

## Original Article

# Genetic alterations of interleukin-17 and related genes in human prostate cancer

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**Abstract:** Interleukin-17 (*IL-17*) has been shown to promote development of hormone-naïve prostate cancer (HNPC) and castration-resistant prostate cancer (CRPC) as well as lymph node metastasis in mouse models. Gene alterations of *IL-17* family of cytokines and their downstream genes in human prostate cancer have not been investigated. We studied 7 datasets archived in cBioPortal and queried gene alterations in a total of 1303 cases of human prostate cancers. 35 genes were examined, including *IL-17* family of cytokines and receptors, *IL-17*-downstream genes, and genes related to *IL-17*-downstream genes. We found that 34/35 (97%) genes had significantly more alterations in metastatic prostate cancer (with alteration rates ranging from 3.42% to 13.01%) than primary prostate cancer (with alteration rates ranging from 0.40% to 2.96%). 15/35 (43%) genes had significantly more alterations in primary CRPC than primary HNPC. 34/35 (97%) genes had significantly more alterations in metastatic CRPC than primary HNPC. Only three genes (*S100A7*, *S100A8*, and *S100A9*) had significantly more alterations in metastatic CRPC than primary CRPC. The gene alterations were mostly gene amplifications (97%), while gene deep deletions, missense mutations, and truncating mutations were very rare. 7/35 (20%) genes had significantly more alterations in primary neuroendocrine prostate cancer (NEPC) than primary adenocarcinoma (AC). 23/35 (66%) genes had significantly more alterations in metastatic NEPC than metastatic AC. Only three genes (*S100A7*, *S100A8*, and *S100A9*) had significantly more alterations in metastatic NEPC than metastatic AC with neuroendocrine features. Most of the gene alterations in metastatic NEPC were gene amplifications (80%), while gene deep deletions, missense mutations, and truncating mutations were very rare. Our findings suggest that gene amplifications of *IL-17* and related genes are more frequently found in metastatic CRPC and NEPC than primary hormone-naïve prostate adenocarcinomas, implying that *IL-17* and related genes may play important roles in the progression from HNPC to CRPC and from primary location to metastasis as well as in development of metastatic NEPC.

**Keywords:** Prostate cancer, metastasis, CRPC, *IL-17*, gene amplification

### Introduction

Prostate cancer is the most common malignancy and the second most common cause of cancer-related deaths in American men; the American Cancer Society estimates that there are approximately 174,650 new cases and 31,620 deaths due to prostate cancer in 2019 [1]. Distant metastases are common findings in autopsies of prostate cancer patients. Hematogenous metastases were present in 35% of 1,589 patients with prostate cancer, with the most frequent involvement being the bone

(90%), lungs (46%), liver (25%), pleura (21%), and adrenals (13%) [2]. Metastatic prostate cancers are usually treated with androgen deprivation therapy (ADT) and they often respond to ADT as they are hormone-naïve prostate cancer (HNPC). Eventually, almost all of them become insensitive to ADT even when the blood levels of androgens are at castration levels, hence they are called castration-resistant prostate cancer (CRPC). A small portion (approximately 0.5%-2%) of prostate cancer, so called neuroendocrine prostate cancer (NEPC), is small cell carcinoma, instead of adenocarcinoma

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(AC). NEPC does not express androgen receptor and is inherently CRPC [3]. Some adenocarcinomas (approximately 17% to 30%) may undergo focal neuroendocrine (NE) differentiation after ADT and present NE features [3]. The molecular and cellular mechanisms underlying the progression from primary prostate cancer to metastatic prostate cancer and from HNPC to CRPC have not been fully understood.

Interleukin-17 (*IL-17*) is a family of proinflammatory cytokines, including *IL-17A*, *IL-17B*, *IL-17C*, *IL-17D*, *IL-17E*, and *IL-17F* [4]. There are five receptors for *IL-17* cytokines, including *IL-17* receptor A (*IL-17RA*), *IL-17RB*, *IL-17RC*, *IL-17RD*, and *IL-17RE* [4]. *IL-17RA* acts as a shared subunit and forms heterodimers with other four receptors [5]. Homodimers of *IL-17A* or *IL-17F* and heterodimer of *IL-17A/IL-17F* bind to *IL-17RA/IL-17RC* receptor complex. Homodimers of *IL-17B* or *IL-17E* bind to *IL-17RA/IL-17RB* receptor complex. *IL-17C* homodimer binds to *IL-17RA/IL-17RE* receptor complex. Recently, it has been reported that *IL-17A*, but not *IL-17F* or *IL-17A/F*, also binds to *IL-17RA/IL-17RD* receptor complex [6]. *IL-17A* and *IL-17F* are produced by T helper 17 (Th17) cells,  $\gamma\delta$  T cells, natural killer cells, and other immune cells [7]. Binding of *IL-17A* or *IL-17F* to *IL-17RA/IL-17RC* receptor complex recruits nuclear factor- $\kappa$ B (NF- $\kappa$ B) activator 1 (Act1) through SEFIR (similar expression to fibroblast growth factor genes, *IL-17* receptors and Toll-*IL-1R*) domains of *IL-17RA*, *IL-17RC*, and Act1. Act1 acts as an E3 ubiquitin ligase to ubiquitinate tumor necrosis factor receptor-associated factor 6 (TRAF6) through lysine-63-linked ubiquitination [8]. Then, TRAF6 activates transforming growth factor- $\beta$ -activated kinase 1 (TAK1) and subsequently I $\kappa$ B kinase (IKK) complex, resulting in activation of NF- $\kappa$ B pathway that initiates transcription of a variety of cytokines, chemokines, matrix metalloproteinases (MMP), and growth factors, such as *IL-1 $\alpha$* , *IL-1 $\beta$* , *IL-6*, tumor necrosis factor  $\alpha$  (*TNF $\alpha$* ), colony stimulating factor (*CSF*), C-X-C motif ligand 1 (*CXCL1*), *CXCL2*, *CXCL5*, *CXCL8*, C-C motif ligand 7 (*CCL7*), S100 Calcium Binding Protein A7 (*S100A7*), *S100A8*, *S100A9*, CCAAT Enhancer Binding Protein Beta (*CEBPB*), Prostaglandin-Endoperoxide Synthase-2 (*PTGS2*), *MMP1*, *MMP2*, *MMP7*, *MMP9*, and *MMP13* [9-15]. *IL-17* also induces expression of programmed cell death protein 1 (*PD-1*) ligand 1 (*PD-L1*), but not *PD-L2* in a human prostate cancer LNCaP cell line [16].

*IL-17* has been shown to promote development of colon cancer [17-20], skin cancer [21, 22], breast cancer [23], prostate cancer [13, 24], lung cancer [25, 26], and pancreas cancer [27]. Using *IL-17rc*-null and phosphatase and tensin homolog (*Pten*)-null mouse models, we have demonstrated that *IL-17rc* knockout inhibits prostate cancer development [13]. *IL-17* induces expression of *MMP7* to cleave E-cadherin, thus activating  $\beta$ -catenin-mediated epithelial-to-mesenchymal transition, which subsequently enhances development of prostate cancer in *Pten*-null mice [14]. We have also shown that *IL-17* promotes development of CRPC in *Pten*-null mice partially through increasing immunosuppressive M2 macrophages and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment [24]. Using an orthotopic allograft model in immunocompetent mice, we found that co-injection of recombinant *IL-17A* and mouse prostate cancer MPC3 cells slightly increased primary tumor growth, however, pelvic lymph node metastasis was significantly enhanced [28]. On the other hand, we found that Th17 inhibitor SR1001 and anti-mouse *IL-17A* antibody are able to partially inhibit formation of prostate cancer in *Pten*-null mice [29]. Recently, we have shown that Th17-polarized splenocytes promoted orthotopic allograft prostate tumor growth compared to the control splenocytes [30]. These studies suggest that Th17 cells and *IL-17* cytokines secreted by Th17 cells may play important roles in development of primary prostate cancer, CRPC, and lymph node metastasis. The objective of this study was to analyze genetic alterations of *IL-17* family of cytokines and related genes aforementioned in primary and metastatic prostate cancers, using publicly archived datasets and bioinformatics tools.

### Materials and methods

#### Data sources

All of the data were obtained through cBioPortal for Cancer Genomics ([www.cbioportal.org](http://www.cbioportal.org)) [31, 32]. cBioPortal has archived 20 datasets for gene alterations in human prostate cancers. We filtered through the datasets and excluded the datasets that potentially used overlapping original samples according to the linked publications. Seven datasets were included, which did not appear to have overlapping original samples (Table 1).

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**Table 1.** Data sources

Datasets <sup>‡</sup>	Author	Year	Included cases (N=1303)	Excluded cases* (N=77)
MCTP	Grasso [33]	2012	59	NA (n=60)
SU2C/PCF Dream Team	Abida [34]	2019	427	Unknown (n=2)
Multi-Institute	Beltran [35]	2016	81	
Broad/Cornell	Barbieri [36]	2012	112	NA (n=11)
Fred Hutchinson CRC	Kumar [37]	2016	61	Not profiled (n=2)
SMMU	Ren [38]	2017	65	
TCGA	TCGA data		498	Not profiled (n=2)

<sup>‡</sup>MCTP, Michigan Center for Translational Pathology; SU2C/PCF Dream Team, Stand Up to Cancer/Prostate Cancer Foundation Dream Team; Fred Hutchinson CRC, Fred Hutchinson Cancer Research Center; SMMU, Second Military Medical University (Shanghai); TCGA, The Cancer Genome Atlas. \*Cases were excluded from analysis if the sample types were “Not available (NA)”, “Unknown”, or “Not profiled”; the number of cases excluded is shown.

