Screening of genomic alterations in head and neck carcinomas of young patients by total exome sequencing.

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BACKGROUND:Head and neck squamous cell carcinomas (HNSCC) generally occur in older men (> 60 years old). The major risk factors involved in HNSCC are HPV infection, heavy smoking and drinking habits. In the last years, an increase in the incidence of HNSCC in younger adults (<45 years) has been observed, especially affecting oropharynx and oral cavity. Interestingly, this subset of patients presents adverse clinical outcome.
HYPOTHESIS:Genomic variants in oral and oropharyngeal carcinomas from young patients have the potential to contribute with the understanding of the disease and point out new molecular drivers.
METHODS: We evaluated 70 matched samples(24 oral cavity and11 oropharynx carcinomas matched with 35 peripheral blood samples) by whole exome sequencing. All cases had less than 50 years old. Libraries were prepared (Illumina Nextera exome Enrichment kit) using high quality DNA from tumor tissue and peripheral blood samples of each patient. The sequencing was performed using the HiSeq2500 (Illumina). The coverage reached an average of 55x per sample. We used an in house pipeline composed by the widely used open source algorithms (Seqyclean, Bowtie2, Picard, Samtools, GATK 2.7, Mutect and Annovar) for cleaning, mapping and SNP calling. Only exclusive variants in tumors were considered. Common variants, based on 1000 Genomes (http://www.1000genomes.org/) and 6500 exomes (evs.gs.washington.edu/), and non-pathogenic variants (predicted to be pathogenic in less than 5 algorithms) were excluded.
RESULTS: A total of 1,157 variants distributed among 857 genes were identified, being 657 (61.8%) classified as new (no previously described) and 374 (38.2%) as rare variants (population frequency ≤0.1%).In 16 tongue tumors, *KRT18, CNN, CTBP2,PABPC3/1* and *PARP4*genes were frequently altered (> 20% of cases). In HPV-positive cases (12/35), *AK2* and *CDC27* presented high frequency of alterations. In addition, HPV-negative patients showed high frequency of *PRSS3, PABPC1, KRT18* and *PRSS1* variants. Interestingly, *TP53* recurrently mutated in HNSCC (frequency ranging from 60% to 80%), harbored only five variants(~3%).The most frequently altered genes in oral cavity tumors were *HLA-DRB1,CTBP2* and *NOTCH2,* while in oropharyngeal carcinoma was the *FBF1*.
CONCLUSION: The preliminary global analysis indicated new genes potentially related with development of HNSCC in young patients. Futureanalyses are being conducted to evaluatethe genetic variants according to age and clinical features.

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