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Research Letter

Genome sequencing of pancreatic cancer: differential expression by location

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Dear Editor

Recent studies have improved understanding of the genomic and transcriptomic landscape of pancreatic ductal adenocarcinoma (PDAC), yet data related to the molecular pathology of PDAC in different tumour locations are scarce. This study compared the clinicopathological features of 128 patients with PDAC, 78 patients with pancreatic head tumours, and 50 patients with body/tail tumours (*Table S1*). Consistent with a previous study[1], tumours in the body/tail were larger than those located in the head; most other features were comparable. Fourteen samples were selected randomly for whole-exome sequencing (*Fig. S1*), as described in *Appendix S1*. The average mean number of mutations detected in body/tail PDAC was significantly higher than for PDAC located in the head (*Fig. 1a*, *Tables S2* and S3). For a similar set of genes, body/tail cancers had more harmful mutations than cancers of the head. For example, the main variation types of *TTN* and *BRCA2* genes were frameshift variants in body/tail cancers, whereas for the head cancers the main type was missense variants. Similar results were observed in The Cancer Genome Atlas (TCGA) data set ($P = 0.030$) (*Fig. 1c,d* and *Fig. S2*).

Body/tail cancer had 1371 genes with high-impact single-nucleotide variations (SNVs), which were mainly associated with chromatin and histone modification (*Fig. 1b*). The head group had only 286 genes with high-impact SNVs, which did not show enrichment in any biological process. Compared with surrounding tissue (outside the cancer), body/tail cancers presented with significantly more dysregulated genes than were found in head cancers. There were 57 differentially expressed genes in the pancreatic head cancers: six upregulated and 51 downregulated genes (*Fig. S3a*). In contrast, a total of 3937 differentially expressed genes were found in body/tail cancers: 1994 upregulated and 1943 downregulated genes (*Fig. S3b*). Further analysis revealed that body/tail cancers were mainly associated with biological processes, such as epidermal development (*LAMB3*, *KRT17*, *COL17A1*), epidermal cell differentiation (associated with epithelial to mesenchymal transition; EMT), cytokeratin, and proteolysis (extracellular matrix, ECM), among others, whereas head cancers were primarily associated with lipid metabolic processes (*Fig. S3c,d*).

Transcriptome and whole-exome sequencing data were combined by taking the intersection of differentially expressed genes in transcriptome sequencing and the genes with high impact SNVs in whole-exome sequencing. In pancreatic head cancers, there was no intersection gene owing to a small base (57 differentially expressed genes and 286 genes with high-impact SNV), whereas there were 262 intersection genes in pancreatic body/tail cancers (3937 differentially expressed genes and 1371 genes with high-impact SNV). Analysis of overlapping genes revealed that they were mainly associated with the ECM and innate immune response (*Fig. S4*).

Taken together, the findings suggest that the worse prognosis of pancreatic body/tail cancer compared with head cancer may be due to greater genetic disorder at the molecular level. The results suggest that increased molecular understanding of PDAC biology may enable refined treatments for cancers based on molecular differences. Body/tail cancers are associated with an increased involvement of genes influencing the EMT, cytokeratin, and ECM, all of which are factors related to poor prognosis. Although the sample size was limited, the results were consistent with previous studies[1], and suggest that cancers of the pancreatic body/tail and head may be two different diseases.

Supplementary material

Supplementary material is available at *BJS* online.