The data of Michigan Center for Translational Pathology (MCTP) were generated by Dr. Arul Chinnaiyan's and Dr. Scott Tomlins' labs at the University of Michigan [33]; the data of Stand Up to Cancer/Prostate Cancer Foundation Dream Team (SU2C/PCF Dream Team) were generated by researchers at Dana-Farber Cancer Institute, Karmanos Cancer Institute, Memorial Sloan Kettering Cancer Center, Royal Marsden, University of Michigan, University of Washington, and Weill Cornell Medicine [34]; the data of Multi-Institute were generated by researchers at Weill Cornell Medicine [35]; the data of Broad/Cornell were generated by Dr. Levi Garraway's lab at Broad Institute and Dr. Mark Rubin's lab at Weill Cornell Medicine [36]; the data of Fred Hutchinson Cancer Research Center were generated by researchers at the University of Washington and Fred Hutchinson Cancer Research Center [37]; the data of the Second Military Medical University (Shanghai) (SMMU) were generated by researchers at Shanghai Changhai Hospital and Fudan University Cancer Center [38]; the data of The Cancer Genome Atlas (TCGA) (<https://www.cancer.gov/tcga>) were a public databank managed by the National Cancer Institute, National Institutes of Health. A total of 1303 cases of prostate cancer samples (N=1303) were included, while 77 cases were excluded from analysis because the sample types were “Not available (NA)”, “Unknown”, or “Not profiled” (Table 1).

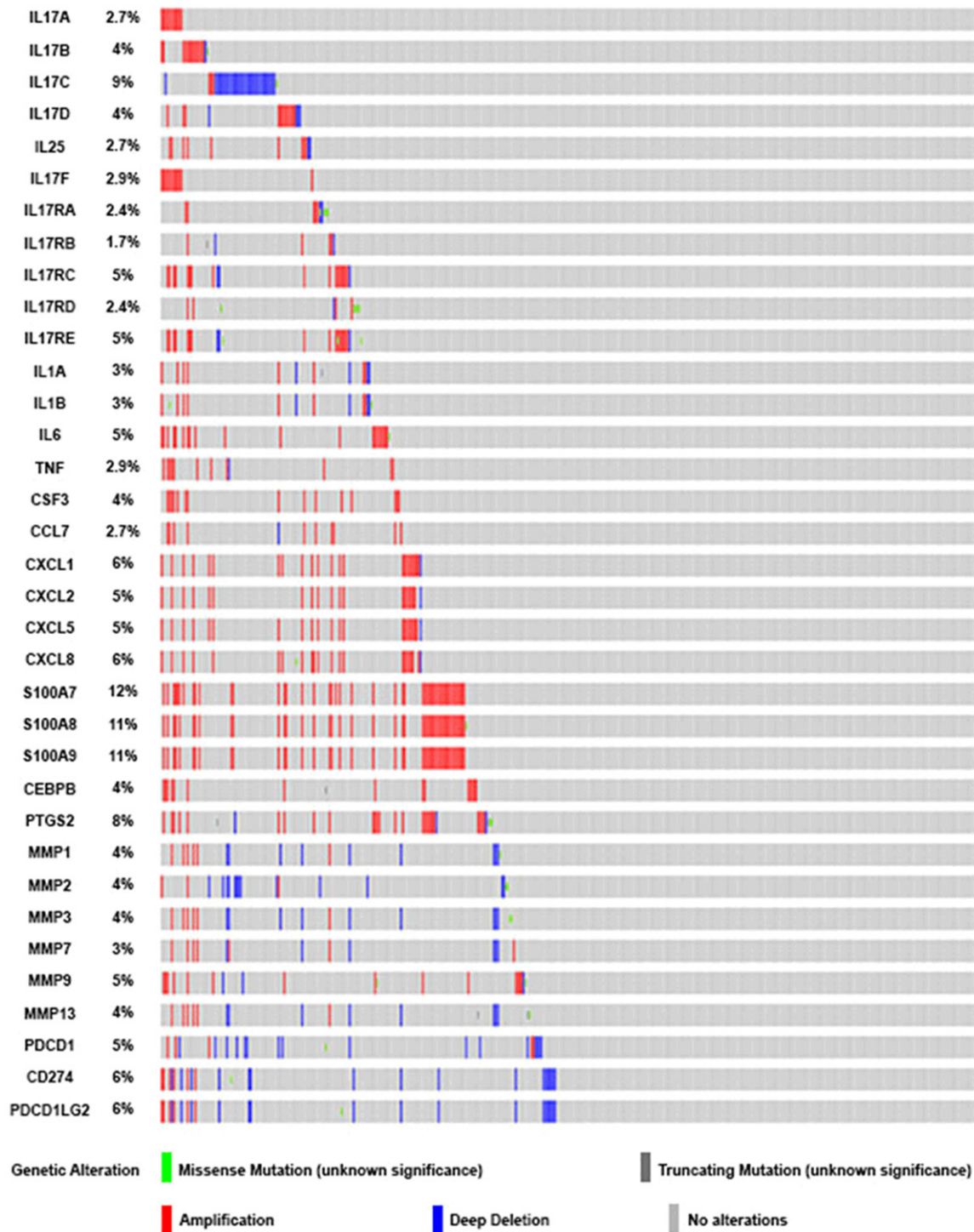
### Bioinformatics analysis

We used cBioPortal query tools to find genetic alterations of 35 *IL-17* and related genes

(Figure 1). These genes were chosen because they are *IL-17* family of cytokines and receptors, *IL-17*-downstream genes, and related to *IL-17*-regulated genes (e.g., *PD-1* and *PD-L2* are related to *PD-L1* that is regulated by *IL-17* [16]). The bioinformatics analysis procedures are briefly described here: first, we chose “Prostate” organ type on the main page of cBioPortal; second,

we chose the dataset named “Metastatic Prostate Adenocarcinoma (MCTP, Nature 2012)” and clicked the round button on the right side; third, we typed in gene names (e.g., *IL17A*) in the query box on right top corner of the page; fourth, we clicked “Charts” below the query box and clicked “Deselect all”; fifth, we chose “Sample Type” and we could see a pie chart on this page where we chose the portion named “metastatic” and clicked “Query” on the right side of query box; sixth, we moved the mouse on the “2.1%” on the right side of “*IL17A*”, which showed “altered/profiled 1/48”. That means the number of overall *IL17A* gene alterations in metastatic prostate cancers was 1, and the number of total cases was 48. We used Object Query Language (OQL) to do queries of the 35 genes. The gene alterations were categorized into copy number alterations (amplifications and deep deletions) and mutations (missense mutations and truncating mutations) according to cBioPortal (Figure 1). Prostate cancer sample types were categorized into primary prostate cancer (including both HNPC and CRPC), metastatic prostate cancer (including both HNPC and CRPC), primary HNPC, primary CRPC, metastatic HNPC (not included in analysis because there was only one case), metastatic CRPC, primary adenocarcinoma (AC), primary NEPC, metastatic AC, metastatic NEPC, primary AC with NE feature (not included in analysis because there was only one case), and metastatic AC with NE feature. We identified and calculated the numbers and percentages of overall gene alterations and individual categories of gene alterations after pooling the query results from the 7 datasets.

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**Figure 1.** Representative illustration of cBioPortal query results. Metastatic prostate cancer samples from the SU2C/PCF Dream Team dataset were queried for overall gene alterations including missense mutations, truncating mutations, amplifications, and deep deletions (color bar-coded). 35 *IL-17* and related genes were analyzed using cBioPortal query tools and the percentages of overall gene alterations are shown.

### Statistical analysis

R software package [R version 3.5.2 (2018-12-20), R Core Team (2018); R: A language

and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria. <https://www.r-project.org/>] was used to perform Fisher's exact test between two

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sample types.  $P < 0.05$  was considered statistically significant.

### Results

#### *Human prostate cancer samples*

Data from a total of 1303 human prostate cancer samples (N=1303) were included in the analysis, while 77 samples were excluded (N=77) (**Table 1**). The samples were categorized into primary prostate cancer (N=742), metastatic prostate cancer (N=584), primary HNPC (N=684), primary CRPC (N=56), metastatic HNPC (N=1), metastatic CRPC (N=583), primary AC (N=724), primary NEPC (N=16), metastatic AC (N=461), metastatic NEPC (N=45), primary AC with NE feature (N=1), and metastatic AC with NE feature (N=12).

#### *Overall gene alterations*

Thirty-four of the 35 *IL-17* and related genes studied had significantly higher rates of gene alterations in metastatic primary cancers (including both HNPC and CRPC) compared to primary prostate cancers (including both HNPC and CRPC) (**Table 2**). *IL17C* is the only gene that the gene alterations showed no significant difference. The alteration rate range was from 3.42% to 13.01%, with the top alterations in *S100A7* (13.01%), *S100A8* (12.50%), *S100A9* (12.33%), and *PTGS2* (10.27%) in metastatic prostate cancers (**Table 2**). Significantly higher rates of gene alterations were found in *S100A7*, *S100A8*, and *S100A9* genes, but not in other genes, in metastatic CRPC, compared to primary CRPC (**Table 3**). However, significantly higher rates of gene alterations were found in 15 of the 35 genes in primary CRPC, compared to primary HNPC (**Table 4**). Further, significantly higher rates of gene alterations were found in 34 of the 35 genes in metastatic CRPC, compared to primary HNPC (**Table 5**).

