Case Report

High tumor mutation burden in a patient with metastatic gastric cancer sensitive to trastuzumab: a case report

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Abstract: Patients with HER2-positive gastric cancer (GC) can benefit from the addition of trastuzumab. However, not all patients with HER2-positive GC respond to trastuzumab. Biomarkers affecting its efficacy in patients with advanced gastric cancer (AGC) are largely unknown. Therefore, classifying GC into molecularly distinct subtypes to accurately distinguish between GC patients who would and would not benefit from trastuzumab is worthwhile. Tumor mutation burden (TMB) is a notable feature in GC and whether TMB influences trastuzumab efficacy is still unknown. Herein, we report the case of a 61-year-old man who was diagnosed with metastatic HER2-positive gastric adenocarcinoma that had spread to the liver (T4aN0M1, stage IV). Esophagogastroduodenoscopy revealed a circular ulcer in the posterior wall of the stomach. A computed tomography (CT) scan revealed a 2-cm diameter liver metastasis. Immunohistochemical analysis of the endoscopic biopsy tumor revealed 3+ positive expression for HER2. Whole-exome sequencing (WES) of the tumor tissue revealed 3,736 somatic mutations in 2,423 genes and a very high TMB of 50.3 mutations/Mb. Immunohistochemistry revealed that the patient had mismatch repair-proficient (pMMR) GC. The patient received first-line trastuzumab-containing chemotherapy, and after 2 courses of sequential metronomic trastuzumab-containing chemotherapy, restaging CT showed that the liver metastasis had disappeared. Following resection, the patient had no recurrence and no new tumor metastasis after a follow-up of period nearly 7 years. This study is the first to report that pMMR GC with a high TMB has a favorable response to trastuzumab. The combination of HER2 positivity and a high TMB may be sufficiently predictive of sensitivity to trastuzumab in AGC.

Keywords: Gastric cancer (GC); HER2; trastuzumab; tumor mutation burden (TMB); targeted therapy; case report

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Introduction

Approximately 20% of gastric cancers (GCs) overexpress the HER2 receptor (1-3). Trastuzumab is a HER2-targeted humanized monoclonal antibody that has been studied as a first-line treatment for patients with HER2-positive advanced gastric cancer (AGC). ToGA (Trastuzumab for Gastric Cancer) revealed a significant overall survival benefit in patients with HER2-positive AGC (2), but the overall response rate was 47%, and the complete response rate was only 5%. Therefore, only a minority of patients derive lasting benefits from trastuzumab therapy. Moreover, the available data clearly demonstrate that high-dose (HD) trastuzumab maintenance dosing is not associated with

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increased efficacy (4). Therefore, potential biomarkers for high response rates to anti-HER2 therapies still need to be identified. Tumor mutation burden (TMB) may predict the clinical response to immune checkpoint inhibitors (ICIs) (5). A high TMB is associated with improved immunotherapy outcomes in patients with esophagogastric cancer, with those with a TMB >9.7 mutations (muts)/Mb (in the top quartile) having the best outcomes (6). However, the role of TMB in targeted therapy in patients based on their response to trastuzumab has not been reported.

Herein, we report a significant elevation in TMB in a liver metastatic GC patient who was highly responsive to trastuzumab. As TMB is a recognized predictive biomarker for the response to ICIs in esophagogastric cancer, we speculated that patients with HER2-positive tumors with a high TMB might receive more benefit from trastuzumab than those with a low TMB. We present the following article/case in accordance with the CARE Reporting Checklist (available at http://dx.doi.org/10.21037/apm-20-132).

Case presentation

A 61-year-old man with a BMI of 24.2 presented with mild discomfort under the xiphoid process from the age of 58 [2009] without apparent cause. He was admitted to our hospital with recurrent increasing abdominal distension for 2 months in October 2012. The patient reported that the distension pain occurred two or three hours after a meal and was accompanied by nausea and vomiting. The patient had no significant medical history, and there was no apparent weight loss or pain in either his abdominal or back and flank pain at that time; thus, the patient did not pay much attention to the condition. During the physical examination, it was noted that the upper abdomen was mildly tender, with no mass felt in the upper abdomen and no swelling upon palpating the superficial lymph nodes (LNs) throughout the body. The liver and could not be palpated under the ribs. Laboratory examinations revealed a low hemoglobin concentration of 108 g/L, carcinoembryonic antigen (CEA) (4.04 ng/mL), alpha-fetoprotein (AFP) (2.94 ng/mL) and carbohydrate antigen 19-9 (CA19-9) (19.22 U/mL) levels were normal. Esophagogastroduodenoscopy revealed a 30-mm circular ulcer in the posterior wall of the lower stomach body. Endoscopic biopsy specimens were obtained, and the pathology of the specimens revealed moderately differentiated gastric adenocarcinoma. Immunohistochemistry was strongly positive for HER2 receptor expression (3+). A computed tomography (CT) scan revealed a thickening of the lower part of the stomach and the wall of the antrum and hepatogastric ligament and swollen LNs near the abdominal aorta, with a metastatic lesion 2 cm in diameter in the lower right lobe of the liver. He was diagnosed with liver metastatic GC in December 2012. The tumor was classified as cT4aN0M1, stage IV.