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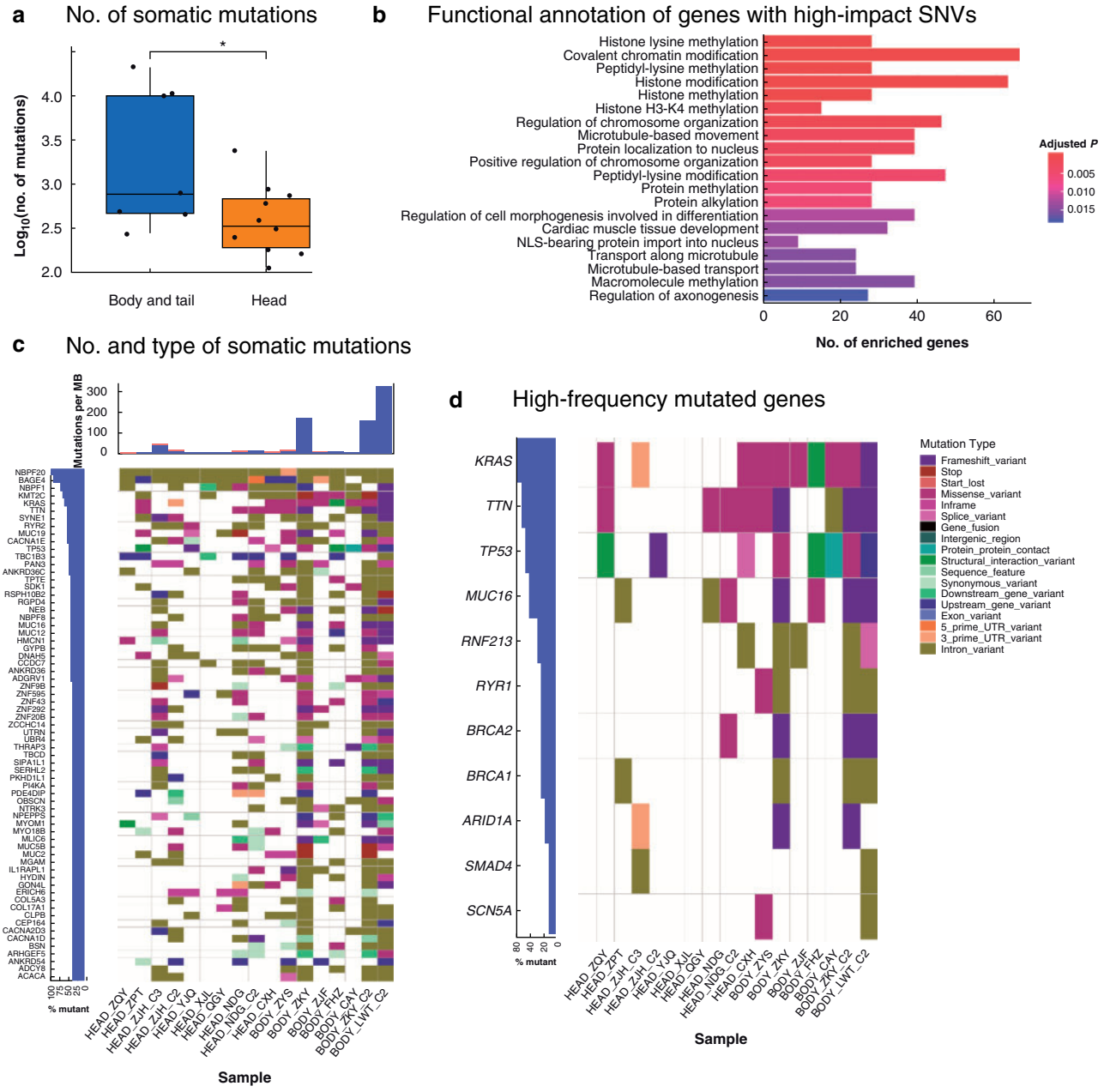

Fig. 1 Comparison of mutation profile between pancreatic cancer of the head and body/tail

a Box plot of number of somatic mutations in pancreatic head cancer and pancreatic body/tail cancer groups. Log_{10} values for different samples are shown along with median values (bold line), i.q.r. (box) and range (error bars). *$P < 0.050$ (Student's t test). **b** Biological process of functional annotation of the 1371 genes with high-impact single-nucleotide variations (SNVs) in pancreatic body/tail cancer. **c** Waterfall plot showing number and type of somatic mutations in pancreatic head cancer and pancreatic body/tail cancer groups. Different colours represent different variation types. The chart is sorted vertically by the frequency of gene mutations and horizontally by sample type. The bar chart at the top shows the tumour mutational burden (somatic mutations per million base-pairs (MB)) for each sample. **d** Waterfall plot showing the distribution of high-frequency mutated genes from previous studies and The Cancer Genome Atlas (TCGA) data in the authors' samples. NLS, Nuclear localization sequence; UTR, untranslated region.

Reference

1. Dreyer SB, Jamieson NB, Upstill-Goddard R, Bailey PJ, McKay CJ. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. *Br J Surg* 2018;105:e183–e191