#### *Individual categories of gene alterations*

We further analyzed the gene alterations by dividing them into four categories, namely, amplifications, deep deletions, missense mutations, and truncating mutations according to the default classification of cBioPortal. We found that 34 of the 35 *IL-17* and related genes studied had significantly higher rates of gene amplifications in metastatic primary cancers

(including both HNPC and CRPC) compared to primary prostate cancers (including both HNPC and CRPC) (**Table 6**). *IL17C* is the only gene that the gene amplifications showed no significant difference. The rate range was from 1.37% to 13.01%, with the top amplifications in *S100A7* (13.01%), *S100A8* (12.33%), *S100A9* (12.33%), and *PTGS2* (9.08%) in metastatic prostate cancers (**Table 6**). Gene deep deletions were significantly higher in *MMP1* (2.23%), *MMP3* (2.23%), *PDCD1* (3.60%), *CD274* (3.60%), and *PDCD1LG2* (3.60%) in metastatic prostate cancers, compared to primary prostate cancers (**Table 7**). In contrast, gene deep deletions were significantly higher in *CSF3* (0.94%) in primary prostate cancers, compared to metastatic prostate cancers (**Table 7**). Gene missense mutations were significantly higher in *IL17RD* (1.03%) and *IL17RE* (0.86%) in metastatic prostate cancers, compared to primary prostate cancers (**Table 8**). However, gene truncating mutations were very rare and there was no significant difference between metastatic and primary prostate cancers (**Table 9**).

#### *Gene alterations in NEPC*

Since NEPC is inherently CRPC, we singled out this prostate cancer type and compared it against AC. We found that 7 of the 35 genes (namely, *IL17B*, *IL25*, *IL17RB*, *TNF*, *CXCL8*, *CEBPB*, and *MMP9*) had significantly more overall gene alterations (12.50%) in primary NEPC, compared to primary AC (**Table 10**). More dramatically, 23 of the 35 genes had significantly more overall gene alterations (ranging from 11.11% to 33.33%) in metastatic NEPC, compared to metastatic AC (ranging from 2.17% to 11.93%) (**Table 11**). *S100A7* (28.89%), *S100A8* (28.89%), *S100A9* (28.89%), *CEBPB* (28.89%), *PTGS2* (28.89%), and *MMP9* (33.33%) were the genes with top alteration rates in metastatic NEPC. *S100A7* (28.89%), *S100A8* (28.89%) and *S100A9* (28.89%) were also the genes with higher rates of gene alterations in metastatic NEPC, compared to metastatic AC with NE feature (**Table 12**). When comparing between metastatic AC with NE feature and metastatic AC, there were some genes with more or less gene alterations, but the differences were not statistically significant (**Table 13**). Further analysis of each individual categories of gene alterations showed that 28 of the 35 genes had significantly higher rates of gene

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**Table 2.** Overall gene alterations in metastatic vs primary prostate cancer

Genes*	Metastatic (N=584)		Primary (N=742)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	23	3.94%	6	0.81%	1.86E-04
<i>IL17B</i>	36	6.16%	11	1.48%	7.10E-06
<i>IL17C</i>	48	8.22%	56	7.55%	6.81E-01
<i>IL17D</i>	31	5.31%	20	2.70%	2.05E-02
<i>IL25</i>	26	4.45%	5	0.67%	8.63E-06
<i>IL17F</i>	23	3.94%	3	0.40%	2.88E-06
<i>IL17RA</i>	24	4.11%	8	1.08%	4.46E-04
<i>IL17RB</i>	26	4.45%	11	1.48%	1.27E-03
<i>IL17RC</i>	42	7.19%	22	2.96%	4.35E-04
<i>IL17RD</i>	32	5.48%	9	1.21%	8.58E-06
<i>IL17RE</i>	43	7.36%	19	2.56%	6.13E-05
<i>IL1A</i>	20	3.42%	9	1.21%	7.58E-03
<i>IL1B</i>	22	3.77%	8	1.08%	1.30E-03
<i>IL6</i>	49	8.39%	13	1.75%	1.11E-08
<i>TNF</i>	28	4.79%	9	1.21%	1.38E-04
<i>CSF3</i>	31	5.31%	15	2.02%	1.36E-03
<i>CCL7</i>	30	5.14%	8	1.08%	1.60E-05
<i>CXCL1</i>	37	6.34%	6	0.81%	1.41E-08
<i>CXCL2</i>	31	5.31%	6	0.81%	6.97E-07
<i>CXCL5</i>	34	5.82%	7	0.94%	4.26E-07
<i>CXCL8</i>	35	5.99%	11	1.48%	1.22E-05
<i>S100A7</i>	76	13.01%	9	1.21%	<2.2e-16
<i>S100A8</i>	73	12.50%	11	1.48%	<2.2e-16
<i>S100A9</i>	72	12.33%	9	1.21%	<2.2e-16
<i>CEBPB</i>	36	6.16%	9	1.21%	7.87E-07
<i>PTGS2</i>	60	10.27%	12	1.62%	3.08E-12
<i>MMP1</i>	38	6.51%	9	1.21%	2.34E-07
<i>MMP2</i>	25	4.28%	14	1.89%	1.33E-02
<i>MMP3</i>	38	6.51%	9	1.21%	2.34E-07
<i>MMP7</i>	34	5.82%	11	1.48%	2.07E-05
<i>MMP9</i>	42	7.19%	14	1.89%	2.85E-06
<i>MMP13</i>	38	6.51%	10	1.35%	7.77E-07
<i>PDCD1</i>	38	6.51%	15	2.02%	5.18E-05
<i>CD274</i>	36	6.16%	11	1.48%	7.10E-06
<i>PDCD1LG2</i>	36	6.16%	12	1.62%	1.13E-05

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene alterations in metastatic than primary prostate cancer.

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**Table 3.** Overall gene alterations in metastatic CRPC vs primary CRPC

Genes*	Metastatic CRPC (N=583)		Primary CRPC (N=56)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	23	3.95%	3	5.36%	4.90E-01
<i>IL17B</i>	36	6.17%	5	8.93%	3.92E-01
<i>IL17C</i>	48	8.23%	1	1.79%	1.11E-01
<i>IL17D</i>	31	5.32%	4	7.14%	5.36E-01
<i>IL25</i>	26	4.46%	4	7.14%	3.24E-01
<i>IL17F</i>	23	3.95%	2	3.57%	1.00E+00
<i>IL17RA</i>	24	4.12%	1	1.79%	7.16E-01
<i>IL17RB</i>	26	4.46%	5	8.93%	1.80E-01
<i>IL17RC</i>	42	7.20%	4	7.14%	1.00E+00
<i>IL17RD</i>	32	5.49%	5	8.93%	3.61E-01
<i>IL17RE</i>	43	7.38%	3	5.36%	7.88E-01
<i>IL1A</i>	20	3.43%	2	3.57%	1.00E+00
<i>IL1B</i>	22	3.77%	2	3.57%	1.00E+00
<i>IL6</i>	49	8.40%	2	3.57%	3.00E-01
<i>TNF</i>	28	4.80%	4	7.14%	5.14E-01
<i>CSF3</i>	31	5.32%	3	5.36%	1.00E+00
<i>CCL7</i>	30	5.15%	3	5.36%	1.00E+00
<i>CXCL1</i>	37	6.35%	3	5.36%	1.00E+00
<i>CXCL2</i>	31	5.32%	3	5.36%	1.00E+00
<i>CXCL5</i>	34	5.83%	3	5.36%	1.00E+00
<i>CXCL8</i>	35	6.00%	5	8.93%	3.83E-01
<i>S100A7</i>	76	13.04%	2	3.57%	3.35E-02
<i>S100A8</i>	73	12.52%	2	3.57%	4.92E-02
<i>S100A9</i>	72	12.35%	2	3.57%	4.92E-02
<i>CEBPB</i>	36	6.17%	4	7.14%	7.71E-01
<i>PTGS2</i>	60	10.29%	4	7.14%	6.41E-01
<i>MMP1</i>	38	6.52%	2	3.57%	5.66E-01
<i>MMP2</i>	25	4.29%	0	0.00%	1.55E-01
<i>MMP3</i>	38	6.52%	2	3.57%	5.66E-01
<i>MMP7</i>	34	5.83%	2	3.57%	7.61E-01
<i>MMP9</i>	42	7.20%	4	7.14%	1.00E+00
<i>MMP13</i>	38	6.52%	2	3.57%	5.66E-01
<i>PDCD1</i>	38	6.52%	1	1.79%	2.40E-01
<i>CD274</i>	36	6.17%	2	3.57%	7.65E-01
<i>PDCD1LG2</i>	36	6.17%	2	3.57%	7.65E-01

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene alterations in metastatic CRPC than primary CRPC.

## Alternations of IL-17 and related genes

**Table 4.** Overall gene alterations in primary CRPC vs primary HNPC

Genes*	Primary CRPC (N=56)		Primary HNPC (N=684)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	3	5.36%	3	0.44%	6.98E-03
<i>IL17B</i>	5	8.93%	6	0.88%	6.77E-04
<i>IL17C</i>	1	1.79%	55	8.04%	1.13E-01
<i>IL17D</i>	4	7.14%	16	2.34%	5.73E-02
<i>IL25</i>	4	7.14%	1	0.15%	1.40E-04
<i>IL17F</i>	2	3.57%	1	0.15%	1.61E-02
<i>IL17RA</i>	1	1.79%	7	1.02%	4.69E-01
<i>IL17RB</i>	5	8.93%	6	0.88%	6.77E-04
<i>IL17RC</i>	4	7.14%	18	2.63%	7.72E-02
<i>IL17RD</i>	5	8.93%	4	0.58%	2.08E-04
<i>IL17RE</i>	3	5.36%	16	2.34%	1.68E-01
<i>IL1A</i>	2	3.57%	7	1.02%	1.44E-01
<i>IL1B</i>	2	3.57%	6	0.88%	1.17E-01
<i>IL6</i>	2	3.57%	11	1.61%	2.58E-01
<i>TNF</i>	4	7.14%	5	0.73%	2.79E-03
<i>CSF3</i>	3	5.36%	12	1.75%	9.75E-02
<i>CCL7</i>	3	5.36%	5	0.73%	1.75E-02
<i>CXCL1</i>	3	5.36%	3	0.44%	6.98E-03
<i>CXCL2</i>	3	5.36%	3	0.44%	6.98E-03
<i>CXCL5</i>	3	5.36%	4	0.58%	1.16E-02
<i>CXCL8</i>	5	8.93%	6	0.88%	6.77E-04
<i>S100A7</i>	2	3.57%	7	1.02%	1.44E-01
<i>S100A8</i>	2	3.57%	9	1.32%	2.00E-01
<i>S100A9</i>	2	3.57%	7	1.02%	1.44E-01
<i>CEBPB</i>	4	7.14%	5	0.73%	2.79E-03
<i>PTGS2</i>	4	7.14%	8	1.17%	9.23E-03
<i>MMP1</i>	2	3.57%	7	1.02%	1.44E-01
<i>MMP2</i>	0	0.00%	14	2.05%	6.16E-01
<i>MMP3</i>	2	3.57%	7	1.02%	1.44E-01
<i>MMP7</i>	2	3.57%	9	1.32%	2.00E-01
<i>MMP9</i>	4	7.14%	10	1.46%	1.67E-02
<i>MMP13</i>	2	3.57%	8	1.17%	1.71E-01
<i>PDCD1</i>	1	1.79%	14	2.05%	1.00E+00
<i>CD274</i>	2	3.57%	9	1.32%	2.00E-01
<i>PDCD1LG2</i>	2	3.57%	10	1.46%	2.28E-01

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene alterations in primary CRPC than primary HNPC.



