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Whole Transcriptome Sequencing Reveals Somatic HMGCR Mutation in a Case of Pancreatic Adenocarcinoma with Long-Term Therapy Response

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Context We merged clinical history of a locally advanced pancreatic cancer (LAPC) patient with data obtained from a whole transcriptome massively parallel sequencing (RNASeq). **Case report** A 56-year-old man with histological diagnosis of LAPC. After obtained informed consent, we collected a fragment of pancreatic lesion. Patient received 6 induction cycles treatment with gemcitabine and oxaliplatin (GEMOX) from November 2011, followed by chemoradiotherapy with bi-weekly gemcitabine 50 mg/m^2 for 6 weeks. CT-scan demonstrated partial response, so patient received additional 12 cycles of GEMOX, with further response, which currently persist since 17 months (to 3.8 cm *vs*. 2.5 cm). At the same time, the RNASeq was performed at 75x2 bp on a HiScanSQ (Illumina Inc., San Diego, CA, USA) platform. Single nucleotide variants (SNVs) were detected with SNVMix2 and filtered on dbSNP, 1000 Genomes Project, and Cosmic databases. Non-synonymous SNVs were analyzed with SNPs&GO and PROVEAN. We highlighted the major oncogenic hits of LAPC, confirming KRAS mutations, CDKN2A and SMAD4 deletions. RNASeq analysis showed a somatic mutation p.H672D involving the catalytic domain of hydroxymethylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzyme in the mevalonate pathway, not yet reported neither in the COSMIC nor in the ICGC databases. Furthermore, 4 new genomic rearrangements leading to fusion genes emerged: 2 in-frame gene fusions regulating RAS-MAPK and apoptotic pathways (ANKRD44-GULP1 on chromosome 2; ATXN10-TMEM49; chromosome 22 and 17) and 2 out-of-frame fusions [*t*(15;3) and *t*(19;22)] leading to SMAD3-KIAA1143 and LTBP4-SPATS2L, both disrupting genes of the TGFbeta pathway. **Conclusion** We found a novel somatic alteration involving HMGCR in LAPC. Due to the key role of HMGCR in cellular transformation, we hypothesize a strong potential in the development and outcome of LAPC, whose the optimal treatment remains to be elucidated. Trials that integrate RNASeq data with clinical options are needed.