

RESEARCH ARTICLE

Cyclin D1 Gene G870A Variants and Primary Brain Tumors

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Abstract

Alterations of cyclin D1, one of the main regulators of the cell cycle, are known to be involved in various cancers. The *CCDN1* G870A polymorphism causes production of a truncated variant with a shorter half-life and thus thought to impact the regulatory effect of *CCDN1*. The aim of the present study was to contribute to existing results to help to determine the prognostic value of this specific gene variant and evaluate the role of *CCDN1* G870A polymorphism in brain cancer susceptibility. A Turkish study group including 99 patients with primary brain tumors and 155 healthy controls were examined. Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism analysis. The *CCDN1* genotype frequencies in meningioma, glioma and control cases were not significantly different ($p > 0.05$). No significant association was detected according to clinical parameters or tumor characteristics; however, a higher frequency of AG genotype was recorded within patients with astrocytic or oligoastrocytic tumors. A significant association between AG genotype and glioblastoma multiforme (GBM) was recorded within the patients with glial tumors (p value = 0.048 OR: 1.87 CI% 1.010-3.463). According to tumor characteristics, no statistically significant difference was detected within astrocytic, oligoastrocytic tumors and oligodendroglomas. However, patients with astrocytic or oligoastrocytic tumors showed a higher frequency of AG genotype (50%) when compared to those with oligodendroglial tumors (27.3%). Our results indicate a possible relation between GBM formation and *CCDN1* genotype.

Keywords: CCND1 - glioma - meningioma - risk

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Introduction

Every year, about 10 per 100 million people are affected by primary brain tumors which correspond to about 2% of all adult primary tumors and 23% of all childhood cancers. Mortality caused by primary brain tumors is about 13,000 deaths per year and it represents 2% of adult and 25% of childhood cancer related deaths (Legler et al., 1999; DeAngelis, 2001; Wrensch et al., 2002; Furnari et al., 2007; Marie and Shinjo, 2011). Gliomas and meningiomas are the two most common primary brain tumors with approximately 50% and 20% proportion respectively. Among these two cancer types, meningiomas are mostly seen in women while gliomas are more common in men (Inskip et al., 1005; Parkin, et al., 2005; Park et al., 2009; Martinez et al., 2010). Glioblastoma multiforme (GBM) is known to be the most common and aggressive one among different primary brain tumor types (Yost et al., 2013).

Primary brain tumors are mostly aggregated in families, suggesting a genetic basis for disease tendency. Thus, in addition to known familial syndromes; effects of the inherited single nucleotide polymorphisms (SNPs) are needed to be understood in order to clarify the molecular

basis of these tumors (Malmer et al., 2002; Bondy et al., 2008).

Since cell cycle regulatory genes are responsible of detecting DNA damage, preventing propagation of errors and activating the cell cycle check points; they are thought to be involved in tumor initiation and proliferation. Hereditary alterations of these critical genes that regulate cell cycle control and apoptosis have been associated with numerous malignancies including brain tumors (Alberts et al., 2002; Vogelstein and Kinzler, 2004; Rajaraman et al., 2007).

EGF/EGFR and glioma risk was reported to be associated however, relation between TP53 and PTEN and glioma is contradictory. CX3CR1 (chemokine receptor 1 gene), CASP8 and CDKN2A (cyclin-dependent kinase inhibitor 2A) was reported to be associated with glioma risk (Gu et al., 2009). Frequent mutations or loss of expression of cell cycle control genes such as MDM2, NF1 and RB, also indicates the importance of cell cycle control in brain tumor formation (Holland, 2001; Rajaraman et al., 2007). However, possible correlations between cell cycle genes and glioma risk are not clear yet.

The Cyclin D1 (*CCDN1*) gene is a cell cycle regulatory gene located at 11q13 which is responsible for G1-S

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transition regulation during cell cycle. Regarding its critical role in cell cycle regulation, *CCND1* has been an attractive subject in cancer investigations. Suppression of *CCND1* through over expression of *CDKN2A* shown to inhibit growth of glioma cell lines (Hall and Peters, 1996; Liu et al., 2011; Zhang et al., 2011).

In addition, amplifications of this specific region is found in numerous cancers such as ovarian, bladder, breast, lung, liver, esophageal (Sherr, 1995; Betticher, 1996; Palmero and Peters, 1996; Hibberts et al., 1999) and known to be correlated with poor prognosis and high incidence of metastasis in a number of tumors including head and neck (Michalides et al., 1995), esophageal (Naitoh et al., 1995), and laryngeal (Jares et al., 1994).