## Alternations of IL-17 and related genes

**Table 5.** Overall gene alterations in metastatic CRPC vs primary HNPC

Genes*	Metastatic CRPC (N=583)		Primary HNPC (N=684)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	23	3.95%	3	0.44%	8.75E-06
<i>IL17B</i>	36	6.17%	6	0.88%	9.91E-08
<i>IL17C</i>	48	8.23%	55	8.04%	9.18E-01
<i>IL17D</i>	31	5.32%	16	2.34%	6.74E-03
<i>IL25</i>	26	4.46%	1	0.15%	1.94E-08
<i>IL17F</i>	23	3.95%	1	0.15%	1.90E-07
<i>IL17RA</i>	24	4.12%	7	1.02%	4.02E-04
<i>IL17RB</i>	26	4.46%	6	0.88%	4.61E-05
<i>IL17RC</i>	42	7.20%	18	2.63%	1.62E-04
<i>IL17RD</i>	32	5.49%	4	0.58%	6.71E-08
<i>IL17RE</i>	43	7.38%	16	2.34%	2.39E-05
<i>IL1A</i>	20	3.43%	7	1.02%	3.28E-03
<i>IL1B</i>	22	3.77%	6	0.88%	7.68E-04
<i>IL6</i>	49	8.40%	11	1.61%	1.32E-08
<i>TNF</i>	28	4.80%	5	0.73%	4.02E-06
<i>CSF3</i>	31	5.32%	12	1.75%	5.23E-04
<i>CCL7</i>	30	5.15%	5	0.73%	1.12E-06
<i>CXCL1</i>	37	6.35%	3	0.44%	3.33E-10
<i>CXCL2</i>	31	5.32%	3	0.44%	4.18E-08
<i>CXCL5</i>	34	5.83%	4	0.58%	1.69E-08
<i>CXCL8</i>	35	6.00%	6	0.88%	1.86E-07
<i>S100A7</i>	76	13.04%	7	1.02%	<2.2e-16
<i>S100A8</i>	73	12.52%	9	1.32%	<2.2e-16
<i>S100A9</i>	72	12.35%	7	1.02%	<2.2e-16
<i>CEBPB</i>	36	6.17%	5	0.73%	2.19E-08
<i>PTGS2</i>	60	10.29%	8	1.17%	1.75E-13
<i>MMP1</i>	38	6.52%	7	1.02%	1.19E-07
<i>MMP2</i>	25	4.29%	14	2.05%	2.28E-02
<i>MMP3</i>	38	6.52%	7	1.02%	1.19E-07
<i>MMP7</i>	34	5.83%	9	1.32%	1.34E-05
<i>MMP9</i>	42	7.20%	10	1.46%	2.33E-07
<i>MMP13</i>	38	6.52%	8	1.17%	2.51E-07
<i>PDCD1</i>	38	6.52%	14	2.05%	8.80E-05
<i>CD274</i>	36	6.17%	9	1.32%	2.55E-06
<i>PDCD1LG2</i>	36	6.17%	10	1.46%	7.09E-06

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene alterations in metastatic CRPC than primary HNPC.

## Alternations of IL-17 and related genes

**Table 6.** Gene amplifications in metastatic vs primary prostate cancer

Genes*	Metastatic (N=584)		Primary (N=742)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	22	3.77%	2	0.27%	1.87E-06
<i>IL17B</i>	34	5.82%	9	1.21%	2.62E-06
<i>IL17C</i>	8	1.37%	6	0.81%	4.19E-01
<i>IL17D</i>	25	4.28%	8	1.08%	2.59E-04
<i>IL25</i>	24	4.11%	4	0.54%	6.93E-06
<i>IL17F</i>	23	3.94%	2	0.27%	9.36E-07
<i>IL17RA</i>	13	2.23%	1	0.13%	1.82E-04
<i>IL17RB</i>	20	3.42%	3	0.40%	2.41E-05
<i>IL17RC</i>	37	6.34%	6	0.81%	1.41E-08
<i>IL17RD</i>	21	3.60%	5	0.67%	1.80E-04
<i>IL17RE</i>	36	6.16%	5	0.67%	5.20E-09
<i>IL1A</i>	14	2.40%	2	0.27%	4.88E-04
<i>IL1B</i>	14	2.40%	2	0.27%	4.88E-04
<i>IL6</i>	47	8.05%	10	1.35%	1.68E-09
<i>TNF</i>	26	4.45%	6	0.81%	1.71E-05
<i>CSF3</i>	31	5.31%	8	1.08%	9.07E-06
<i>CCL7</i>	27	4.62%	3	0.40%	1.62E-07
<i>CXCL1</i>	36	6.16%	4	0.54%	9.29E-10
<i>CXCL2</i>	30	5.14%	4	0.54%	1.29E-07
<i>CXCL5</i>	32	5.48%	5	0.67%	8.43E-08
<i>CXCL8</i>	33	5.65%	8	1.08%	1.59E-06
<i>S100A7</i>	76	13.01%	9	1.21%	<2.2e-16
<i>S100A8</i>	72	12.33%	8	1.08%	<2.2e-16
<i>S100A9</i>	72	12.33%	9	1.21%	<2.2e-16
<i>CEBPB</i>	35	5.99%	8	1.08%	4.51E-07
<i>PTGS2</i>	53	9.08%	6	0.81%	8.75E-14
<i>MMP1</i>	23	3.94%	3	0.40%	2.88E-06
<i>MMP2</i>	8	1.37%	1	0.13%	1.29E-02
<i>MMP3</i>	23	3.94%	3	0.40%	2.88E-06
<i>MMP7</i>	24	4.11%	4	0.54%	6.93E-06
<i>MMP9</i>	33	5.65%	8	1.08%	1.59E-06
<i>MMP13</i>	23	3.94%	3	0.40%	2.88E-06
<i>PDCD1</i>	16	2.74%	8	1.08%	3.59E-02
<i>CD274</i>	14	2.40%	1	0.13%	8.44E-05
<i>PDCD1LG2</i>	14	2.40%	1	0.13%	8.44E-05

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene amplifications in metastatic than primary prostate cancer.

## Alternations of IL-17 and related genes

**Table 7.** Gene deep deletions in metastatic vs primary prostate cancer

Genes*	Metastatic (N=584)		Primary (N=742)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	0	0.00%	1	0.13%	1.00E+00
<i>IL17B</i>	1	0.17%	1	0.13%	1.00E+00
<i>IL17C</i>	39	6.68%	50	6.74%	1.00E+00
<i>IL17D</i>	6	1.03%	12	1.62%	4.75E-01
<i>IL25</i>	2	0.34%	1	0.13%	5.86E-01
<i>IL17F</i>	0	0.00%	1	0.13%	1.00E+00
<i>IL17RA</i>	7	1.20%	3	0.40%	1.17E-01
<i>IL17RB</i>	5	0.86%	5	0.67%	7.57E-01
<i>IL17RC</i>	4	0.68%	14	1.89%	9.17E-02
<i>IL17RD</i>	5	0.86%	3	0.40%	3.11E-01
<i>IL17RE</i>	4	0.68%	14	1.89%	9.17E-02
<i>IL1A</i>	5	0.86%	6	0.81%	1.00E+00
<i>IL1B</i>	5	0.86%	6	0.81%	1.00E+00
<i>IL6</i>	1	0.17%	2	0.27%	1.00E+00
<i>TNF</i>	1	0.17%	2	0.27%	1.00E+00
<i>CSF3</i>	0	0.00%	7	0.94%	2.01E-02
<i>CCL7</i>	3	0.51%	4	0.54%	1.00E+00
<i>CXCL1</i>	1	0.17%	2	0.27%	1.00E+00
<i>CXCL2</i>	1	0.17%	2	0.27%	1.00E+00
<i>CXCL5</i>	1	0.17%	2	0.27%	1.00E+00
<i>CXCL8</i>	1	0.17%	2	0.27%	1.00E+00
<i>S100A7</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A8</i>	0	0.00%	1	0.13%	1.00E+00
<i>S100A9</i>	0	0.00%	0	0.00%	1.00E+00
<i>CEBPB</i>	0	0.00%	0	0.00%	1.00E+00
<i>PTGS2</i>	3	0.51%	2	0.27%	6.60E-01
<i>MMP1</i>	13	2.23%	5	0.67%	1.74E-02
<i>MMP2</i>	15	2.57%	12	1.62%	2.44E-01
<i>MMP3</i>	13	2.23%	5	0.67%	1.74E-02
<i>MMP7</i>	10	1.71%	6	0.81%	2.04E-01
<i>MMP9</i>	3	0.51%	2	0.27%	6.60E-01
<i>MMP13</i>	12	2.05%	6	0.81%	5.83E-02
<i>PDCD1</i>	21	3.60%	6	0.81%	5.65E-04
<i>CD274</i>	21	3.60%	10	1.35%	9.50E-03
<i>PDCD1LG2</i>	21	3.60%	10	1.35%	9.50E-03

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene deep deletions in metastatic than primary prostate cancer and green indicates significantly more gene deep deletions in primary than metastatic prostate cancer.

