Comprehensive genomic profiling of desmoplastic small round cell tumor

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BACKGROUND: Molecular profiling of rare tumors is an important strategy to gain insights on the biological pathways involved in tumor onset and to improve the management and treatment of neglected diseases. Desmoplastic small round cell tumor (DSRCT) is a type of sarcoma arising typically from abdominal peritoneum in male adolescents and young adults. At the genetic level, a specific translocation, t(11;22)(p13;q12), juxtaposing the Ewing´s Sarcoma gene (EWSR1) to the Wilm´s Tumor gene (WT1) is considered the molecular hallmark of the tumor. Apart from this, no other recurrent genomic alteration has been reported. Here, we carried out a complete characterization of the genomic alterations putatively involved with DSRCT, using a family-based approach, and established a approach for patient monitoring based on liquid biopsy.
METHODS: In this study, we performed genomic profiling of a DSRCT affecting a 26-years-old male, by combining targeted-sequencing, whole-exome and whole-genome using the ION PGM, ION Proton and SOLiD platforms. Array-CGH was carried out in a whole-genome 180K platform (Agilent Technologies; design 22060). Detection of circulating tumor DNA (ctDNA) was screened in plasma samples by digital droplet PCR (BioRad).
RESULTS: By combining targeted-sequencing of a cancer-oriented gene panel and whole-exome sequencing of both tumor and germline samples we identified 18 somatic acquired variants, 14 of which are protein-affecting variants (one nonsense mutation, one splice site mutation and 12 non-synonymous mutations) and were validated by capillary sequencing. Additionally, by performing whole-exome sequencing of the parents we identified 11 genes that were affected by germline compound heterozygous mutations (where one variant allele is inherited from the mother and the other variant allele in the same gene is inherited from the father) and found 3 rare polymorphisms inherited in homozygosity in the patient, leading to non-synonymous alterations. All variants were validated by Sanger sequencing. Regarding genomic rearrangements, only a few copy number alterations (CNA) were detected, mainly gain of chromosomes 5 and 18 and chromosomes 11p, 13q and 22q losses. The CNA in chromosomes 11p and 22q are indicative of the presence of the translocation t(11:22)(p13;q12). This translocation, initially detected by FISH for diagnostic purposes, was confirmed by whole-genome sequencing, allowing the definition of the genomic breakpoint. We then used this somatic gene fusion event as a tumor biomarker for monitoring the patient along the follow-up period using liquid biopsies-based approach. We searched for ctDNA in plasma samples collected in 3 clinical appointments post-treatment during 3 years after surgery and did not detect the presence of this tumor marker. This results are in agreement with patient's clinical aspects. To check for specificity and sensibility of this assay we tested the detection of the fusion event in 5 serial dilutions using tumor DNA, and we were able to detect the biomarker even in tiny quantities (0,006ng), whereas no fusion event was detected in DNA from the leucocytes.
CONCLUSION: Our findings revealed potential genes associated with this rare type of sarcoma. Additionally, we established a liquid biopsy approach for monitoring patient follow-up based on genomic information for this rare tumor.