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Prostate Cancer Risk Alleles and Their Associations with Other Malignancies

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Abstract

Objectives—Prostate cancer (CaP) has been associated with other common malignancies. Recently, numerous single nucleotide polymorphisms (SNPs) have been associated with CaP susceptibility; however, it is unknown whether these risk alleles are responsible for the relationship between CaP and other malignancies.

Methods—We have genotyped 1121 CaP patients for 36 risk alleles known to be significantly associated with CaP susceptibility and determined their relationships to other malignancies in CaP probands and in their first-degree relatives.

Results—The most common other malignancies in CaP probands were non-melanoma skin cancer (13.6%), leukemia (7.3%), melanoma (3.9%), non-Hodgkin's lymphoma (0.7%), colorectal cancer (0.6%), and multiple myeloma (0.3%). Among probands, there was a significantly increased frequency of leukemia in carriers of SNP rs2736098 (5p15, P=0.03) and melanoma in carriers of either SNP rs1512268 (8p21, P=0.006) or SNP rs5759167 (22q13, P=0.02). Multiple myeloma was more common in carriers of SNP rs9364554 (6q25, P=0.02). Probands who were carriers of SNP rs16901979 (8q24) were significantly more likely to report a family history of melanoma (P=0.03), while probands with family histories of multiple myeloma and non-Hodgkin's disease were significantly more likely to be carriers of SNPs rs12621278 (2q31, P=0.04) and rs6465657 (7q21, P=0.02), respectively.

Conclusions—Certain alleles associated with CaP susceptibility may be associated with increased or decreased risk of other malignancies in CaP probands and their first-degree relatives. Further studies are warranted to examine the underlying mechanisms of these SNPs in CaP and other malignancies.

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DISCLOSURES

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Keywords

Single nucleotide polymorphism (SNP); prostate cancer; genetic predisposition; other malignancy; family history

INTRODUCTION

Prostate cancer (CaP) is the most common non-cutaneous cancer in US men and one of the most heritable of cancers.[1,2] Recent years have witnessed major breakthroughs in CaP genetics with linkage analyses, genome-wide association studies (GWAS), and fine-mapping studies uncovering risk alleles influencing susceptibility to CaP. The genetic predisposition to CaP is complex, as no one gene or locus explains a majority of risk. More than 30 low-penetrance, common loci have been identified through GWAS and have together reproducibly explained a small proportion of the attributable risk in the population.[3]

Some of the CaP risk alleles lie in close proximity to risk alleles for other cancers. For example, risk alleles in different locations on 8q24 are associated not only with CaP but also with colon, breast, bladder, and ovarian cancer, as well as chronic lymphocytic leukemia.[4] Previous genetic studies have linked CaP to other cancers, e.g., *BRCA* mutation (breast cancer)[5] and *Brn-3a*(l) (ovarian cancer).[6] In addition, some CaP risk alleles have been associated with other malignancies. For example, the single nucleotide polymorphism (SNP) rs401681 on chromosome 5p15 has been associated with basal cell carcinoma, as well as cancers of the lung, bladder, and cervix.[7]

Both CaP patients and their relatives have been found to have other malignancies at higher rates than the general population.[8] Genomic testing has recently become available to assess the risk of CaP and other human disease, despite a scarcity of data on the utility of these tests in clinical practice.

Our objective was to determine, in a population of men with CaP, whether 36 known CaP risk alleles that we have genotyped in our CaP patients are associated with a personal or first-degree family history of other malignancies. Such information may provide insights into possible underlying common pathways and mechanisms of carcinogenesis and also help to evaluate the potential scope of risk information provided by genotyping CaP patients.

MATERIAL AND METHODS

Our study cohort included 1121 men of European ancestry who were diagnosed with CaP between 1982 and 2009. Of these patients, 1060 underwent radical prostatectomy, 21 underwent radiation or hormone therapy, 2 chose active surveillance, and in 38 the management was unknown.