## Alterations of IL-17 and related genes

**Table 8.** Gene missense mutations in metastatic vs primary prostate cancer

Genes*	Metastatic (N=584)		Primary (N=742)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	1	0.17%	3	0.40%	6.35E-01
<i>IL17B</i>	1	0.17%	1	0.13%	1.00E+00
<i>IL17C</i>	2	0.34%	0	0.00%	1.94E-01
<i>IL17D</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL25</i>	0	0.00%	1	0.13%	1.00E+00
<i>IL17F</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RA</i>	5	0.86%	3	0.40%	3.11E-01
<i>IL17RB</i>	0	0.00%	2	0.27%	5.07E-01
<i>IL17RC</i>	1	0.17%	2	0.27%	1.00E+00
<i>IL17RD</i>	6	1.03%	1	0.13%	4.84E-02
<i>IL17RE</i>	5	0.86%	0	0.00%	1.64E-02
<i>IL1A</i>	0	0.00%	1	0.13%	1.00E+00
<i>IL1B</i>	3	0.51%	0	0.00%	8.52E-02
<i>IL6</i>	1	0.17%	1	0.13%	1.00E+00
<i>TNF</i>	1	0.17%	1	0.13%	1.00E+00
<i>CSF3</i>	0	0.00%	0	0.00%	1.00E+00
<i>CCL7</i>	0	0.00%	1	0.13%	1.00E+00
<i>CXCL1</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL2</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL5</i>	1	0.17%	0	0.00%	4.40E-01
<i>CXCL8</i>	1	0.17%	1	0.13%	1.00E+00
<i>S100A7</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A8</i>	1	0.17%	2	0.27%	1.00E+00
<i>S100A9</i>	0	0.00%	0	0.00%	1.00E+00
<i>CEBPB</i>	0	0.00%	0	0.00%	1.00E+00
<i>PTGS2</i>	2	0.34%	4	0.54%	7.00E-01
<i>MMP1</i>	2	0.34%	1	0.13%	5.86E-01
<i>MMP2</i>	2	0.34%	1	0.13%	5.86E-01
<i>MMP3</i>	2	0.34%	1	0.13%	5.86E-01
<i>MMP7</i>	0	0.00%	1	0.13%	1.00E+00
<i>MMP9</i>	5	0.86%	4	0.54%	5.18E-01
<i>MMP13</i>	1	0.17%	1	0.13%	1.00E+00
<i>PDCD1</i>	1	0.17%	1	0.13%	1.00E+00
<i>CD274</i>	1	0.17%	0	0.00%	4.40E-01
<i>PDCD1LG2</i>	1	0.17%	1	0.13%	1.00E+00

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene missense mutations in metastatic than primary prostate cancer.

## Alternations of IL-17 and related genes

**Table 9.** Gene truncating mutations in metastatic vs primary prostate cancer

Genes*	Metastatic (N=584)		Primary (N=742)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17B</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17C</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17D</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL25</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17F</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RA</i>	0	0.00%	1	0.13%	1.00E+00
<i>IL17RB</i>	1	0.17%	1	0.13%	1.00E+00
<i>IL17RC</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RD</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RE</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL1A</i>	1	0.17%	0	0.00%	4.40E-01
<i>IL1B</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL6</i>	0	0.00%	0	0.00%	1.00E+00
<i>TNF</i>	0	0.00%	0	0.00%	1.00E+00
<i>CSF3</i>	0	0.00%	0	0.00%	1.00E+00
<i>CCL7</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL1</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL2</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL5</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL8</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A7</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A8</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A9</i>	0	0.00%	0	0.00%	1.00E+00
<i>CEBPB</i>	1	0.17%	0	0.00%	4.40E-01
<i>PTGS2</i>	2	0.34%	0	0.00%	1.94E-01
<i>MMP1</i>	0	0.00%	0	0.00%	1.00E+00
<i>MMP2</i>	0	0.00%	0	0.00%	1.00E+00
<i>MMP3</i>	0	0.00%	0	0.00%	1.00E+00
<i>MMP7</i>	0	0.00%	0	0.00%	1.00E+00
<i>MMP9</i>	1	0.17%	0	0.00%	4.40E-01
<i>MMP13</i>	2	0.34%	0	0.00%	1.94E-01
<i>PDCD1</i>	0	0.00%	0	0.00%	1.00E+00
<i>CD274</i>	0	0.00%	0	0.00%	1.00E+00
<i>PDCD1LG2</i>	0	0.00%	0	0.00%	1.00E+00

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*.

## Alternations of IL-17 and related genes

**Table 10.** Overall gene alterations in primary NEPC vs primary AC

Genes*	Primary NEPC (N=16)		Primary AC (N=724)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	1	6.25%	5	0.69%	1.23E-01
<i>IL17B</i>	2	12.50%	8	1.10%	1.78E-02
<i>IL17C</i>	0	0.00%	56	7.73%	6.25E-01
<i>IL17D</i>	0	0.00%	20	2.76%	1.00E+00
<i>IL25</i>	2	12.50%	3	0.41%	4.22E-03
<i>IL17F</i>	1	6.25%	2	0.28%	6.36E-02
<i>IL17RA</i>	0	0.00%	8	1.10%	1.00E+00
<i>IL17RB</i>	2	12.50%	9	1.24%	2.15E-02
<i>IL17RC</i>	1	6.25%	20	2.76%	3.72E-01
<i>IL17RD</i>	1	6.25%	8	1.10%	1.80E-01
<i>IL17RE</i>	1	6.25%	18	2.49%	3.43E-01
<i>IL1A</i>	1	6.25%	8	1.10%	1.80E-01
<i>IL1B</i>	1	6.25%	7	0.97%	1.61E-01
<i>IL6</i>	0	0.00%	13	1.80%	1.00E+00
<i>TNF</i>	2	12.50%	7	0.97%	1.45E-02
<i>CSF3</i>	1	6.25%	14	1.93%	2.82E-01
<i>CCL7</i>	1	6.25%	7	0.97%	1.61E-01
<i>CXCL1</i>	0	0.00%	6	0.83%	1.00E+00
<i>CXCL2</i>	0	0.00%	6	0.83%	1.00E+00
<i>CXCL5</i>	0	0.00%	7	0.97%	1.00E+00
<i>CXCL8</i>	2	12.50%	9	1.24%	2.15E-02
<i>S100A7</i>	0	0.00%	9	1.24%	1.00E+00
<i>S100A8</i>	0	0.00%	11	1.52%	1.00E+00
<i>S100A9</i>	0	0.00%	9	1.24%	1.00E+00
<i>CEBPB</i>	2	12.50%	7	0.97%	1.45E-02
<i>PTGS2</i>	0	0.00%	11	1.52%	1.00E+00
<i>MMP1</i>	1	6.25%	8	1.10%	1.80E-01
<i>MMP2</i>	0	0.00%	14	1.93%	1.00E+00
<i>MMP3</i>	1	6.25%	8	1.10%	1.80E-01
<i>MMP7</i>	1	6.25%	10	1.38%	2.15E-01
<i>MMP9</i>	2	12.50%	12	1.66%	3.43E-02
<i>MMP13</i>	1	6.25%	9	1.24%	1.97E-01
<i>PDCD1</i>	1	6.25%	14	1.93%	2.82E-01
<i>CD274</i>	0	0.00%	11	1.52%	1.00E+00
<i>PDCD1LG2</i>	0	0.00%	12	1.66%	1.00E+00

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene alterations in primary NEPC than primary AC.

## Alternations of IL-17 and related genes

**Table 11.** Overall gene alterations in metastatic NEPC vs metastatic AC

Genes*	Metastatic NEPC (N=45)		Metastatic AC (N=461)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	10	22.22%	11	2.39%	1.95E-06
<i>IL17B</i>	9	20.00%	24	5.21%	1.19E-03
<i>IL17C</i>	2	4.44%	33	7.16%	7.58E-01
<i>IL17D</i>	8	17.78%	22	4.77%	2.75E-03
<i>IL25</i>	9	20.00%	15	3.25%	7.50E-05
<i>IL17F</i>	10	22.22%	10	2.17%	1.09E-06
<i>IL17RA</i>	3	6.67%	16	3.47%	2.34E-01
<i>IL17RB</i>	6	13.33%	17	3.69%	1.12E-02
<i>IL17RC</i>	8	17.78%	31	6.72%	1.54E-02
<i>IL17RD</i>	7	15.56%	20	4.34%	6.24E-03
<i>IL17RE</i>	10	22.22%	30	6.51%	1.29E-03
<i>IL1A</i>	5	11.11%	11	2.39%	9.25E-03
<i>IL1B</i>	6	13.33%	13	2.82%	3.97E-03
<i>IL6</i>	9	20.00%	39	8.46%	2.73E-02
<i>TNF</i>	12	26.67%	14	3.04%	2.19E-07
<i>CSF3</i>	9	20.00%	22	4.77%	7.15E-04
<i>CCL7</i>	10	22.22%	19	4.12%	6.45E-05
<i>CXCL1</i>	5	11.11%	30	6.51%	2.24E-01
<i>CXCL2</i>	5	11.11%	25	5.42%	1.73E-01
<i>CXCL5</i>	5	11.11%	27	5.86%	1.90E-01
<i>CXCL8</i>	5	11.11%	28	6.07%	2.00E-01
<i>S100A7</i>	13	28.89%	55	11.93%	4.39E-03
<i>S100A8</i>	13	28.89%	52	11.28%	3.63E-03
<i>S100A9</i>	13	28.89%	52	11.28%	3.63E-03
<i>CEBPB</i>	13	28.89%	22	4.77%	1.37E-06
<i>PTGS2</i>	13	28.89%	42	9.11%	3.64E-04
<i>MMP1</i>	6	13.33%	30	6.51%	1.19E-01
<i>MMP2</i>	1	2.22%	19	4.12%	1.00E+00
<i>MMP3</i>	6	13.33%	30	6.51%	1.19E-01
<i>MMP7</i>	6	13.33%	26	5.64%	5.40E-02
<i>MMP9</i>	15	33.33%	26	5.64%	2.02E-07
<i>MMP13</i>	6	13.33%	29	6.29%	1.13E-01
<i>PDCD1</i>	5	11.11%	26	5.64%	1.81E-01
<i>CD274</i>	9	20.00%	22	4.77%	7.15E-04
<i>PDCD1LG2</i>	9	20.00%	23	4.99%	9.28E-04

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene alterations in metastatic NEPC than metastatic AC.