Based on the strong positivity for HER2 (*Figure 1A*), trastuzumab-based XELOX chemotherapy [consisting of a 2-h i.v. infusion of 130 mg/m^2 oxaliplatin on day 1 and 1,000 mg/m^2 oral capecitabine twice daily on days 1–15, plus 8 mg/kg trastuzumab on day 1 (second course 6 mg/kg)] was administered every 3 weeks from December 14, 2012, and repeated for 12 courses. After 2 trastuzumab-based chemotherapy courses, restaging CT showed that the liver metastasis had disappeared on February 2, 2012, and that the size of the primary tumor in the stomach was similar to before. CT scans showed partial response (PR) in gastric and liver metastases by RECIST version 1.1. The patient tolerated trastuzumab treatment well, without severe adverse events. Serum tumor marker levels were evaluated, including CEA (3.04 ng/mL), AFP (1.64 ng/mL) and CA19-9 (8.82 U/mL). After 12 courses, the patient was confirmed to have stable disease (SD) by CT. Primary tumor changes were not obvious, therefore, the patient underwent radical gastric resection on November 2013; a persistent histopathological diagnosis was made of moderately differentiated adenocarcinoma, tumor cell expansive invasion to the peritoneal layer of the stomach, and 27 LNs without metastasis. The patient was classified as having stage IV (pT4aN0M1) disease. Nevertheless, HER2 immunohistochemistry in the surgical biopsy demonstrated the loss of HER2 positivity. After surgery, the patient was placed on a regimen of tegafur-uracil (120 mg per day orally) for sixteen months. The patient tolerated treatment with trastuzumab and chemotherapy well. Except for mild nausea and vomiting, which subsided after symptomatic treatment, no additional adverse events were observed. The patient returned for regular follow-up visits at the hospital without adjuvant treatment (see treatment timeline, *Figure 1B*). Follow-up visits in the outpatient department every 3–6 months. Laboratory data indicated normal levels of tumor markers, and subsequent monitoring by CT and MRI showed no regional LN swelling, no ascites and multiple metastatic tumors. In addition, no adverse event was observed in the follow up period. As of November 2019, the patient did not have any recurrence or new metastases for 72 months.

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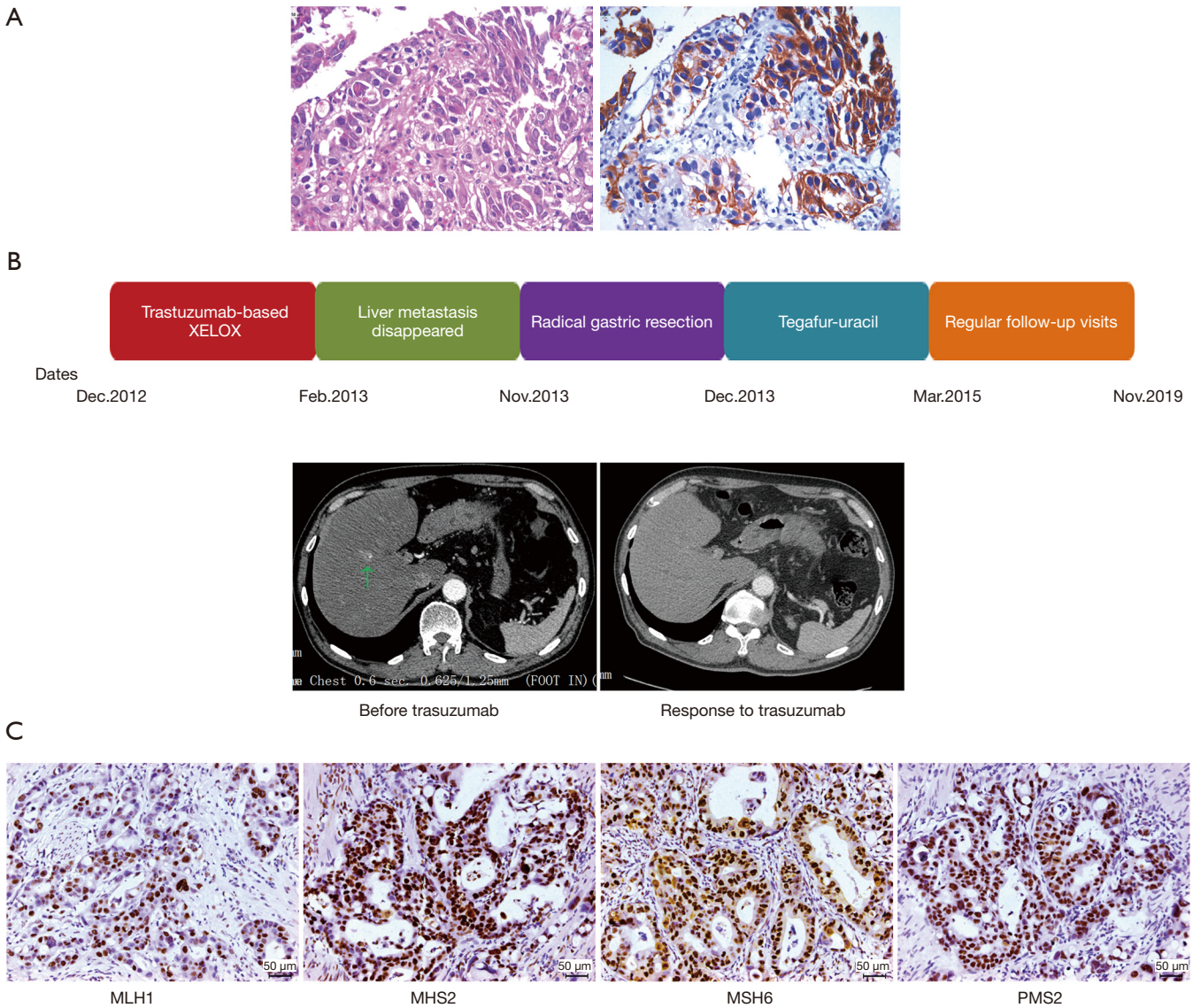