The study was approved by Northwestern University's Institutional Review Board, and all participants provided written informed consent. The patients were enrolled from a prospective database for which they had filled out a questionnaire and provided a blood sample used for genotyping. The CaP probands were questioned about the occurrence of malignancies in themselves and their first-degree relatives. The data on diagnoses in probands were supplemented by medical record diagnostic codes as well as annual surgery follow-up questionnaires. The following malignancies were selected based on the presence of sufficient data for statistical analysis from the probands and 451 of their first-degree relatives with cancer: hematologic malignancies (leukemia, non-Hodgkin's lymphoma,

multiple myeloma); skin cancers (melanoma, non-melanoma); colorectal cancer; and breast cancer (in female relatives only).

DNA was extracted from whole blood at deCODE genetics Inc., in Reykjavik, Iceland, and the Centaurus (Nanogen) genotyping methods were used. Their accuracy have been previously described.[9–13] Each sample was genotyped for 36 CaP risk alleles. We assayed for six susceptibility alleles on 8q24: rs10086908, rs1447295, rs16901979, rs16902094, rs445114, and rs6983267. Genotypes were also determined for rs721048 on chromosome 2p15, rs1465618 on 2p21, rs12621278 on 2q31, rs2660753 on 3p12, rs10934853 on 3q21, rs12500426 and rs179021918 on 4q22, rs7679673 on 4q24, rs2736098 and rs401681 on 5p15, rs9364554 on 6q25, rs10486567 on 7p15, rs6465657 on 7q21, rs1512268 on 8p21, rs1571801 on 9q33, rs10993994 on 10q11, rs4962416 on 10q26, rs11228565 and rs10896450 and 12418451 on 11q13, rs7127900 on 11p15, rs4054823 on 17p12, rs11649743 and rs4430796 on 17q12, rs1859962 on 17q24, rs8102476 and rs2735839 on 19q13, rs9623117 and rs5759167 on 22q13, and rs5945572 on Xp11.

For each of the 36 risk alleles, the best-fit genetic model (dominant or recessive) for autosomal alleles was considered the model with the lowest Akaike information criterion, and the carrier status of each allele was then determined for all participants, as previously described.[14] No genotype information from relatives was available for analyses.

Other malignancies reported in the probands may have been diagnosed antecedent to, concomitant with, or subsequent to the CaP diagnosis. For each malignancy and for each risk allele, the carrier frequencies of those with versus those without the other malignancy were compared using the Chi-square test or Fischer's exact test.

Separately, for each malignancy and for each risk allele, the carrier frequencies of those who reported one or more first-degree relatives with that malignancy were compared with the carrier frequencies of those who did not report first-degree relatives with that malignancy, using the Chi-square test or Fischer's exact test. A *P*-value of <0.05 was considered nominally significant, and a multivariate analysis, accounting for other significant SNPs found to be associated with the same malignancy, was also performed. All statistical calculations were performed using SAS 9.2 (Cary, NC).

RESULTS

Detailed clinicopathologic characteristics were available for 1033 of the 1121 men (Table 1). The median age at diagnosis was 61 years, and the median pre-treatment PSA was 4.9 ng/mL. The majority (73.8%) had clinical stage T1c disease. Most patients had a biopsy Gleason score of 6 (67.6%) or 7 (27.6%). On pathological examination, the majority had organ-confined disease (80.3%).

Among probands with CaP, the reported frequencies of non-melanoma skin cancer, leukemia, and melanoma were 153 (13.6%), 82 (7.3%), and 44 (3.9%), respectively (Table 2). In addition, non-Hodgkin's lymphoma, colorectal cancer, and multiple myeloma were reported in 8 (0.7%), 7 (0.6%), and 3 (0.3%) patients, respectively. The carrier frequencies of each of the 36 different risk alleles were assessed in CaP probands with and those without these other malignancies. Twelve CaP risk alleles had statistically significant associations with the risk of another malignancy: rs12621278 (2q31), rs12500426 (4q22), rs2736098 (5p15), rs9364554 (6q25), rs6465657 (7q21), rs1512268 (8p21), rs16901979 and rs6983267 and rs10086908 (8q24), rs12418451 (11q13), rs11649743 (17q12), and rs5759167 (22q13; Tables 3 and 4). After multivariate analysis controlling for other significant associations between other SNPs and the same malignancy in the same cohort (probands or family history), all associations with $P<0.05$ remained significant except those between rs6983267

and non-Hodgkin's lymphoma in probands and between rs12500426 and melanoma in probands.