A specific variant of this gene (G870A) was reported to be associated with increased risk of glioma and poor prognosis in various malignancies (Monteiro et al., 2004; Izzo et al., 2005; Knudsen et al., 2006; Wang et al., 2006; Zhang et al., 2006; Rajaraman et al., 2007; Jain et al., 2007).

This guanine to adenine substitution in position 870 results in a silent variant in codon 241 and does not affect the amino acid sequence of the protein (Pro241-Pro). *CCND1* 870A allele presence results with a truncated splice variant, called transcript b, without the exon 5 which contains PEST domain. Since PEST domain is critical for the protein degradation, 870A allele encoded protein has a longer half-life than its wild type variant. As a result, it is suggested that individuals with *CCND1* 870A allele can more easily bypass G1-S checkpoint and more likely to develop cancer (Betticher et al., 1995; Weinstein et al., 1997; Sawa et al., 1998; Solomon et al., 2003; Schernhammer et al., 2006).

This hypothesis has been tested in various cancer types with variable results. Several studies, including meta-analysis, indicated the association of *CCND1* 870A genotype with a great variety of cancers such as colorectal (Zhang et al., 2011), lung (Quiling et al., 2003), esophageal (Wang et al., 2003, Zhang et al., 2003), breast (Griew et al., 2003; Krippel et al., 2003; Shu, et al., 2005), oral (Huang et al., 2012) and squamous cell carcinoma of head and neck (Zheng et al., 2001). However there are a number of studies, specifically those subjected to esophageal (Jain et al., 2007; Zhou et al., 2012), breast and colorectal (Griew et al., 2003) carcinomas, reported the lack of association between *CCND1* genotypes and cancer risk.

Although *CCND1* polymorphisms have been investigated in numerous cancer types, only a limited number of studies indicate the role of alterations in this gene for brain cancers. Thus, in the current study we aimed to establish whether the *CCND1* G879A genotype and allelic variants could be related to the risk of developing brain meningioma and/or glioma in a group of 99 Turkish patients with brain tumors and 155 healthy controls.

Materials and Methods

Study participants

CCND1 G870A polymorphisms was investigated in 99 brain cancer patients (including 42 meningioma cases

and 57 glioma cases) and 155 compatible healthy control subjects who were in the follow-up Cerrahpaşa Faculty of Medicine- Department of Neurosurgery in Istanbul University. The mean ages of glioma and meningioma patients and control group were 42.18±14.8, 49.06±12.47 and 44.08±14.73 years, respectively. All participants provided written informed constant prior to study. A standardized questionnaire was applied to all participants. The control subjects, which were not taking any regular medication by the time, were randomly selected among volunteers. The blood samples were collected after the pathological diagnosis and prior to any chemotherapeutic or radiation therapy from those patients who had not been undergone blood transfusion. Medical Ethics Committee of Istanbul Medical Faculty approval was obtained for the study. The protocol followed was consistent with the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human subjects).

Isolation of DNA

Genomic DNA was extracted from peripheral whole blood containing EDTA according to salting-out technique. DNA was isolated from the blood leukocytes in 10 ml EDTA by the previously described method based on sodium dodecyl sulphate lysis, ammonium acetate extraction, and ethanol precipitation (Miller et al., 1988).

Polymerase chain reaction (PCR) for *CCND1* gene

Template DNA (0.5-1.0µg) was used in a PCR under sterile conditions. A concentration of 0.4µmol/l of each primer was used for the reaction. The forward primer was 5'GTGAAGTTCATTTCCAATCCGC-3' and the reverse primer was 5'GGGACATCACCTCACTTAC-3' in a volume of 25µl containing 1.5mM MgCl₂, 50mM KCl, 10 mM Tris-HCl (pH 8.4), 0.16mM each of deoxynucleotide triphosphate (MBI Fermentas, Vilnius, Lithuania), and 1 unit of Taq polymerase (MBI Fermentas, Vilnius, Lithuania). The reaction mixture was initially denatured at 94°C for 5 minutes, followed by 35 cycles with denaturation steps at 94°C for 45 seconds, annealing at 55°C for 45 seconds, and extension at 72°C for 45 seconds. The PCR programme was completed by a final extension cycle at 72°C for 5 minutes. The PCR product exhibited a 167 base pair fragment. PCR products (10 ml) were digested with 15U NciI (MBI Fermentas) at 37°C for 3 hours, and visualized by electrophoresis on 3% agarose containing 0.5mg/ml ethidium bromide. The 167 bp PCR product generated is not cut by NciI if the A allele is present, whereas the product from the G allele is cut to produce fragments of 145 and 22bp. *CCND1*

Table 1. General Demographic Informations and Parameters of Patients and Control Groups (values as average±standard deviation)