Figure 1 HER2 immunohistochemistry and therapy timeline. (A) Left, histopathology of the GC specimens obtained from the endoscopic biopsy, H&E stain; right, immunohistochemical positivity for the HER2 protein. Original magnification ×400. (B) Therapy timeline; CT image showing a complete response in the liver metastasis (green arrow) of this patient after 2 courses of trastuzumab treatment. (C) Representative immunohistochemistry images of GC samples showing strong nuclear expression of MMR proteins (immunohistochemistry ×100, the scale bar indicates 50 μm). GC, gastric cancer; CT, computed tomography; MMR, mismatch repair.

We collected formalin-fixed paraffin-embedded (FFPE) tissue slides containing gastric carcinoma tissue and paired noncarcinoma tissue for whole-exome sequencing (WES) with the Illumina NovaSeq system. We obtained 70-fold mean sequence coverage of the targeted exonic regions, with 97.53% of loci covering >10-fold sequences. To confirm the somatic (i.e., tumor-specific) nature of these mutations, we compared these data with those from the matched normal tissue. We identified a total of 3,736 putative somatic point mutations in 2,423 genes. The somatic mutation types and their prevalence in the patient are shown in *Table 1*. Several mutations were located in nine highly variable genes: AHNAK2, MUC4, SULT1A1, NBPF1, ABO, MST1L, ZNF718, MUC12 and MUC16 (Table S1). In particular, a very high TMB was observed in this patient (50.3 muts/Mb). Notably, WES revealed a lack of mutations in mismatch

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Table 1 Summary of somatic mutation types and prevalence in patient

Mutation types	Prevalence
Coding regions and essential splice sites	
SNV	
Synonymous	755
Nonsynonymous	
Missense	839
Splicing	21
Stopgain	17
Stoploss	0
Non-coding regions	
Indel	78
SNV	1,633
Indel	393

SNV, single-nucleotide variations.

repair (MMR) genes (MLH1, MSH2, PMS2 and MSH6), and following immunohistochemistry, the MMR proteins retained nuclear staining and were deemed mismatch-repair proficient (*Figure 1C*).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The patient of this case report agreed and signed consent forms, which are attached to the medical records. Written informed consent was for the purpose of publication of the present case report and any relevant images.

Discussion

GC is a biologically heterogeneous tumor (7). The characterization of GC into subtypes based on genotype has evolved over the past decade (8). The Cancer Genome Atlas (TCGA) categorized 295 GC samples into four key subtypes, namely, Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), genomically stable (GS) and chromosomal instability (CIN) (9). Similarly, the Asian Cancer Research Group (ACRG) analyzed 300 primary GC samples and described four molecular subtypes linked to distinct clinical outcomes and prognoses, namely, MSI, microsatellite stable (MSS) mesenchymal-like type tumors, and TP53-active (MSS/TP53+) and TP53-inactive (MSS/TP53–) (10); furthermore, they differentiated between two distinct molecular subtypes, namely, the mesenchymal phenotype (MP) and the epithelial phenotype (EP). The MP subtype is associated with markedly poor survival and resistance to standard chemotherapy (7). However, multiplex subtypes cannot serve as biomarkers to evaluate the treatment response to immunotherapy or to aid in decisions regarding targeted therapy.