Patients with melanoma were significantly more likely to be carriers of SNP rs1512268 (90.9%, versus 72.2% of those without melanoma, *P*=0.006), and SNP rs5759167 (30.3%, versus 14.4%, *P*=0.02; Table 3). Leukemia was significantly associated with carrier status for SNP rs2736098 (17.1%, versus 9.2% of those without leukemia, *P*=0.03), and multiple myeloma was significantly associated with carrier status for SNP rs9364554 (66.7%, versus in 8.7% of those without multiple myeloma, *P*=0.02). SNP rs11649743 was less frequent among men with non-melanoma skin cancer (58.8% versus in 70.4% of those without non-melanoma skin cancer, *P*=0.004), and SNP rs12500426 was less frequent among those with melanoma (7.0% versus in 25.4% of those without melanoma, *P*=0.006). SNP rs6983267 was less frequent in those with non-Hodgkin's lymphoma (50.0% versus in 81.9% of those without non-Hodgkin's lymphoma, *P*=0.04).

Probands reported having a first-degree family history of other malignancies at the following frequencies: breast (n=167, 14.9%), colon (n=113, 10.1%), melanoma skin cancer, (n=47, 4.2%), non-melanoma skin cancer (n=46, 4.1%), leukemia (n=38, 3.4%), non-Hodgkin's lymphoma (n=35, 3.1%), and multiple myeloma (n=4, 0.4%; Table 2).

We next compared the CaP risk allele carrier frequencies in probands with a family history and probands without a family history of other malignancies (Table 4). Carriers of SNP rs16901979 were significantly more likely to have a family history of melanoma (21.3%, versus 10.8% of those without, *P*=0.03), while carriers of SNP rs10086908 were less likely have a family history of melanoma (83.0% versus in 93.7% of those without, *P*=0.01). SNP rs12621278 was significantly associated with having a family history of multiple myeloma (50.0%, versus 8.21% in those without, *P*=0.04), while probands with a family history of non-Hodgkin's lymphoma were significantly more likely to be carriers of SNP rs6465657 (40.0%, versus in 22.6% of those without, *P*=0.02). Decreased frequencies of SNP rs16901979 were found among men having a family history of colon cancer (4.4%, versus in 12.0% of those without, *P*=0.02), and SNP rs12418451 was less frequent in men with a family history of non-melanoma skin cancer (38.6%, versus 53.8% in those without, *P*=0.049).

COMMENT

Both CaP patients and their relatives have been reported to have increased rates of other malignancies.[8] In the largest study to date, Cannon-Albright et al utilized data from the Utah Surveillance, Epidemiology and End Results (SEER) registry to identify 16,744 CaP cases and 140,275 relatives. Multiple other cancers were observed in excess in first-degree relatives of the CaP patients, including cancers of the colon, rectum, breast, leukemia, non-Hodgkin's lymphoma, multiple myeloma, melanoma, and several others. The same study reported increased rates of many of the same cancers co-occurring among CaP patients with at least three first- or second-degree relatives diagnosed with CaP. Although other studies have shown similarly increased rates of other malignancies among the relatives of CaP cases, prior studies on the risk of other cancers in CaP patients themselves have reported conflicting results.[15,16] The rates of malignancies in our patient cohort were not consistently higher or lower than the SEER lifetime risk (Table 2).

These observed links between malignancies may be explained by inherited genes or SNPs that affect more than one malignancy. For example, *BRCA1* is a predisposition gene that has been associated with cancers of the breast, ovaries, prostate, and colon.[17] The SNPs

identified by GWAS are less penetrant and in the majority the mechanism of action is poorly understood.

SNPs associated with many common cancers have been identified,[18] and while most of these variants have as yet been shown to affect only one cancer site, some have been shown to be associated with more than one malignancy.[7] Additionally, some SNPs seem to have diverging relationships with different malignant and non-malignant disease processes. For example, SNP rs4430796 is associated with both an increased risk of CaP and a decreased risk of type 2 diabetes,[10] while SNP rs6983267 is associated with an increased risk of several cancers but a decreased risk of bladder cancer.[19]

As the mechanisms through which these SNPs – many of which lie in "gene deserts" – affect carcinogenesis remain unexplained, it is unclear how a SNP might affect cancers seemingly unrelated to its location along the chromosome, or how a SNP might increase risk of one cancer and also be protective of another.