Parameters	Meningioma Cases (mean±SD) (n=42)	Glioma Cases (mean±SD) (n=57)	Controls (mean±SD) (n=155)
Age (years)	49.0±12.5	42.2±14.8	44.1±14.7
Gender Male	18 (42.9%)	32 (56.1%)	76 (49%)
Female	24 (57.1%)	25 (43.9%)	79 (51%)

Table 2. Genotype and Allele Frequencies of Study Group and Controls

SNP	Cases (n=155)	Controls		Meningioma		Glioma		Cases	Frequency	Chi-s quare (n=56)	Significance (p)
		Cases	Frequency (%)	Cases (n=)	Frequency	Chi-s quare	Significance (p)				
GG	40	25/8	10	23/8	0.2	0.8	13	22/8	1/9	0.3	
AG	73	47.1	19	45.2			23	40.4			
AA	42	27/1	13	31			21	36.6			
Alleles A	157	50.6	45	53.6	0.2	0.6	65	43	1/3	0.2	
G	153	49.4	39	46.4			49	57			

G870GA polymorphism was typed by visualization under ultraviolet light and photographing with a Polaroid camera. The CCND1 G870A alleles were identified in each sample. The allele types were determined as follows: a single 167 bp fragment for the AA genotype, two fragments of 22 and 145 bp for the GG genotype, and three fragments of 22, 145 and 167 bp for the AG genotype.

Statistical analysis

All statistical analyses were carried out using SPSS version 7.5 for Windows (SPSS Inc, Chicago, USA). Numeric values were analyzed by Student's t-test. Differences in characteristics between brain cancer patients and controls, as well as disparities in genotype and allele frequencies, were assessed with the chi-square test. CCND1 G870A allele frequencies were estimated by gene counting methods. Odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated to estimate the risk for brain cancer. The threshold for significance was $p < 0.05$.

Results

In the current study, we analyzed 99 primary brain tumor (including 42 meningioma, 57 glioma) samples and 155 healthy controls. The clinical characteristics of the study groups are represented in Table 1. There were No significant differences detected between study groups. Genotype and allele frequencies of cases and controls are shown in Table 2.

The CCND1 genotype frequencies in meningioma, glioma and control cases were not significantly different ($p > 0.05$).

Among brain cancer patients, there were no significant association between the CCND1 genotypes and some clinical parameters including age, smoking, using alcohol and some pathological parameters such as tumor types, vascular endothelial proliferation or tumor location (Data are not shown).

Histological characteristics of glial tumors were heterogeneous. There were 32 patients with Astrocytoma (64%) while 20 of those (40%) had glioblastoma multiforme. Among all glial tumors, 8 patients (16%) had Oligodendroglioma, 7 patients (14%) had oligoastrocytoma and 3 patients (6%) had other types (ependymoma, hemangioblastoma, paraganglioma vs).

According to tumor characteristics, no statistically significant difference was detected within astrocytic, oligoastrocytic tumors and oligodendroglial however patients with astrocytic astrocytic or oligoastrocytic

tumors showed a higher frequency of AG genotype (50%) when compared to those with oligodendroglial tumors (27.3%).

For patients with meningioma, individuals with the AA genotype were 2.2 fold higher in males when compared to females, however the difference was not statistically significant (p value=0.101).

In patients with glial tumors, glioblastoma multiforme (GBM) showed remarkable results; 3 individuals (14.3%) showed GG genotype, 12 individuals (57.1%) AG genotype and 6 individuals (28.6%) showed AA genotype. These results did not show any statistical significance within the patients with GBM (p value=0.135). However, when compared with all glial tumor types, AG genotype was significantly higher in patients with GBM (p value=0.048 OR: 1.87 CI% 1.010-3.463).

Discussion

Primary brain tumors are known to be multifactorial disorders however, understanding the genetic basis of the disease is needed in order to define the potential risk factors, just as other cancer types. One big difference of the primary brain tumors than other cancer types is that, primary brain tumors are mostly aggregated in families. A number of genetic syndromes have been confirmed as risk factors for brain cancer. At least three of these familial syndromes; retinoblastoma, neurofibromatosis and Li-Fraumeni syndrome are related with germ line mutations affecting cell cycle regulation and apoptosis (Inskip et al., 1995; Wrensch et al., 2002; Schwartzbaum et al., 2006; Rajaraman et al., 2007; Gu et al., 2009).