TMB, as measured by WES, has been shown to strongly correlate with objective responses to ICIs in several tumor types (5,11,12), and research has validated the role of TMB as a biomarker for patient selection for immunotherapy (13,14). However, whether TMB is related to the appropriate selection of targeted therapy remains unclear. Moreover, the TMB cutoff points associated with improved survival vary markedly among cancer types. In esophagogastric cancer patients, the TMB cutoff point for the top 20% was approximately 8.8/Mb, although the effect did not reach statistical significance, possibly because of the small sample size, and relevant numerical data have been reported only once (5). Janjigian *et al.* also revealed that three patients with long immunotherapy responses had a high TMB (59.4, 28.3, and 14.2 muts/Mb), and these patients remained alive for 19.5 to 44.7 months following the initiation of immunotherapy despite prior rapid progression while receiving standard chemotherapies (6). In our case report, the TMB of the patient was 50.3 muts/Mb, which is much higher than the cutoff value used to define the top 20%, but the MMR proteins were mismatch-repair proficient. Trastuzumab is assumed to prime antibody-dependent cellular cytotoxicity (ADCC) (15) and is the main antitumor mechanism of trastuzumab (16). Samples with a high TMB have been associated with increased activated natural killer (NK) cells in non-small-cell lung cancer (17). Our findings suggest that a high TMB activates NK cell-mediated GC cell lysis, such as ADCC, which is associated with a favorable response to trastuzumab in the treatment of GC. This study provided the first data on the effectiveness of trastuzumab therapy in a late-stage GC patient with high TMB, pMMR and positive HER2 expression. However, due to the ethical issues with performing a liver biopsy, it has not been possible to compare the molecular pattern between primary tumor and liver metastasis. Moreover, whether GC patient with high TMB and negative HER2 expression would have a favorable response to trastuzumab and whether GC patient with high TMB and mismatch repair-deficient

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(dMMR) GC would experience more benefit than those with pMMR remains to be explored.

Targeting HER2 with trastuzumab is associated with prolonged overall survival and progression-free survival in individuals with HER2-positive AGC (2) and remains an important strategy for the treatment of patients with HER2-positive, metastatic or AGC. However, the value of trastuzumab combined with chemotherapy has rarely been investigated in the perioperative setting. A recent trial reported that a histopathological complete response was achieved in 8.3% and 22.2% of patients with stomach and esophagogastric junction adenocarcinoma, respectively (18,19). Cunningham *et al.* reported that the 5-year survival rate of patients with metastatic GC was approximately 20%, which was less than that for patients who underwent perioperative chemotherapy (36%) (20). The HER2-positive patient with a high TMB described in this report received 12 courses of trastuzumab-based XELOX chemotherapy, and his liver metastasis completely disappeared, providing him with the chance to undergo radical resection; this patient showed a favorable course of disease. His general condition was stable, without comorbidities, and remains alive today. Thus, TMB might be an important biomarker for perioperative targeted therapy.

Recently, studies have suggested that chemotherapy, especially trastuzumab treatment, is associated with a significant loss of HER2 overexpression in breast cancer (21) and GC (22,23). Although these studies suggest the need to reexamine the HER2 status before initiating second-line anti-HER2 treatment, there is disagreement on the prognostic role of the loss of HER2 positivity in patients receiving first-line trastuzumab-based treatment (22,24,25). Therefore, the loss of HER2 expression is not well established as a valid indicator of trastuzumab treatment.

Conclusions

In this case, we report an elderly man with HER2-positive liver metastatic pMMR gastric adenocarcinoma who had a very high TMB and a strong response to trastuzumab therapy, with nearly complete disappearance of the metastasis, providing the patient with the chance to undergo primary lesion resection and significantly prolonging his survival time. We suggest that considering the patient's TMB status can lead to a more accurate prediction of the response to trastuzumab than considering the patient's HER2 status, and trastuzumab therapy should be considered for patients who were previously regarded as unsuitable. Our study provides a new option for maximizing the benefit of trastuzumab therapy in late-stage GC patients. The determination of TMB can allow for a precise identification of the patient population who can potentially benefit from targeted therapy with trastuzumab.

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Footnote

Reporting Checklist: The authors have completed the CARE Reporting Checklist. Available at http://dx.doi.org/10.21037/apm-20-132

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-132). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The patient of this case report agreed and signed consent forms, which are attached to the medical records. Written informed consent was for the purpose of publication of the present case report and any relevant images.