We examined associations between 36 CaP SNPs and other malignancies in a large cohort of men with CaP and found several associations with other malignancies not previously reported. In this population, leukemia was more common among carriers of rs2736098, which corresponds to A305A in the telomerase reverse transcriptase (*TERT*). Another *TERT* variant, A1062T, has previously been associated with chronic lymphocytic leukemia.[20] Although not previously associated with leukemia, SNP rs2736098 has been associated with several cancers including lung and bladder cancer, as well as basal cell carcinoma.[7] We also found two SNPs not previously associated with non-melanoma skin cancer: rs12418451 (11q13), which tended to be less common (P=0.049) among men with a family history of with non-melanoma skin cancer, and rs11649743 (17q12), which was less common among probands with non-melanoma skin cancer. This latter SNP lies within an intron of *HNF1B*, a gene that affects the development and function of the pancreas and the kidney.[21,22] A previous study has shown that patients diagnosed with nonmelanoma skin cancer have a significantly decreased risk for subsequent CaP diagnosis (SIR = 0.87, 95 percent CI: 0.77, 0.98).[23] At least one previous study has identified a SNP, rs401681, that confers susceptibility to basal cell carcinoma but protects against melanoma.[24] We did not confirm these associations in our CaP population.

In our study, melanoma was more common in probands who were carriers of either SNP rs5759167 (22q13) or SNP rs1512268 (8p21), which was the strongest positive association in our cohort (P=0.006). Interestingly, rearranged chromosomes in melanoma tumors have been seen to have a breakpoint at 8p21.[25]

The 8q24 region contains several SNPs associated with malignancies in addition to CaP, including colon cancer, ovarian cancer, breast cancer, bladder cancer, and chronic lymphocytic leukemia.[4] We found a higher occurrence of melanoma in relatives of probands carrying rs16901979 (8q24), a SNP 624 kb centromeric to the proto-oncogene *Myc*. Of the twelve SNPs significantly associated with other cancers in our study, three were found more often in probands with either a personal history (rs5759167 and rs1512268) or family history (rs16901979) of melanoma. This is supported by results from a recent study examining familial melanoma cases and cancers in their relatives found only CaP to be in excess among their first-degree relatives, suggesting a heritable syndrome.[26]

A negative association was observed between rs16901979 and probands reporting a family history of colon cancer. A previous study found a slightly lower odds ratio for colon cancer (95% CI, 0.89, 0.77–1.06), but it was not significant (P=0.36). Another study observed a decreased risk of kidney cancer for this SNP (OR, 0.48; 95% CI, 0.23–1.00).[19,27] While not previously associated with melanoma, rs16901979 has been positively associated with upper

aerodigestive tract and oropharynx cancers.[24] The 8q24 region contains one CaP SNP, rs6983267, that has been associated with both colon and ovarian cancers; we did not observe an association between rs6983267 and colorectal cancer in our population but rather a decreased frequency of the SNP among probands with non-Hodgkin's lymphoma. Finally, our study showed two previously unreported associations between multiple myeloma and CaP risk alleles, and only one of the 36 SNPs was marginally associated with breast cancer.

Our study has several limitations. Though our CaP population is one of the largest that has both genotype information for most of the CaP risk alleles and phenotype information for other cancers in probands and their relatives, our sample size is relatively limited and follow-up was relatively short; the development of other malignancies may be underreported in some cases. This may be especially true in a relatively young population of patients largely treated with radical prostatectomy. As personal and family histories of other malignancies were primarily ascertained by self-report, this is subject to recall bias or inaccuracy. We have not genotyped their family members. Assessing our findings in a control (non-CaP) population would provide a more robust analysis; however, we were unable to find a control population with both the same genotype and phenotype information available. Our study was limited to men of European ancestry and therefore the frequency and clinical significance of these genetic variants may differ in men of other racial backgrounds. Finally, while some associations we report are statistically significant after multivariate analysis controlling for other significant SNPs, none would be significant with a Bonferroni correction. However, our purpose was to identify possible associations, and our findings should be regarded as hypotheses eventually to be tested in larger populations.

