The most abundant types of genetic variation are single nucleotide variants (SNVs) and copy number variants (CNVs). Association studies involving the large-scale analysis of both SNVs and CNVs in thousands of patients can help to identify relevant mutations in these patients. We identified a total of 339 pathogenic variants having an average of 4.3 (1-26) mutations per tumour. We found that PTEN mutations are strongly associated with shorter survival in patients with GBM (P=0.000412). We also found mutations in several actionable genes, such as PARP and BRAF genes. Our results demonstrate that the molecular characterisation of GBM tumours using NGS multigene panels could be a good strategy to improve the management of these patients.

Mutational characterisation of glioblastomas for the identification of prognostic markers and therapeutic alternatives. Glioblastoma (GBM) is the most common and aggressive malignant brain tumour in adults. Despite the advances in surgical resection, the prognosis for patients with GBM remains poor, with a median survival of 15 months, and tumours generally recur after standard multimodal treatments. We have performed the genetic characterisation of 89 primary tumours from GBM patients recruited from the Hospital Clinico San Carlos and Hospital 12 de Octubre, using a custom NGS panel with 1313 amplicons of 48 genes including 26 genes significantly mutated in GBMs in the Cancer Genome Atlas Project, and also 22 actionable genes to identify clinically relevant mutations in these patients. We identified a total of 22 actionable genes to identify clinically relevant mutations in these patients. We identified a total of 339 pathogenic variants having an average of 4.3 (1-26) mutations per tumour. We found that PTEN mutations are strongly associated with shorter survival in patients with GBM (P=0.000412). We also found mutations in several actionable genes, such as PARP and BRAF genes. Our results demonstrate that the molecular characterisation of GBM tumours using NGS multigene panels could be a good strategy to improve the management of these patients.

**OVERVIEW**

The most abundant types of genetic variation are single nucleotide variants (SNVs) and copy number variants (CNVs). Association studies involving the large-scale analysis of both SNVs and CNVs in thousands of patients can help to identify relevant mutations in these patients. We identified a total of 339 pathogenic variants having an average of 4.3 (1-26) mutations per tumour. We found that PTEN mutations are strongly associated with shorter survival in patients with GBM (P=0.000412). We also found mutations in several actionable genes, such as PARP and BRAF genes. Our results demonstrate that the molecular characterisation of GBM tumours using NGS multigene panels could be a good strategy to improve the management of these patients.

**RESEARCH HIGHLIGHTS**

Searching for predictive biomarkers of anthracycline-induced cardiotoxicity (AIC). Cardiotoxicity can become a leading cause of death, even surpassing metastases and relapses. For that reason, and with the aim of identifying genetic factors associated with AIC, we recruited a cohort of 877 breast cancer patients treated with epirubicin (a type of anthracycline). We carried out whole exome sequencing in 28 patients that presented extreme phenotypes. Thanks to that approach, we identified several rare variants associated with a higher risk to develop cardiotoxicity in two genes TTN (P=9.29 x 10^-10) and HCN2 (P=1.1 x 10^-8). After replication in an independent cohort, the implementation of these biomarkers in the clinic may allow to discriminate those breast cancer patients with a high risk of developing AIC.

Genetic factors underlying the risk of persistent chemotherapy-induced aleupma in patients treated with docetaxel. Persistent chemotherapy-induced aleupma (pCIA) appears in its more severe grade (grade 2) in up to 10% of breast cancer patients treated with docetaxel-based therapies, and has severe psychological impact on these patients. We identified a genome-wide association study (GWAS) to identify variants associated with the risk to develop this adverse effect. A regulatory variant located in an enhancer element that interacts with the ABCB1 promoter was found to be associated with pCIA appearance; this finding was validated in the replication cohort (ORcombined 4.05; 95% IQR, 2.46-6.67; P=3.94 x 10^-8). This variant affects ABCB1 mRNA expression and is the risk allele associated with decreased ABCB1 expression levels (P=1.64 x 10^-10). To our knowledge, this is the first study to identify a genetic factor related to this adverse effect.

Mutational characterisation of glioblastomas for the identification of prognostic markers and therapeutic alternatives. Glioblastoma (GBM) is the most common and aggressive malignant brain tumour in adults. Despite the advances in surgical resection, the prognosis for patients with GBM remains poor, with a median survival of 15 months, and tumours generally recur after standard multimodal treatments. We have performed the genetic characterisation of 89 primary tumours from GBM patients recruited from the Hospital Clinico San Carlos and Hospital 12 de Octubre, using a custom NGS panel with 1313 amplicons of 48 genes including 26 genes significantly mutated in GBMs in the Cancer Genome Atlas Project, and also 22 actionable genes to identify clinically relevant mutations in these patients. We identified a total of 339 pathogenic variants having an average of 4.3 (1-26) mutations per tumour. We found that PTEN mutations are strongly associated with shorter survival in patients with GBM (P=0.000412). We also found mutations in several actionable genes, such as PARP and BRAF genes. Our results demonstrate that the molecular characterisation of GBM tumours using NGS multigene panels could be a good strategy to improve the management of these patients.