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Supplementary

Table S1 The list of nine highly variable genes in patient revealed by whole-exome analysis

Gene name	Chromosome	Position	dbSNP ID	REF	ALT	ExonicFunc	Gene	AAChange	cytoBand	cosmic82	SIFT
AHNAK2	14	105411781	rs10438247	G	A	Missense SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.C10007T:p.P3336L	14q32.33	ID=COSM432734;OCCURENCE=1(thyroid)	0.014,D
AHNAK2	14	105413223	rs55797226	A	G	Synonymous SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.T8565C:p.D2855D	14q32.33	NA	NA
AHNAK2	14	105414810	rs10145032	C	G	Synonymous SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.G6978C:p.L2326L	14q32.33	NA	NA
AHNAK2	14	105414923	rs200761412	T	C	Missense SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.A6865G:p.K2289E	14q32.33	ID=COSM5438893;OCCURENCE=1(oesophagus)	0.148,T
AHNAK2	14	105417588	rs557610829	G	A	Synonymous SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.C4200T:p.P1400P	14q32.33	ID=COSM4147906;OCCURENCE=1(thyroid)	NA
AHNAK2	14	105417597	rs572861020	T	C	Synonymous SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.A4191G:p.P1397P	14q32.33	ID=COSM4147907;OCCURENCE=1(thyroid)	NA
AHNAK2	14	105417598	rs201134968	G	A	Missense SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.C4190T:p.P1397L	14q32.33	ID=COSM4147908;OCCURENCE=1(thyroid)	0.486,T
AHNAK2	14	105417837	rs76231332	A	G	Synonymous SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.T3951C:p.A1317A	14q32.33	NA	NA
AHNAK2	14	105418264	rs55650155	G	A	Missense SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.C3524T:p.A1175V	14q32.33	ID=COSM4147917;OCCURENCE=1(thyroid),1(large_intestine),1(liver)	1.0,T
AHNAK2	14	105418344	rs55791176	T	G	Missense SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.A3444C:p.E1148D	14q32.33	ID=COSM1368638;OCCURENCE=2(thyroid)	0.765,T
AHNAK2	14	105418391	rs11625007	C	T	Missense SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.G3397A:p.V1133I	14q32.33	ID=COSM1368639;OCCURENCE=2(central_nervous_system),1(lung),1(thyroid)	1.0,T
AHNAK2	14	105419243	NA	C	T	Missense SNV	*NM_138420*	AHNAK2:NM_138420:exon7:c.G2545A:p.G849S	14q32.33	NA	0.446,T
MUC4	3	195489009	rs2246901	C	A	Missense SNV	*NM_004532,NM_018406,NM_138297*	MUC4:NM_138297:exon12:c.G1600T:p.A534S,MUC4:NM_004532:exon13:c.G1753T:p.A585S,MUC4:NM_018406:exon14:c.G14461T:p.A4821S	3q29	ID=COSM4157536,COSM4157534,COSM4157535;OCCURENCE=2(thyroid)	0.241,T
MUC4	3	195489067	rs2246980	C	G	Synonymous SNV	*NM_004532,NM_018406,NM_138297*	MUC4:NM_138297:exon12:c.G1542C:p.S514S,MUC4:NM_004532:exon13:c.G1695C:p.S565S,MUC4:NM_018406:exon14:c.G14403C:p.S4801S	3q29	ID=COSM1421868,COSM1421867,COSM1421869;OCCURENCE=1(large_intestine)	NA
MUC4	3	195510762	rs2911273	G	A	Synonymous SNV	*NM_018406*	MUC4:NM_018406:exon2:c.C7689T:p.V2563V	3q29	ID=COSM149590,COSM149589;OCCURENCE=3(large_intestine),1(thyroid),1(upper_aerodigestive_tract),3(central_nervous_system),1(stomach),1(kidney)	NA
MUC4	3	195512446	rs550380149	G	A	Missense SNV	*NM_018406*	MUC4:NM_018406:exon2:c.C6005T:p.P2002L	3q29	NA	0.032,D
MUC4	3	195512597	rs6799339	G	A	Missense SNV	*NM_018406*	MUC4:NM_018406:exon2:c.C5854T:p.P1952S	3q29	ID=COSM4157817,COSM1042915;OCCURENCE=1(endometrium),2(central_nervous_system),15(upper_aerodigestive_tract),4(thyroid),2(large_intestine),2(haematopoietic_and_lymphoid_tissue),2(prostate)	0.14,T