## Alternations of IL-17 and related genes

**Table 12.** Overall gene alterations in metastatic NEPC vs metastatic AC with NE feature

Genes*	Metastatic NEPC (N=45)		Metastatic AC with NE feature (N=12)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	10	22.22%	0	0.00%	9.97E-02
<i>IL17B</i>	9	20.00%	1	8.33%	6.71E-01
<i>IL17C</i>	2	4.44%	1	8.33%	5.15E-01
<i>IL17D</i>	8	17.78%	1	8.33%	6.67E-01
<i>IL25</i>	9	20.00%	1	8.33%	6.71E-01
<i>IL17F</i>	10	22.22%	0	0.00%	9.97E-02
<i>IL17RA</i>	3	6.67%	1	8.33%	1.00E+00
<i>IL17RB</i>	6	13.33%	1	8.33%	1.00E+00
<i>IL17RC</i>	8	17.78%	2	16.67%	1.00E+00
<i>IL17RD</i>	7	15.56%	2	16.67%	1.00E+00
<i>IL17RE</i>	10	22.22%	2	16.67%	1.00E+00
<i>IL1A</i>	5	11.11%	1	8.33%	1.00E+00
<i>IL1B</i>	6	13.33%	1	8.33%	1.00E+00
<i>IL6</i>	9	20.00%	1	8.33%	6.71E-01
<i>TNF</i>	12	26.67%	0	0.00%	5.28E-02
<i>CSF3</i>	9	20.00%	1	8.33%	6.71E-01
<i>CCL7</i>	10	22.22%	1	8.33%	4.26E-01
<i>CXCL1</i>	5	11.11%	0	0.00%	5.73E-01
<i>CXCL2</i>	5	11.11%	0	0.00%	5.73E-01
<i>CXCL5</i>	5	11.11%	0	0.00%	5.73E-01
<i>CXCL8</i>	5	11.11%	0	0.00%	5.73E-01
<i>S100A7</i>	13	28.89%	0	0.00%	4.98E-02
<i>S100A8</i>	13	28.89%	0	0.00%	4.98E-02
<i>S100A9</i>	13	28.89%	0	0.00%	4.98E-02
<i>CEBPB</i>	13	28.89%	1	8.33%	2.58E-01
<i>PTGS2</i>	13	28.89%	3	25.00%	1.00E+00
<i>MMP1</i>	6	13.33%	1	8.33%	1.00E+00
<i>MMP2</i>	1	2.22%	2	16.67%	1.09E-01
<i>MMP3</i>	6	13.33%	1	8.33%	1.00E+00
<i>MMP7</i>	6	13.33%	1	8.33%	1.00E+00
<i>MMP9</i>	15	33.33%	1	8.33%	1.48E-01
<i>MMP13</i>	6	13.33%	1	8.33%	1.00E+00
<i>PDCD1</i>	5	11.11%	1	8.33%	1.00E+00
<i>CD274</i>	9	20.00%	2	16.67%	1.00E+00
<i>PDCD1LG2</i>	9	20.00%	2	16.67%	1.00E+00

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene alterations in metastatic NEPC than metastatic AC with NE feature.



## Alternations of IL-17 and related genes

**Table 13.** Overall gene alterations in metastatic AC with NE feature vs metastatic AC

Genes*	Metastatic AC with NE feature (N=12)		Metastatic AC (N=461)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	0	0.00%	11	2.39%	1.00E+00
<i>IL17B</i>	1	8.33%	24	5.21%	4.83E-01
<i>IL17C</i>	1	8.33%	33	7.16%	5.96E-01
<i>IL17D</i>	1	8.33%	22	4.77%	4.54E-01
<i>IL25</i>	1	8.33%	15	3.25%	3.42E-01
<i>IL17F</i>	0	0.00%	10	2.17%	1.00E+00
<i>IL17RA</i>	1	8.33%	16	3.47%	3.59E-01
<i>IL17RB</i>	1	8.33%	17	3.69%	3.76E-01
<i>IL17RC</i>	2	16.67%	31	6.72%	2.01E-01
<i>IL17RD</i>	2	16.67%	20	4.34%	1.03E-01
<i>IL17RE</i>	2	16.67%	30	6.51%	1.92E-01
<i>IL1A</i>	1	8.33%	11	2.39%	2.68E-01
<i>IL1B</i>	1	8.33%	13	2.82%	3.06E-01
<i>IL6</i>	1	8.33%	39	8.46%	1.00E+00
<i>TNF</i>	0	0.00%	14	3.04%	1.00E+00
<i>CSF3</i>	1	8.33%	22	4.77%	4.54E-01
<i>CCL7</i>	1	8.33%	19	4.12%	4.08E-01
<i>CXCL1</i>	0	0.00%	30	6.51%	1.00E+00
<i>CXCL2</i>	0	0.00%	25	5.42%	1.00E+00
<i>CXCL5</i>	0	0.00%	27	5.86%	1.00E+00
<i>CXCL8</i>	0	0.00%	28	6.07%	1.00E+00
<i>S100A7</i>	0	0.00%	55	11.93%	3.76E-01
<i>S100A8</i>	0	0.00%	52	11.28%	3.78E-01
<i>S100A9</i>	0	0.00%	52	11.28%	3.78E-01
<i>CEBPB</i>	1	8.33%	22	4.77%	4.54E-01
<i>PTGS2</i>	3	25.00%	42	9.11%	9.62E-02
<i>MMP1</i>	1	8.33%	30	6.51%	5.61E-01
<i>MMP2</i>	2	16.67%	19	4.12%	9.48E-02
<i>MMP3</i>	1	8.33%	30	6.51%	5.61E-01
<i>MMP7</i>	1	8.33%	26	5.64%	5.10E-01
<i>MMP9</i>	1	8.33%	26	5.64%	5.10E-01
<i>MMP13</i>	1	8.33%	29	6.29%	5.49E-01
<i>PDCD1</i>	1	8.33%	26	5.64%	5.10E-01
<i>CD274</i>	2	16.67%	22	4.77%	1.19E-01
<i>PDCD1LG2</i>	2	16.67%	23	4.99%	1.28E-01

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Purple indicates more gene alterations in metastatic AC with NE feature than metastatic AC and blue indicates more gene alterations in metastatic AC than metastatic AC with NE feature, but without statistical significance.

## Alterations of IL-17 and related genes

amplifications in metastatic NEPC, compared to metastatic AC (**Table 14**). Gene deep deletions (**Table 15**), gene missense mutations (**Table 16**), and gene truncating mutations (**Table 17**) were very rare and there were no significant differences between metastatic NEPC and metastatic AC, except that *MMP9* had significantly higher rate of gene missense mutations in metastatic NEPC than metastatic AC (**Table 16**).

### Discussion

In the present study, we included 1303 cases of human prostate cancers in 7 datasets archived in cBioPortal and queried gene alterations in 35 *IL-17* and related genes. We found that 34/35 (97%) genes had significantly more alterations in metastatic prostate cancer (with alteration rates ranging from 3.42% to 13.01%) than primary prostate cancer (with alteration rates ranging from 0.40% to 2.96%). 15/35 (43%) genes had significantly more alterations in primary CRPC than primary HNPC. 34/35 (97%) genes had significantly more alterations in metastatic CRPC than primary HNPC. Only three genes (*S100A7*, *S100A8*, and *S100A9*) had significantly more alterations in metastatic CRPC than primary CRPC. The gene alterations were mostly gene amplifications (97%), while gene deep deletions, missense mutations, and truncating mutations were very rare. 7/35 (20%) genes had significantly more alterations in primary NEPC than primary AC. 23/35 (66%) genes had significantly more alterations in metastatic NEPC (ranging from 11.11% to 33.33%) than metastatic AC (ranging from 2.17% to 11.93%). Only three genes (*S100A7*, *S100A8*, and *S100A9*) had significantly more alterations in metastatic NEPC than metastatic AC with neuroendocrine features. Most of the gene alterations in metastatic NEPC were gene amplifications (80%), while gene deep deletions, missense mutations, and truncating mutations were very rare. A prominent trend is that gene amplifications are more frequently found in metastatic CRPC and NEPC than primary hormone-naïve prostate adenocarcinomas (**Figure 2**).