If we consider the familial aggregation of the primary brain tumors, some more common genetic factors than rare familial syndromes are thought to be involved in brain cancer formation. At this point, single nucleotide polymorphisms (SNPs) step in. A number of studies have tested the variants of numerous genes as risk factors for brain cancer. Although none of these results are sufficient to propose "accurate" risk factors as in familial syndromes, they represent a new era in understanding brain tumor formation. Variants of DNA repair genes such as ERCC1, ERCC2, GLTSCR1, PRKDC, MGMT and CHAF1A have been shown to be significantly associated with glioma and/or glioma subtypes (Wei et al., 1997; Hegi et al., 2005; Wiencke et al., 2005; Yang et al., 2005; Bethke et al., 2007; Felini et al., 2007). ATM and cell cycle genes have been reported to be associated with meningioma and glioblastoma and BRIP-1 was associated with meningioma (Malmer et al., 2007; Rajaraman et al., 2007;

Bethke et al., 2008). A significant association was shown between radiation and *CCDN1* and p16 variants (Sadetzki et al., 2005). This list is tend to be extended however, it should be noted that variation of genes affecting cell cycle regulation and apoptosis are mostly involved in brain tumor formation.

Cylin and cyclin depended kinases are main regulators of cell cycle. *CCDN1* is one of these main regulators and overexpression of it has been shown to shorten the G1 phase and lead to tumor formation (Quelle et al., 1993; Musgrove et al., 1994; Betticher et al., 1996; Simpson et al., 2001).

Over expression of *CCDN1* is commonly reported in malignancies. The basis of such a correlation with cancer development and *CCDN1* amplification relies on the critical role of *CCDN1* gene in cell cycle control. Since cyclin d1 regulates the G1-S transition during cell division, high activity of it leads to premature cell passage thus, propagation of DNA damage and accumulation of genetic errors, which leads to selective advantage for abnormal cell proliferation (Hall and Peters, 1996; Pabalan et al., 2008). However, as well as altered expression, a specific SNP that affects gene splicing, thus maintenance of the cyclin D1 protein, is taking attention as a risk factor for cancer formation.

This specific SNP (G870A) causes production of a splice variant without PEST domain which is responsible of degradation of the protein so, individuals with *CCDN1* 870A genotype has a longer half-life *CCDN1* protein than individuals with *CCDN1* G870 genotype (Solomon et al., 2003; Pabalan et al., 2008).

Up to date G870A has been investigated as a potential risk factor in numerous studies for a wide range of cancer types. However, findings are contradictory. Some of these studies indicated the association of *CCDN1* G870A with cancer risk, prognosis, survival or characteristics of tumors such as larynx and oral cavity (Izzo, 2003), non-small lung cancer (Betticher et al., 1995), breast cancer (Yaylim-Eraltan et al., 2009), head and neck cancer (Zheng et al., 2001), ovarian cancer (Dhar et al., 1999), pituitary adenomas (Simpson et al., 2001). A meta-analysis which also includes our previous study (Yaylim-Eraltan et al., 2010), reported a significant association between colorectal cancer risk and G870A polymorphism. (Zhang et al., 2011). On the other hand, only a weak association for breast (Shu et al., 2005), and no significant association between G870A polymorphism and bladder cancer (Sanyal et al., 2004), pituitary adenomas (Gazioglu et al., 2007) was detected.

Despite the broad number of studies in various cancer types, there are only a restricted number of studies that have investigated the *CCDN1* genotypes and brain cancer association. A non-functional *CCDN1* polymorphism was reported to putatively modify the risk for radiation-associated meningioma and also suggested to be in possible linkage disequilibrium with functional G870A polymorphism (Sadetzki et al., 2005).

A prior study suggested a relation between G870A polymorphism and increased the risk of glioma however to accept the *CCDN1* gene as a brain tumor susceptibility gene, this results need to be verified with a number of

studies (Rajaraman et al., 2007).

In current study, we investigated the effects of *CCDN1* G870A polymorphism on brain cancers. The aim of the study was to contribute to existing results and help to determine the prognostic value of this specific gene variant. Even we did not absorbed a significant association between cancer patients and control, patients having glioblastoma multiforme (GBM) subtype of glial tumors, showed significantly higher frequency of AG genotype.

GBM is known to be one of the most devastating cancer types (Yost et al., 2013). When the severity of the disease and the importance of the *CCDN1* in cell cycle regulation are considered, it is possible to suggest a relation between GBM formation and *CCDN1* genotypes. Alterations of such a key regulator may lead to an irreversible damage. Moreover, heterozygosis could create an advantage for pre-tumor cells. Having one copy of such a cell cycle promoting gene with a prolonged half-life, may gain the proliferative advantage without waken the safety mechanisms.

Indeed, these hypotheses need further validation but our results represent a possible relation between of *CCDN1* G870A polymorphism and GBM. Aside from limitations of our study such as limited case number, these results have potential to lighten the way for more detailed and comprehensive studies.

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