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Deletion at 6q24.2–26 predicts longer survival of high-grade serous epithelial ovarian cancer patients

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ABSTRACT

Standard treatments for advanced high-grade serous ovarian carcinomas (HGSOCs) show significant side-effects and provide only short-term survival benefits due to disease recurrence. Thus, identification of novel prognostic and predictive biomarkers is urgently needed. We have used 42 paraffin-embedded HGSOCs, to evaluate the utility of DNA copy number alterations, as potential predictors of clinical outcome. Copy number-based unsupervised clustering stratified HGSOCs into two clusters of different immunohistopathological features and survival outcome (HR = 0.15, 95%CI = 0.03–0.81; P_{adj} = 0.03). We found that loss at 6q24.2–26 was significantly associated with the cluster of longer survival independently from other confounding factors (HR = 0.06, 95%CI = 0.01–0.43, P_{adj} = 0.005). The prognostic value of this deletion was validated in two independent series, one consisting of 36 HGSOCs analyzed by fluorescent *in situ* hybridization (P = 0.04) and another comprised of 411 HGSOCs from the Cancer Genome Atlas study (TCGA) (HR = 0.67, 95% CI = 0.48–0.93, P_{adj} = 0.019). In addition, we confirmed the association of low expression of the genes from the region with longer survival in 799 HGSOCs (HR = 0.74, 95% CI = 0.61–0.90, log-rank P = 0.002) and 675 high-FIGO stage HGSOCs (HR = 0.76, 95% CI = 0.61–0.96, log-rank P = 0.02) available from the online tool KM-plotter. Finally, by integrating copy number, RNAseq and survival data of 296 HGSOCs from TCGA we propose a few candidate genes that can potentially explain the association. Altogether our findings indicate that the 6q24.2–26 deletion is an independent marker of favorable outcome in HGSOCs with potential clinical value as it can be analyzed by FISH on tumor sections and guide the selection of patients towards more conservative therapeutic strategies in order to reduce side-effects and improve quality of life.

1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecological malignancy and fifth leading cause of cancer-related death in Western countries (Ferlay et al., 2008). High-grade serous ovarian carcinomas (HGSOCs), the most common and aggressive ovarian cancer subtype, account for the majority (60–80%) of EOC deaths (Cannistra, 2004). HGSOCs show a very poor prognosis due to late stage at presentation and the development of chemoresistance (Seidman et al., 2004). In spite of high rates (~80%) of initial response to platinum-based treatment, the majority of patients relapse (Piccart et al., 2001). Although, over recent decades treatment has advanced significantly thanks to improved surgical techniques and chemotherapy regimens, the 5-year survival rate has remained relatively unchanged (between 35 and 40%) (Berns and Bowtell, 2012; Siegel et al., 2013). It is therefore essential to improve our understanding of the molecular events underlying the pathogenesis of HGSOCs in order to develop better prognostic and predictive markers. Given the fact that the presence of widespread DNA copy number changes is a hallmark of HGSOCs (Bowtell, 2010; TCGA, 2011), such alterations may serve as relevant markers for predicting prognosis, progression and drug sensitivity.

Comparative genomic hybridization (CGH) has been the most widely used method for the global assessment of DNA copy number alterations (CNAs). To date, there have been several studies utilizing either conventional metaphase chromosome-based CGH (Bruchim et al., 2009; Ramus et al., 2003), or array-based high-resolution techniques to identify the landscape of copy number events in ovarian cancer (Leunen et al., 2009; TCGA, 2011). Among the most frequently reported gained regions are 1q, 3q, 8q and 20q, while common lost regions include 4q, 5q, 6q, 8p, 17p, 18q and 22q (Bruchim et al., 2009; Gorringe and Campbell, 2009; Ramus et al., 2003). Especially interesting are losses and rearrangements at the long arm of chromosome 6, which have been recurrently described not only in ovarian cancer (Foulkes et al., 1993; Orphanos et al., 1995; Saito et al., 1992), but also in other types of carcinomas and in non-epithelial tumors including melanoma and hematological and central nervous system malignancies (Burkhardt et al., 2006; Guo et al., 2011; Li et al., 2013; Nelson et al., 2008; Theile et al., 1996; Vajdic et al., 2003).

In particular, loss at 6q24–27 has been extensively studied for its potential role in tumor suppression (Hayashi et al., 2012; Sun et al., 2003) and some candidate genes have been proposed such as *PLAGL1* (Abdollahi et al., 2003), *GRM1*, *SOD2* (Shridhar et al., 1999), *SASH1* (Zeller et al., 2003) or *Parkin* (Denison et al., 2003). However, few studies so far have aimed