Three *S100* family members (*S100A7*, *S100A8*, and *S100A9*) are among the genes with the highest gene amplifications (12-13% in metastatic prostate cancers and 28.89% in metastatic NEPC, respectively). *S100* proteins comprise a family of 23 different members charac-

terized by high homology, low-molecular weight, and two calcium-binding EF-hands, as well as tissue-specific expression [39]. *S100A7/8/9* are induced by *IL-17* to recruit neutrophils that protect against infections [40] or exacerbate psoriasis [41]. *S100A7* protein expression was found to be increased in prostate cancer compared to normal prostate, and *S100A7* promotes survival and invasiveness of prostate cancer cells [42]. *S100A8* and *S100A9* were found to be up-regulated in prostatic intraepithelial neoplasia and preferentially in high-grade adenocarcinomas, and *S100A9* serum levels were significantly elevated in prostate cancer patients compared with patients with benign prostatic hypertrophy or healthy individuals [43]. Gene amplifications of *S100A7/8/9* genes in metastatic CRPC/NEPC may lead to overexpression of them at mRNA and protein levels, which remains to be determined. It is not known if *S100A7/8/9* proteins play any roles in the progression from HNPC to CRPC/NEPC and from the primary tumor to metastatic tumor, which warrants future studies.

One potential caveat of the present study is that we cannot completely rule out the possibility of redundant samples among different datasets. For example, we are not sure if any of the sample data from the five U.S. datasets were also deposited into the TCGA dataset. We checked the patient identification (ID) numbers and sample IDs and could not find any overlapping numbers, however, we did not know if the IDs were separately assigned in different datasets. We had to use different datasets because TCGA dataset contains only primary adenocarcinomas. The five U.S. datasets might also share some samples, but we did not find any identical patient IDs. Since more gene amplifications are found in metastatic CRPC/NEPC that mostly (N=415) came from SU2C/PCF Dream Team, we think that the gene alteration rates might not be dramatically affected even if there were a few overlapping cases. Another caveat is that we did not include all *IL-17*-downstream genes, which may miss some genes that may be more important than the ones studied. The choice of these genes is arbitrarily based on our previous research work and we include only the well-known *IL-17*-downstream genes.

In summary, our findings suggest that gene amplifications of *IL-17* and related genes are more frequently found in metastatic CRPC and

## Alternations of IL-17 and related genes

**Table 14.** Gene amplifications in metastatic NEPC vs metastatic AC

Genes*	Metastatic NEPC (N=45)		Metastatic AC (N=461)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	10	22.22%	10	2.17%	1.09E-06
<i>IL17B</i>	9	20.00%	22	4.77%	7.15E-04
<i>IL17C</i>	2	4.44%	6	1.30%	1.54E-01
<i>IL17D</i>	7	15.56%	18	3.90%	3.88E-03
<i>IL25</i>	9	20.00%	15	3.25%	7.50E-05
<i>IL17F</i>	10	22.22%	10	2.17%	1.09E-06
<i>IL17RA</i>	3	6.67%	8	1.74%	6.54E-02
<i>IL17RB</i>	6	13.33%	13	2.82%	3.97E-03
<i>IL17RC</i>	8	17.78%	26	5.64%	6.45E-03
<i>IL17RD</i>	6	13.33%	13	2.82%	3.97E-03
<i>IL17RE</i>	8	17.78%	25	5.42%	5.29E-03
<i>IL1A</i>	5	11.11%	7	1.52%	2.21E-03
<i>IL1B</i>	5	11.11%	7	1.52%	2.21E-03
<i>IL6</i>	9	20.00%	37	8.03%	1.38E-02
<i>TNF</i>	12	26.67%	12	2.60%	6.98E-08
<i>CSF3</i>	9	20.00%	22	4.77%	7.15E-04
<i>CCL7</i>	10	22.22%	16	3.47%	2.09E-05
<i>CXCL1</i>	5	11.11%	29	6.29%	2.12E-01
<i>CXCL2</i>	5	11.11%	24	5.21%	1.66E-01
<i>CXCL5</i>	5	11.11%	25	5.42%	1.73E-01
<i>CXCL8</i>	5	11.11%	27	5.86%	1.90E-01
<i>S100A7</i>	13	28.89%	55	11.93%	4.39E-03
<i>S100A8</i>	13	28.89%	52	11.28%	3.63E-03
<i>S100A9</i>	13	28.89%	52	11.28%	3.63E-03
<i>CEBPB</i>	13	28.89%	21	4.56%	9.18E-07
<i>PTGS2</i>	12	26.67%	37	8.03%	4.58E-04
<i>MMP1</i>	6	13.33%	16	3.47%	8.87E-03
<i>MMP2</i>	1	2.22%	6	1.30%	4.81E-01
<i>MMP3</i>	6	13.33%	16	3.47%	8.87E-03
<i>MMP7</i>	6	13.33%	17	3.69%	1.12E-02
<i>MMP9</i>	13	28.89%	20	4.34%	6.04E-07
<i>MMP13</i>	6	13.33%	16	3.47%	8.87E-03
<i>PDCD1</i>	4	8.89%	12	2.60%	4.50E-02
<i>CD274</i>	8	17.78%	5	1.08%	1.95E-06
<i>PDCD1LG2</i>	8	17.78%	5	1.08%	1.95E-06

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene amplifications in metastatic NEPC than metastatic AC.

## Alternations of IL-17 and related genes

**Table 15.** Gene deep deletions in metastatic NEPC vs metastatic AC

Genes*	Metastatic NEPC (N=45)		Metastatic AC (N=461)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17B</i>	0	0.00%	1	0.22%	1.00E+00
<i>IL17C</i>	0	0.00%	26	5.64%	1.54E-01
<i>IL17D</i>	1	2.22%	4	0.87%	3.74E-01
<i>IL25</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17F</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RA</i>	0	0.00%	6	1.30%	1.00E+00
<i>IL17RB</i>	0	0.00%	3	0.65%	1.00E+00
<i>IL17RC</i>	0	0.00%	4	0.87%	1.00E+00
<i>IL17RD</i>	0	0.00%	4	0.87%	1.00E+00
<i>IL17RE</i>	0	0.00%	4	0.87%	1.00E+00
<i>IL1A</i>	0	0.00%	4	0.87%	1.00E+00
<i>IL1B</i>	0	0.00%	4	0.87%	1.00E+00
<i>IL6</i>	0	0.00%	1	0.22%	1.00E+00
<i>TNF</i>	0	0.00%	1	0.22%	1.00E+00
<i>CSF3</i>	0	0.00%	0	0.00%	1.00E+00
<i>CCL7</i>	0	0.00%	3	0.65%	1.00E+00
<i>CXCL1</i>	0	0.00%	1	0.22%	1.00E+00
<i>CXCL2</i>	0	0.00%	1	0.22%	1.00E+00
<i>CXCL5</i>	0	0.00%	1	0.22%	1.00E+00
<i>CXCL8</i>	0	0.00%	1	0.22%	1.00E+00
<i>S100A7</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A8</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A9</i>	0	0.00%	0	0.00%	1.00E+00
<i>CEBPB</i>	0	0.00%	0	0.00%	1.00E+00
<i>PTGS2</i>	1	2.22%	1	0.22%	1.70E-01
<i>MMP1</i>	0	0.00%	12	2.60%	6.13E-01
<i>MMP2</i>	0	0.00%	11	2.39%	6.10E-01
<i>MMP3</i>	0	0.00%	12	2.60%	6.13E-01
<i>MMP7</i>	0	0.00%	9	1.95%	1.00E+00
<i>MMP9</i>	0	0.00%	3	0.65%	1.00E+00
<i>MMP13</i>	0	0.00%	11	2.39%	6.10E-01
<i>PDCD1</i>	1	2.22%	13	2.82%	1.00E+00
<i>CD274</i>	1	2.22%	17	3.69%	1.00E+00
<i>PDCD1LG2</i>	1	2.22%	17	3.69%	1.00E+00

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*.

## Alternations of IL-17 and related genes

**Table 16.** Gene missense mutations in metastatic NEPC vs metastatic AC

Genes*	Metastatic NEPC (N=45)		Metastatic AC (N=461)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	0	0.00%	1	0.22%	1.00E+00
<i>IL17B</i>	0	0.00%	1	0.22%	1.00E+00
<i>IL17C</i>	1	2.22%	1	0.22%	1.70E-01
<i>IL17D</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL25</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17F</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RA</i>	0	0.00%	2	0.43%	1.00E+00
<i>IL17RB</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RC</i>	0	0.00%	1	0.22%	1.00E+00
<i>IL17RD</i>	1	2.22%	3	0.65%	3.12E-01
<i>IL17RE</i>	2	4.44%	3	0.65%	6.51E-02
<i>IL1A</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL1B</i>	1	2.22%	2	0.43%	2.44E-01
<i>IL6</i>	0	0.00%	1	0.22%	1.00E+00
<i>TNF</i>	0	0.00%	1	0.22%	1.00E+00
<i>CSF3</i>	0	0.00%	0	0.00%	1.00E+00
<i>CCL7</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL1</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL2</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL5</i>	0	0.00%	1	0.22%	1.00E+00
<i>CXCL8</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A7</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A8</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A9</i>	0	0.00%	0	0.00%	1.00E+00
<i>CEBPB</i>	0	0.00%	0	0.00%	1.00E+00
<i>PTGS2</i>	0	0.00%	2	0.43%	1.00E+00
<i>MMP1</i>	0	0.00%	2	0.43%	1.00E+00
<i>MMP2</i>	0	0.00%	2	0.43%	1.00E+00
<i>MMP3</i>	0	0.00%	2	0.43%	1.00E+00
<i>MMP7</i>	0	0.00%	0	0.00%	1.00E+00
<b><i>MMP9</i></b>	<b>2</b>	<b>4.44%</b>	<b>2</b>	<b>0.43%</b>	<b>4.14E-02</b>
<i>MMP13</i>	0	0.00%	1	0.22%	1.00E+00
<i>PDCD1</i>	0	0.00%	1	0.22%	1.00E+00
<i>CD274</i>	0	0.00%	0	0.00%	1.00E+00
<i>PDCD1LG2</i>	0	0.00%	1	0.22%	1.00E+00

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*. Red indicates significantly more gene missense mutations in metastatic NEPC than metastatic AC.