MUC4	3	195513063	NA	G	A	Synonymous SNV	*NM_018406*	MUC4:NM_018406:exon2:c.C5388T:p.T1796T	3q29	NA	NA
MUC4	3	195513345	rs71321841	A	C	Synonymous SNV	*NM_018406*	MUC4:NM_018406:exon2:c.T5106G:p.V1702V	3q29	ID=COSM4002588,COSM4002587;OCCURENCE=2(haematopoietic_and_lymphoid_tissue),2(large_intestine),2(thyroid),1(upper_aerodigestive_tract)	NA
MUC4	3	195515008	rs201451131	C	G	Missense SNV	*NM_018406*	MUC4:NM_018406:exon2:c.G3443C:p.G1148A	3q29	ID=COSM1485032,COSM4591321;OCCURENCE=3(central_nervous_system),17(upper_aerodigestive_tract),1(prostate)	1.0,T
MUC4	3	195517321	rs1104760	G	A	Missense SNV	*NM_018406*	MUC4:NM_018406:exon2:c.C1130T:p.T377I	3q29	ID=COSM4005514,COSM4005515;OCCURENCE=1(urinary_tract)	1.0,T
SULT1A1	16	28617507	rs41278160	C	T	Synonymous SNV	*NM_001055,NM_177529,NM_177530,NM_177534,NM_177536*	SULT1A1:NM_177536:exon5:c.G411A:p.L137L,SULT1A1:NM_177534:exon6:c.G645A:p.L215L,SULT1A1:NM_001055:exon7:c.G645A:p.L215L,SULT1A1:NM_177529:exon7:c.G645A:p.L215L,SULT1A1:NM_177530:exon7:c.G645A:p.L215L	16p11.2	ID=COSM4415626,COSM4415625;OCCURENCE=2(soft_tissue),1(liver),1(large_intestine),1(thyroid),1(breast),2(haematopoietic_and_lymphoid_tissue)	NA
SULT1A1	16	28617572	rs117124912	G	A	Unknown	*NM_001055,NM_177529,NM_177530,NM_177534,NM_177536*	unknown	16p11.2	ID=COSN26728343;OCCURENCE=1(breast)	NA
SULT1A1	16	28618237	rs9282862	T	C	Unknown	*NM_001055,NM_177529,NM_177530,NM_177534,NM_177536*	unknown	16p11.2	ID=COSN17140510,COSN17144487,COSN17146316,COSN17133335,COSN17139650,COSN26727881,COSN17148089,COSN17141357,COSN17147203,COSN17135963,COSN17136811,COSN17135064,COSN17145383,COSN17152807,COSN17149916;OCCURENCE=14(soft_tissue),1(breast)	NA
SULT1A1	16	28618446	rs2925623	T	C	Unknown	*NM_001055,NM_177529,NM_177530,NM_177534,NM_177536*	unknown	16p11.2	ID=COSN17149917,COSN17136812,COSN17135964,COSN17145384,COSN17135065,COSN17133336,COSN17152808,COSN17147204,COSN17140511,COSN17139651,COSN17148090,COSN26728421,COSN17146317,COSN16516 1,COSN17144488,COSN17141358;OCCURENCE=14(soft_tissue),1(breast),1(stomach)	NA
SULT1A1	16	28618469	rs376487988	A	T	Unknown	*NM_001055,NM_177529,NM_177530,NM_177534,NM_177536*	unknown	16p11.2	ID=COSN15330618,COSN26728685,COSN19667205,COSN20345033;OCCURENCE=1(haematopoietic_and_lymphoid_tissue),1(breast),2(large_intestine)	NA
SULT1A1	16	28618636	rs3020804	A	G	Unknown	*NM_001055,NM_177529,NM_177530,NM_177534,NM_177536*	unknown	16p11.2	ID=COSN26732151,COSN19708983;OCCURENCE=1(breast),1(large_intestine)	NA
SULT1A1	16	28619911	rs1126447	T	C	Synonymous SNV	*NM_001055,NM_177529,NM_177530,NM_177534*	SULT1A1:NM_177534:exon2:c.A162G:p.V54V,SULT1A1:NM_001055:exon3:c.A162G:p.V54V,SULT1A1:NM_177529:exon3:c.A162G:p.V54V,SULT1A1:NM_177530:exon3:c.A162G:p.V54V	16p11.2	ID=COSM148063;OCCURENCE=1(haematopoietic_and_lymphoid_tissue),1(breast),13(soft_tissue),1(stomach)	NA
SULT1A1	16	28619920	rs1126446	A	G	Synonymous SNV	*NM_001055,NM_177529,NM_177530,NM_177534*	SULT1A1:NM_177534:exon2:c.T153C:p.T51T,SULT1A1:NM_001055:exon3:c.T153C:p.T51T,SULT1A1:NM_177529:exon3:c.T153C:p.T51T,SULT1A1:NM_177530:exon3:c.T153C:p.T51T	16p11.2	ID=COSM148064;OCCURENCE=1(stomach),13(soft_tissue),1(haematopoietic_and_lymphoid_tissue),1(breast),1(large_intestine)	NA
