with the NCBI dbSNP, with recently released SNP data from other groups and with in-house SNP data confirmed that >90 % of the identified variants were previously reported SNPs that did not seem to explain BCR resistance of prolactinomas. Ten variant genes were selected for further study: *C1orf170, DPCR1*, *DSPP*, *KRTAP10-3, MUC4*, *MX2*, *POTEF*, *PRB3*, *PRG4* and *RP1L1* (Table 3).

Table 4 Differential expression fold of genes (statistical method: two-tailed Student's *t* tests)

	Responsive	Resistant	*p* value
PRB3	0.628333833	0.18319136	0.020
PRG4	0.000109963	0.000281276	0.700
MUC4	0.010466577	0.015666494	0.700
DSPP	0.010298289	0.021137023	0.513
DPCR1	0.3257084	0.154926532	0.060
RP1L1	0.023944092	0.006293673	0.400
MX2	0.108311332	0.18653675	0.807
POTEF	0.146750534	0.150689894	0.655
C1orf170	0.043853399	0.024682049	0.150
KRTAP10-3	0.003738342	0.006845497	0.827

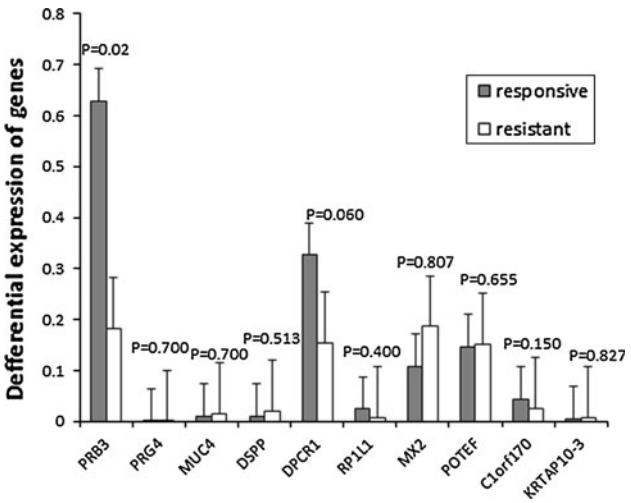

Fig. 1 RT-qPCR analysis of 10 variant genes in BCR-responsive and BCR-resistant prolactinomas. Only the differential expression of *PRB3* was statistically significant

Analysis of the expression of variant genes by RT-qPCR

We used RT-qPCR to test whether BCR resistance in prolactinomas was associated with differences in expression levels of any of the 10 variant genes, Indeed, expression levels of *PRB3*, *DPCR1*, *RP1L1* and *C1orf170* were lower in resistant tumors than in responsive tumors. In particular, levels of *PRB3* mRNA were about fourfold lower in resistant prolactinomas than in the responsive tumors ($p = 0.02$), but other differences did not achieve statistical significance. For detailed data, see the Table 4. In contrast, mRNA levels of *PRG4*, *MUC4*, *DSPP*, *MX2*, *POTEF* and *KRTAP10-3* were higher in resistant prolactinomas than in the responsive tumors, but these differences did not achieve statistical significance. Mean expression levels of the 10 genes are shown in Fig. 1; Table 4 (statistical method: two-tailed Student's *t* tests).

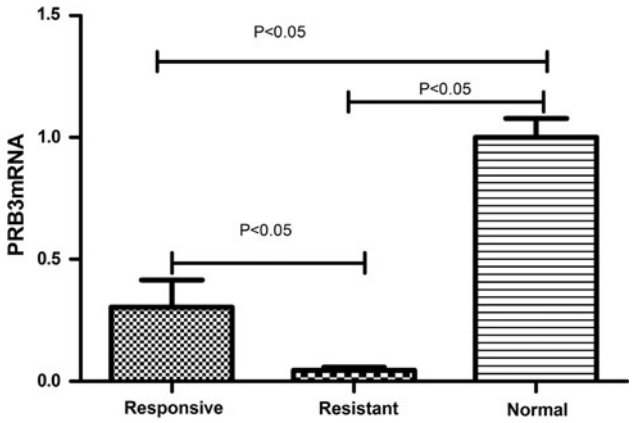

Fig. 2 Mean *PRB3* mRNA levels in BCR-responsive and BCR-resistant prolactinomas and in normal pituitary. *PRB3* expression was measured by RT-qPCR in 6 BCR-responsive prolactinomas, 6 BCR-resistant prolactinomas and 6 normal pituitary glands. *Horizontal lines* above the *bars* represent standard deviations (statistical method: one-way analyses of variance)

Low PRB3 expression is associated with BCR resistance and tumor recurrence in prolactinomas

To investigate the potential role of *PRB3* in BCR resistance, we measured *PRB3* expression by RT-qPCR in 6 resistant prolactinomas, 6 sensitive prolactinomas and six normal pituitary glands (Fig. 2). The levels of *PRB3* mRNA in BCR-resistant prolactinomas were about fourfold lower than in the responsive tumors ($p < 0.05$), and about fivefold lower than in normal pituitary glands (statistical method: one-way analyses of variance).

Between 2007 and 2012, 24 patients with prolactinomas were enrolled in our study. Follow-up periods ranged from 6 months to 5 years (mean 3.5 years). The median expression level was used as the cutoff. Low PRB3 mRNA levels were defined as values below the 50th percentile of the 12 patients; values at or above the 50th percentile were classified as high levels. We then asked whether low *PRB3* mRNA levels in prolactinomas were associated with any clinical parameters (Table 5) (statistical method: Chi squared tests). There was no significant correlation between *PRB3* mRNA levels and age, gender, tumor size or PRL serum levels. However, low *PRB3* mRNA levels were more frequently observed in recurrent tumors ($p = 0.037$) and BCR-resistant tumors ($p = 0.011$) (recurrence was defined as the discovery of an elevated PRL level at any time in the postoperative surveillance period after an initial remission [1]). Furthermore, binary multivariate regression revealed that low levels of *PRB3* mRNA were independently associated with tumor recurrence (odd ratio [OR] 0.065, 95 % confidence interval [CI] 0.05–0.832, $p = 0.036$).