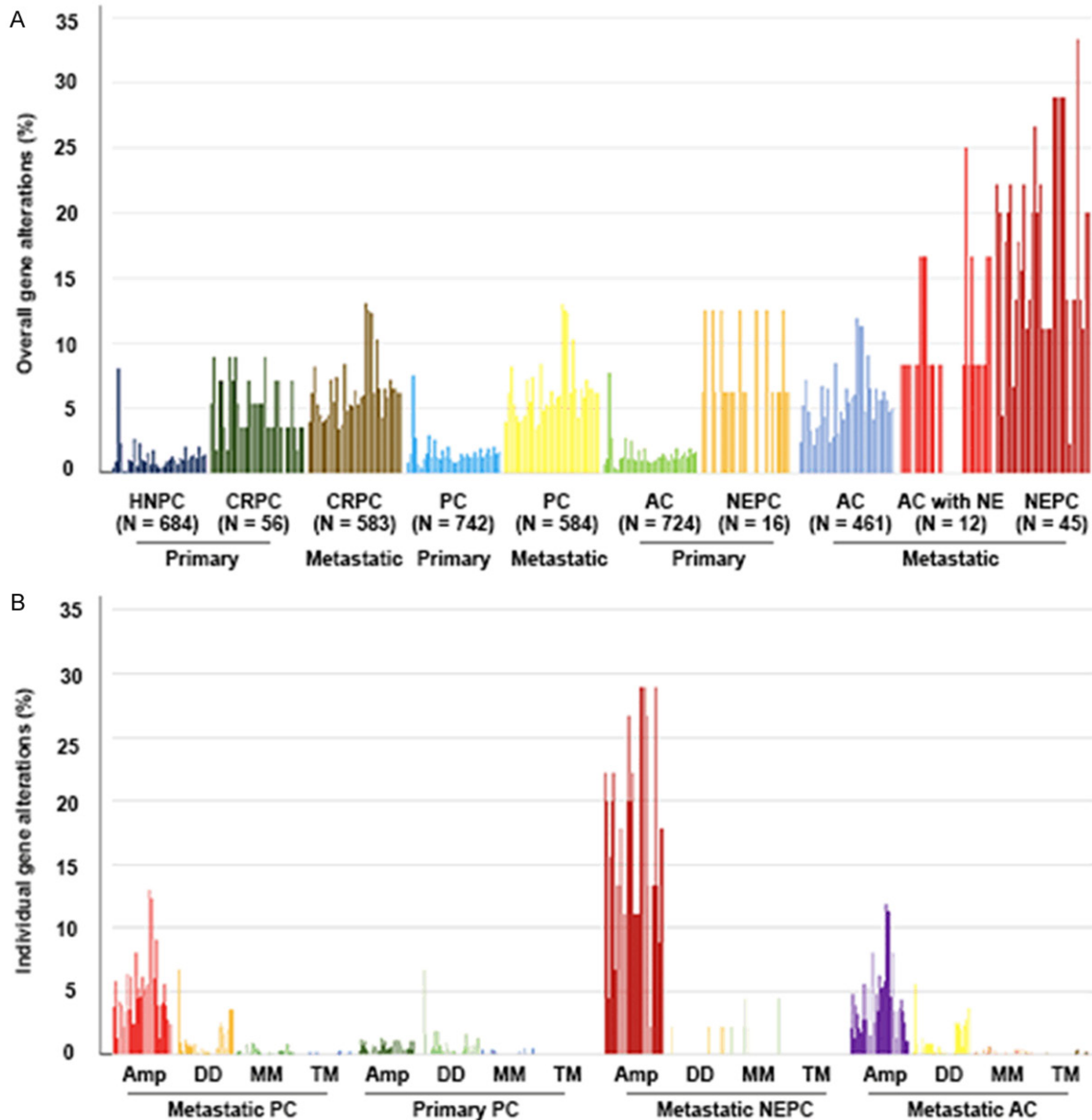
## Alternations of IL-17 and related genes

**Table 17.** Gene truncating mutations in metastatic NEPC vs metastatic AC

Genes*	Metastatic NEPC (N=45)		Metastatic AC (N=461)		P-value (Fisher's exact)
	Number	Percent	Number	Percent	
<i>IL17A</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17B</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17C</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17D</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL25</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17F</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RA</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RB</i>	0	0.00%	1	0.22%	1.00E+00
<i>IL17RC</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RD</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL17RE</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL1A</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL1B</i>	0	0.00%	0	0.00%	1.00E+00
<i>IL6</i>	0	0.00%	0	0.00%	1.00E+00
<i>TNF</i>	0	0.00%	0	0.00%	1.00E+00
<i>CSF3</i>	0	0.00%	0	0.00%	1.00E+00
<i>CCL7</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL1</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL2</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL5</i>	0	0.00%	0	0.00%	1.00E+00
<i>CXCL8</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A7</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A8</i>	0	0.00%	0	0.00%	1.00E+00
<i>S100A9</i>	0	0.00%	0	0.00%	1.00E+00
<i>CEBPB</i>	0	0.00%	1	0.22%	1.00E+00
<i>PTGS2</i>	0	0.00%	2	0.43%	1.00E+00
<i>MMP1</i>	0	0.00%	0	0.00%	1.00E+00
<i>MMP2</i>	0	0.00%	0	0.00%	1.00E+00
<i>MMP3</i>	0	0.00%	0	0.00%	1.00E+00
<i>MMP7</i>	0	0.00%	0	0.00%	1.00E+00
<i>MMP9</i>	0	0.00%	1	0.22%	1.00E+00
<i>MMP13</i>	0	0.00%	1	0.22%	1.00E+00
<i>PDCD1</i>	0	0.00%	0	0.00%	1.00E+00
<i>CD274</i>	0	0.00%	0	0.00%	1.00E+00
<i>PDCD1LG2</i>	0	0.00%	0	0.00%	1.00E+00

\**IL17A*, also named interleukin-17A, *IL17*; *IL17B*, also named interleukin-17B, *IL-20*; *IL17C*, also named interleukin-17C, *CX2*; *IL17D*, also named interleukin-17D, *IL-27*; *IL25*, also named interleukin-25, *IL17E*; *IL17F*, also named interleukin-17F, *IL-17F*; *IL17RA*, also named interleukin-17 Receptor A, *IL-17RA*; *IL17RB*, also named interleukin-17 Receptor B, *IL-17RB*; *IL17RC*, also named interleukin-17 Receptor C, *IL-17RL*; *IL17RD*, also named interleukin-17 Receptor D, *IL-17RD*; *IL17RE*, also named interleukin-17 Receptor E, *IL-17RE*; *IL1A*, also named interleukin-1 Alpha, *IL1F1*; *IL1B*, also named interleukin-1 Beta, *IL-1 Beta*; *IL6*, also named interleukin-6, *IL-6*; *TNF*, also named Tumor Necrosis Factor, *TNFA*; *CSF3*, also named Colony Stimulating Factor-3, *GCSF*; *CCL7*, also named C-C Motif Chemokine Ligand-7, *SCYA6*; *CXCL1*, also named C-X-C Motif Chemokine Ligand-1, *NAP-3*; *CXCL2*, also named C-X-C Motif Chemokine Ligand-2, *MIP2A*; *CXCL5*, also named C-X-C Motif Chemokine Ligand-5, *SCYB5*; *CXCL8*, also named C-X-C Motif Chemokine Ligand-8, *GCP-1*; *S100A7*, also named S100 Calcium Binding Protein A7, *PSOR1*; *S100A8*, also named S100 Calcium Binding Protein A8, *CAGA*; *S100A9*, also named S100 Calcium Binding Protein A9, *MRP-14*; *CEBPB*, also named CCAAT Enhancer Binding Protein Beta, *TCF5*; *PTGS2*, also named Prostaglandin-Endoperoxide Synthase-2, *PGHS-2*; *MMP1*, also named Matrix Metalloproteinase-1, *CLG*; *MMP2*, also named Matrix Metalloproteinase-2, *CLG4A*; *MMP3*, also named Matrix Metalloproteinase-3, *STMY1*; *MMP7*, also named Matrix Metalloproteinase-7, *MMP-7*; *MMP9*, also named Matrix Metalloproteinase-9, *CLG4B*; *MMP13*, also named Matrix Metalloproteinase-13, *MMP-13*; *PDCD1*, also named Programmed Cell Death 1, *PD1*; *CD274*, also named CD274 Molecule, *PD-L1*; *PDCD1LG2*, also named Programmed Cell Death 1 Ligand 2, *PD-L2*.

## Alterations of IL-17 and related genes



**Figure 2.** Trend of gene alterations in prostate cancers. A. Overall gene alterations. B. Individual gene alterations including amplifications (Amp), deep deletions (DD), missense mutations (MM), and truncating mutations (TM). Each bar represents a gene; gene names (from left to right) within each color-coded block are the same as shown in **Figure 1** or **Table 2** (from top to bottom). HNPC, hormone-naïve prostate cancer; CRPC, castration-resistant prostate cancer; PC, prostate cancer including HNPC and CRPC; AC, adenocarcinoma; NEPC, neuroendocrine prostate cancer; NE, neuroendocrine feature.

NEPC than primary hormone-naïve prostate adenocarcinomas, implying that *IL-17* and related genes may play important roles in the progression from HNPC to CRPC and from primary location to metastasis as well as in development of metastatic NEPC. Future studies shall determine if expression at mRNA and protein levels of these genes is increased in metastatic CRPC and NEPC and if the genes function to promote prostate cancer progression.

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## Alternations of IL-17 and related genes

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### Disclosure of conflict of interest

None.

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