SULT1A1	16	28620120	rs34513973	C	T	Synonymous SNV	*NM_001055,NM_177529,NM_177530,NM_177534*	SULT1A1:NM_177534:exon1:c.G57A:p.P19P,SULT1A1:NM_001055:exon2:c.G57A:p.P19P,SULT1A1:NM_177529:exon2:c.G57A:p.P19P,SULT1A1:NM_177530:exon2:c.G57A:p.P19P	16p11.2	ID=COSM3754830;OCCURENCE=1(haematopoietic_and_lymphoid_tissue),1(liver),1(large_intestine),4(soft_tissue)	NA
NBPF1	1	16890417	NA	T	G	Unknown	*NM_017940*	unknown	1p36.13	NA	NA
NBPF1	1	16890441	rs3863779	C	T	Unknown	*NM_017940*	UNKNOWN	1p36.13	ID=COSN17908214,COSN19726322,COSN20442428,COSN9365785;OCCURENCE=1(skin),2(large_intestine),1(kidney)	NA
NBPF1	1	16890484	rs12117084	G	C	Unknown	*NM_017940*	UNKNOWN	1p36.13	ID=COSN26856318,COSN17907833,COSN26856984,COSN20442427,COSN19670624,COSN26860000;OCCURENCE=1(skin),2(large_intestine),3(thyroid)	NA
NBPF1	1	16892282	rs202078823	C	A	Unknown	*NM_017940*	UNKNOWN	1p36.13	ID=COSN19624539,COSN20280143,COSN20401972,COSN23914604;OCCURENCE=1(large_intestine),3(haematopoietic_and_lymphoid_tissue)	NA
NBPF1	1	16893598	rs927016856	G	A	Unknown	*NM_017940*	unknown	1p36.13	ID=COSN1091962;OCCURENCE=1(liver)	NA
NBPF1	1	16903026	rs3897291	C	A	Unknown	*NM_017940*	unknown	1p36.13	ID=COSN8861695,COSN15653441;OCCURENCE=1(haematopoietic_and_lymphoid_tissue),1(upper_aerodigestive_tract)	NA
NBPF1	1	16907164	rs201839566	C	T	Unknown	*NM_017940*	unknown	1p36.13	ID=COSN19749507,COSN15655724,COSN19700541,COSN19629792;OCCURENCE=1(haematopoietic_and_lymphoid_tissue),1(upper_aerodigestive_tract),2(large_intestine)	NA
NBPF1	1	16918411	rs199725761	T	C	Unknown	*NM_017940*	UNKNOWN	1p36.13	ID=COSN19740211;OCCURENCE=1(large_intestine)	NA
ABO	9	136131188	rs8176749	C	T	Unknown	*NM_020469*	UNKNOWN	9q34.2	NA	NA
ABO	9	136131315	rs8176747	C	G	Unknown	*NM_020469*	UNKNOWN	9q34.2	ID=COSM3952439;OCCURENCE=1(lung)	NA
ABO	9	136131322	rs8176746	G	T	Unknown	*NM_020469*	UNKNOWN	9q34.2	NA	NA
ABO	9	136131415	rs8176743	C	T	Unknown	*NM_020469*	UNKNOWN	9q34.2	NA	NA
ABO	9	136131461	rs8176741	G	A	Unknown	*NM_020469*	UNKNOWN	9q34.2	NA	NA
ABO	9	136131592	rs7853989	G	C	Unknown	*NM_020469*	UNKNOWN	9q34.2	NA	NA
ABO	9	136132754	rs8176722	C	A	Unknown	*NM_020469*	unknown	9q34.2	NA	NA
MST1L	1	17084086	rs749078168	A	G	Missense SNV	*NM_001271733*	MST1L:NM_001271733:exon14:c.T1835C:p.I612T	1p36.13	NA	NA
MST1L	1	17084152	rs202123117	C	T	Missense SNV	*NM_001271733*	MST1L:NM_001271733:exon14:c.G1769A:p.G590D	1p36.13	ID=COSM1317624;OCCURENCE=1(large_intestine),2(upper_aerodigestive_tract),1(haematopoietic_and_lymphoid_tissue),1(breast),3(central_nervous_system)	NA
MST1L	1	17085046	rs200838083	C	G	Missense SNV	*NM_001271733*	MST1L:NM_001271733:exon11:c.G1429C:p.D477H	1p36.13	ID=COSM1491885,COSM1491886;OCCURENCE=1(thyroid),1(large_intestine),2(pancreas),1(kidney)	NA
MST1L	1	17086236	rs61769737	G	C	Unknown	*NM_001271733*	unknown	1p36.13	ID=COSN15107201,COSN19643620,COSN19618339;OCCURENCE=2(haematopoietic_and_lymphoid_tissue),1(oesophagus)	NA
MST1L	1	17086273	NA	T	A	Unknown	*NM_001271733*	unknown	1p36.13	ID=COSN20838787,COSN21670862;OCCURENCE=2(breast)	NA
MST1L	1	17087432	rs2446554	G	T	Unknown	*NM_001271733*	unknown	1p36.13	ID=COSN19672857;OCCURENCE=1(large_intestine)	NA