CONCLUSIONS

CaP risk alleles may provide a genetic basis for the higher or lower rates of other malignancies that have been observed in both CaP patients and their relatives.

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Table 1
Clinicopathological characteristics of prostate cancer cases

1121 patients were included in this study; however, detailed clinical data was available for 1033. For the purposes of this table, percentages are calculated utilizing 1033 patients.

Variable	Cases (n=1033)
European ancestry	100%
Median age (years) at prostate cancer diagnosis	61 (Range: 37–87)
Median pre-treatment PSA (ng/mL)	4.9 (Range: 0–63.6)
Clinical stage T1c	762 (73.8%)
Biopsy Gleason score	
≤6	698 (67.6%)
7	285 (27.6%)
8–10	50 (4.8%)
Organ-confined disease (≤T2)	830 (80.3%)
Prostatectomy Gleason score	
≤6	531 (51.4%)
7	443 (42.9%)
8–10	59 (5.7%)
Positive surgical margins	117 (11.3%)
Extracapsular extension (T3a)	29 (2.8%)
Seminal vesicle invasion	47 (4.5%)
Lymph node metastases	10 (1.0%)

Table 2

Frequencies of other malignancies in 1121 prostate cancer (CaP) probands and their first-degree relatives

Malignancy	No. (%) of CaP probands with malignancy	No. (%) of CaP probands with at least 1 first-degree relative with malignancy	Lifetime risk (%) of being diagnosed with cancer – caucasian males[28]	Lifetime risk (%) of being diagnosed with cancer – caucasian females[28]
Non-melanoma skin cancer	153 (13.6%)	46 (4.1%)	20[29]	20[29]
Leukemia	82 (7.3%)	38 (3.4%)	1.62	1.15
Melanoma	44 (3.9%)	47 (4.2%)	2.73	1.82
Non-Hodgkin's lymphoma	8 (0.7%)	35 (3.1%)	2.43	2.02
Colorectal cancer	7 (0.6%)	113 (10.1%)	5.30	4.90
Multiple myeloma	3 (0.3%)	4 (0.4%)	0.70	0.51
Breast	*	167 (14.9%)	0.13	12.57

* Breast cancer in CaP patients was not examined.

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Table 3

Associations of prostate cancer (CaP) risk alleles with other malignancies among CaP probands

Carrier frequencies were compared between carriers who had the malignancy (case) with those who did not (control). Only values with $P<0.1$ are shown.

SNP	Chromosome location	Risk allele	Best-fit genetic model	Cancer type	Population frequency	Percent of patients with malignancy who are carriers	Percent of patients without malignancy who are carriers	P-value	OR	95% CI (Low)	95% CI (High)
rs1465618	2p21	A	Recessive	Non-Hodgkin's	0.7 (8/1121)	25.0 (2/8)	4.6 (51/1108)	0.05	6.91	1.36	35.08
rs12500426	4q22	A	Recessive	Melanoma	3.9 (44/1121)	7.0 (3/43)	25.4 (271/1067)	0.006	0.22	0.07	0.72
rs2736098	5p15	A	Recessive	Leukemia	7.3 (82/1121)	17.1 (14/82)	9.2 (96/1039)	0.03	2.02	1.10	3.73
rs9364554	6q25	T	Recessive	Multiple Myeloma	0.3 (3/1121)	66.7 (2/3)	8.7 (97/1110)	0.02	20.89	1.88	232.43
rs1512268	8p21	A	Dominant	Melanoma	3.9 (44/1121)	90.9 (40/44)	72.2 (771/1068)	0.006	3.85	1.37	10.86
rs6983267	8q24	G	Dominant	Non-Hodgkin's lymphoma	0.7 (8/1121)	50.0 (4/8)	81.9 (911/1113)	0.04	0.22	0.06	0.89
rs1447295	8q24	A	Dominant	Leukemia	7.3 (82/1121)	15.9 (13/82)	25.0 (259/1039)	0.08	0.57	0.31	1.04
rs16901979	8q24	A	Dominant	Non-Melanoma	13.6 (153/1121)	15.7 (24/153)	10.5 (102/968)	0.06	1.58	0.98	2.56
rs11228565	11q13	A	Dominant	Non-Hodgkin's	0.7 (8/1121)	75.0 (6/8)	43.3 (481/1112)	0.08	3.94	0.79	19.58
rs11649743	17q12	G	Recessive	Non-melanoma skin cancer	13.6 (153/1121)	58.8 (90/153)	70.4 (681/968)	0.004	0.60	0.42	0.85
rs11649743	17q12	G	Recessive	Non-Hodgkin's lymphoma	0.7 (8/1121)	100.0 (8/8)	68.6 (763/1113)	0.06	NA		
rs1859962	17q24	G	Recessive	Non-Hodgkin's lymphoma	0.7 (8/1121)	62.5 (5/8)	30.3 (337/1113)	0.06	3.84	0.91	16.15
rs5759167	22q13	T	Recessive	Melanoma	3.9 (44/1121)	30.3 (10/33)	14.4 (123/854)	0.02	2.58	1.20	5.56