Table 5 Relationship between *PRB3* mRNA levels in prolactinomas and various clinical parameters(statistical method: Chi squared tests)

Feature	*PRB3* mRNA levels			
	High[a]	Low	Chi square	*p* value
All cases	12	12		
Patient's age			0.689	0.406
≥50	4	6		
<50	8	6		
Patient's gender			4.332	0.037
Male	4	8		
Female	9	3		
Serum PRL levels			0.168	0.682
≥915 μg/ml[b]	5	6		
<915 μg/ml	7	6		
Tumor size			0.670	0.413
≥1 cm	5	7		
<1 cm	7	5		
Recurrence[c]			4.332	0.037
Yes	3	8		
No	9	4		
Resistance to BRC[d]			6.511	0.011
	4	10		
	8	2		

[a] The median expression level was used as the cutoff. Low *PRB3* mRNA levels were defined as values below the 50th percentile of the 12 patients; values at or above the 50th percentile were classified as high levels

[b] The median serum PRL level was used as the cutoff: 915 μg/ml. Low serum PRL levels were defined as values below the 50th percentile of the 12 patients; values at or above the 50th percentile were classified as high levels

[c] Recurrence was defined as the discovery of an elevated PRL level at any time in the postoperative surveillance period after an initial remission [1]

[d] Resistant tumors were defined as those from patients whose serum PRL levels remained abnormally high after at least 3 months of treatment with a daily dose of 15 mg BRC [1]

Discussion

In the present study, we used whole-exome sequencing to search for gene variants associated with BCR resistance in prolactinomas. Previous studies showed that some DA-resistant prolactinomas have a reduced density of D2Rs using different methods [10, 11]. Other studies have demonstrated that the proportion of D2R-encoding mRNA corresponding to the D2S isoform was lower in resistant prolactinomas than in responsive tumors [5, 12]. Our analysis of BCR-resistant and BCR-responsive prolactinomas by whole-exome sequencing revealed sequence variants associated with 10 genes, but not with the D2R-encoding gene.

We then measured mRNA levels for the 10 genes by RT-qPCR, and found that differences in gene expression between resistant and responsive prolactinomas reached statistical significance only for the *PRB3* gene. *PRB3* encodes a proline-rich salivary protein that is a major constituent of parotid saliva. Although the function of this protein is not clear, it is proposed to act as a bacterial receptor. *PRB3* and five other genes that also encode salivary proline-rich proteins (PRPs), together with a gene encoding a lacrimal gland PRP, form a PRP gene cluster in the 12p13 region of chromosome 12 [13].

Scully et al. [14]. reported that a number of PRPs mRNAs, including *PRB3* mRNA, in saliva have been tested in over 300 saliva samples from OSCC (oral squamous cell carcinomas) patients and healthy people, and the signature was always present in higher levels in the saliva of OSCC patients than in saliva from healthy people, with an overall accuracy rate of about 85 %. Raponi et al. [15]. identified that PRPs were associated with epidermal development function during the process of squamous cell carcinomas. T.F. Warner et al. think that salivary PRPs by binding ingested tannins protect the oesophagus from the carcinogenic effects of the latter. It is also possible that genetic variants of PRPs may influence the incidence of oesophageal cancer in different populations [16]. Therefore, we thought glycosylated proline-rich glycoprotein and PRB3 mRNAs may play a role in tumors aggressivity.

We found in the present study that *PRB3* mRNA levels were about four-fold lower in BCR-resistant prolactinomas than in BCR-responsive prolactinomas ($p = 0.02$). Further analysis of our data confirmed that low levels of *PRB3* mRNA were more frequently observed in in recurrent tumors ($p = 0.037$).

Pellegrini et al. [10] in 1989 found that D2R levels was lower in dopamine resistant prolactinomas. And then, the same group showed also a lower expression of pituitary specific PIT1 (POU1F1) transcription factor in dopamine resistant prolactinomas [17]. Delgrange et al. [18] reported that resistant prolactinomas tend to be more invasive and to recur more often than responsive tumors. Furthermore, recurrent prolactinomas were more likely to be resistant to the drug therapy. Raverot et al. [19] found already seven genes mRNA level variation, notably PPTG and CCNB1, were associated with tumor recurrence or progression. In our study, binary multivariate regression revealed that low levels of *PRB3* mRNA were independently associated with prolactinoma recurrence (OR 0.065, 95 % CI 0.05–0.832, $p = 0.036$).

Although 8 of the 12 patients with low *PRB3* mRNA levels had a higher recurrence rate (Table 5), additional factors probably contribute to recurrence, considering that 4 patients with low levels did not show recurrence, whereas 3 patients with high *PRB3* mRNA levels also showed

recurrence by the study definition. This indicates that prolactinoma recurrence has other causes, for instance: preoperative tumor size, invasion of the cavernous or sphenoid sinus, tumor blood supply, postoperative retained tumor, and even the surgeon's experience [1, 19].

Taken together, our results suggest that low levels of *PRB3* mRNA may contribute in some unknown way to promoting drug resistance and tumor recurrence of prolactinomas. It is tempting to speculate that abnormally low levels of the PRB3 protein may have a role in these processes. However, differences in mRNA levels (as reported here) do not necessarily result in differences in levels of the corresponding functional protein. Nevertheless, the potential links between *PRB3*, drug resistance and tumor recurrence should be further investigated.

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