ZNF718	4	53310	rs761021532	C	T	Unknown	*NM_001039127,NM_001286052,NM_001286053,NM_001286054,NM_182524*	unknown	4p16.3	NA	NA
ZNF718	4	53360	rs75858144	C	G	Unknown	*NM_001039127,NM_001286052,NM_001286053,NM_001286054,NM_182524*	unknown	4p16.3	ID=COSN26958394;OCCURENCE=1(lung)	NA
ZNF718	4	59350	rs1045387254	A	G	Missense SNV	*NM_001039127,NM_001286052,NM_182524*	ZNF718:NM_001039127:exon2:c.A31G:p.I11V	4p16.3	ID=COSM3760687;OCCURENCE=2(large_intestine),1(thyroid),1(liver),1(adrenal_gland),1(prostate)	0.15,T
ZNF718	4	59469	rs6834940	A	G	Unknown	*NM_001039127,NM_001286052,NM_001286053,NM_001286054,NM_001289931,NM_182524*	unknown	4p16.3	ID=COSN19749630,COSN26670632,COSN19766576,COSN26679945;OCCURENCE=2(liver),2(large_intestine)	NA
ZNF718	4	60210	rs3908749	G	A	Unknown	*NM_001039127,NM_001286052,NM_001286053,NM_001286054,NM_001289931,NM_182524*	unknown	4p16.3	ID=COSN19615617,COSN20466351,COSN19695458,COSN17001606,COSN20335714,COSN19746410,COSN19618066,COSN20279079;OCCURENCE=4(large_intestine),1(prostate),3(haematopoietic_and_lymphoid_tissue)	NA
ZNF718	4	67801	rs77175674	C	T	Unknown	*NM_001039127,NM_001286052,NM_001286053,NM_001286054,NM_001289931,NM_182524*	unknown	4p16.3	ID=COSN19699753,COSN19751413;OCCURENCE=2(large_intestine)	NA
MUC12	7	100635014	rs542320663	C	T	Synonymous SNV	*NM_001164462*	MUC12:NM_001164462:exon2:c.C1170T:p.H390H	7q22.1	NA	NA
MUC12	7	100635205	rs4729631	C	T	Missense SNV	*NM_001164462*	MUC12:NM_001164462:exon2:c.C1361T:p.A454V	7q22.1	ID=COSM4004183,COSM4004182;OCCURENCE=2(haematopoietic_and_lymphoid_tissue)	0.044,D
MUC12	7	100637193	rs10247974	C	A	Missense SNV	*NM_001164462*	MUC12:NM_001164462:exon2:c.C3349A:p.P1117T	7q22.1	ID=COSM4004188,COSM4004189;OCCURENCE=1(haematopoietic_and_lymphoid_tissue),1(thyroid),6(upper_aerodigestive_tract)	0.0,D
MUC12	7	100638828	rs56914801	C	T	Missense SNV	*NM_001164462*	MUC12:NM_001164462:exon2:c.C4984T:p.P1662S	7q22.1	ID=COSM4004198,COSM4004197;OCCURENCE=2(haematopoietic_and_lymphoid_tissue),2(thyroid)	0.237,T
MUC12	7	100646938	rs199993063	C	G	Missense SNV	*NM_001164462*	MUC12:NM_001164462:exon2:c.C13094G:p.T4365R	7q22.1	NA	0.0,D
MUC12	7	100647073	rs140284525	C	T	Missense SNV	*NM_001164462*	MUC12:NM_001164462:exon2:c.C13229T:p.T4410M	7q22.1	ID=COSM4004202,COSM4004201;OCCURENCE=2(upper_aerodigestive_tract),2(haematopoietic_and_lymphoid_tissue)	0.003,D
MUC16	19	9024994	rs67631215	C	T	Missense SNV	*NM_024690*	MUC16:NM_024690:exon16:c.G36868A:p.E12290K	19p13.2	ID=COSM148476;OCCURENCE=1(NS),1(haematopoietic_and_lymphoid_tissue),1(breast),1(stomach)	0.044,D
MUC16	19	9059159	rs12462651	T	G	Missense SNV	*NM_024690*	MUC16:NM_024690:exon3:c.A28287C:p.K9429N	19p13.2	ID=COSM4419540,COSM4419541;OCCURENCE=1(large_intestine),1(haematopoietic_and_lymphoid_tissue)	0.013,D
MUC16	19	9060656	rs2216663	C	T	Synonymous SNV	*NM_024690*	MUC16:NM_024690:exon3:c.G26790A:p.E8930E	19p13.2	ID=COSM148481,COSM148479,COSM148480;OCCURENCE=1(haematopoietic_and_lymphoid_tissue),1(stomach)	.
MUC16	19	9061454	NA	C	A	Missense SNV	*NM_024690*	MUC16:NM_024690:exon3:c.G25992T:p.L8664F	19p13.2	NA	0.164,T
MUC16	19	9062847	rs79203775	A	G	Missense SNV	*NM_024690*	MUC16:NM_024690:exon3:c.T24599C:p.I8200T	19p13.2	NA	0.003,D
MUC16	19	9080462	rs2547065	C	G	Missense SNV	*NM_024690*	MUC16:NM_024690:exon2:c.G9569C:p.S3190T	19p13.2	NA	1.0,T