Table 4

Associations of prostate cancer (CaP) risk alleles with a history of other malignancies in first-degree relatives of CaP probands

Carrier frequencies were determined for each single nucleotide polymorphism (SNP), and the carrier frequencies were compared between carriers who reported a history of the malignancy in first-degree relatives (case) with those who did not (control). Only values with $P<0.1$ are shown.

SNP	Chromosome location	Risk allele	Best-fit genetic model	Cancer type	Population frequency	Percent of patients with family history of malignancy who are carriers	Percent of patients without family history of malignancy who are carriers	P-value	OR	95% CI (Low)	95% CI (High)
rs12621278	2q31	G	Dominant	Multiple myeloma	0.4 (4/1121)	50.0 (2/4)	8.2 (91/1109)	0.04	11.19	1.56	80.35
rs2660753	3p12	T	Recessive	Multiple myeloma	0.4 (4/1121)	25.0 (1/4)	1.71 (19/1114)	0.07	24.33	2.39	247.56
rs9364554	6q25	T	Recessive	Non-melanoma skin cancer	4.1 (46/1121)	17.8 (8/45)	8.5 (91/1068)	0.05	2.32	1.05	5.13
rs6465657	7q21	C	Recessive	Non-Hodgkin's lymphoma	3.1 (35/1121)	40.0 (14/35)	22.6 (245/1082)	0.02	2.28	1.14	4.55
rs16901979	8q24	A	Dominant	Melanoma	4.2 (47/1121)	21.3 (10/47)	10.8 (116/1074)	0.03	2.23	1.08	4.61
rs16901979	8q24	A	Dominant	Colorectal	10.1 (113/1121)	4.4 (5/108)	12.0 (121/1013)	0.02	0.34	0.14	0.85
rs10086908	8q24	C	Dominant	Melanoma	4.2 (47/1121)	83.0 (39/47)	93.7 (1006/1074)	0.01	0.33	0.15	0.73
rs12418451	11q13	A	Dominant	Non-melanoma skin cancer	4.1 (46/1121)	38.6 (17/44)	53.8 (569/1058)	0.049	0.54	0.29	1.00
rs4054823	17p12	T	Dominant	Non-Hodgkin's lymphoma	3.1 (35/1121)	64.7 (22/34)	77.7 (838/1079)	0.08	0.53	0.26	1.08
rs1859962	17q24	G	Recessive	Multiple myeloma	0.4 (4/1121)	75.0 (3/4)	30.4 (339/1117)	0.09	6.89	0.71	66.43
rs2735839	19q13	G	Dominant	Multiple myeloma	0.4 (4/1121)	75.0 (3/4)	98.4 (1096/1114)	0.07	0.05	0.00	0.50
rs8102476	19q13	C	Dominant	Non-Hodgkin's lymphoma	3.1 (35/1121)	74.3 (26/35)	84.6 (919/1086)	0.10	0.53	0.24	1.14
rs5759167	22q13	T	Recessive	Multiple myeloma	0.4 (4/1121)	66.7 (2/3)	14.8 (131/884)	0.06	11.50	1.04	127.69
rs5945572	Xp11	A	Dominant	Breast Cancer	14.9 (167/1121)	44.5 (73/164)	37.0 (354/957)	0.07	1.37	0.98	1.91

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