Mutations in the homologous recombination (HR) pathway in 13 cancer types

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Abstract #1589

Background: The HR pathway is important in DNA double-strand break repair. HR defects promote carcinogenesis and are associated with selective sensitivity to PARP-inhibitors and DNA-damaging agents like platinum.

Method: We used next-generation sequencing (NGS) to survey genes in the HR pathway in 1029 tumors in 13 cancer types. NGS on 591 genes was performed using formalin-fixed paraffin-embedded samples on the Illumina NextSeq platform (Caris Life Sciences, AZ). All variants were detected with > 99 % confidence and with the analytical sensitivity of 5%. Deletions larger than 27bp may not be detected by this method. Pathogenic or presumed pathogenic variants are counted as mutations.

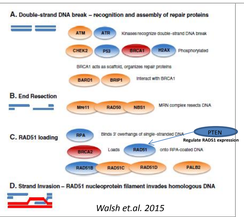
Results: The table shows mutation rates of 7 key HR genes (ATM, BRCA1, BRCA2, CHEK1, CHEK2, PALB2 and PTEN) included in this pilot study. Analysis of 17 additional HR genes (ATR, ATRX, BARD1, BLM, BRIP1, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, MRE11A, NBN, RAD50, RAD51, RAD51B) is ongoing. PTEN mutations were seen in 6.3% of tumors, ATM in 5%, BRCA1 in 2%, BRCA2 in 2%, PALB2 in 1% and CHEK2 in 1%. CHEK1 mutations were not seen in this cohort. Overall, 15% of tumors carry one or more mutations of the 7 genes, and the highest mutation rates were seen in endometrial (43%), GBM (34%) and gastric cancers (23%). The highest rates of ATM, BRCA2 and PALB2 mutations were seen in gastric cancer while the highest rates of CHEK2, BRCA1 and PTEN mutations were seen in cholangiocarcinoma, ovarian and endometrial tumors, respectively. Tumor profiling on the biopsy of a 53-year old patient with metastatic poorly-differentiated adenocarcinoma of the stomach revealed a PALB2 nonsense mutation (S326*). Other HRD genes were wild type and ERCC1 IHC showed intact expression. The patient was given 4 cycles of FOLFOX without surgery and achieved ongoing radiographic partial response and a dramatic relief of symptoms.

Conclusions: Thus, mutation rates of at least 8 to 43% in the HR pathway are reported from 13 cancer types. This method can potentially identify responders to DNA-damaging agents including platinum.

	ATM	BRCA1	BRCA2	CHEK1	CHEK2	PALB2	PTEN	Any of 7
Endometrial (N=35)	3%	0	0	0	2.9%	3.0%	44.1%	42.9%
GBM (N=47)	2.1%	2.1%	0	0	0	0	32.6%	36.2%
Gastric (N=31)	9.7%	0	6.5%	0	0	6.5%	0	22.6%
Bladder (N=38)	2.6%	0	5.4%	0	0	0	10.8%	18.4%
Kidney (N=41)	2.5%	0	0	0	5.0%	0	10.0%	17.1%
Ovarian (N=82)	3.7%	7.3%	1.2%	0	1.2%	0	1.3%	14.6%
Breast (N=108)	4.6%	2.8%	1.9%	0	0.9%	1.0%	3.8%	13.9%
Cholangiocarcinoma (N=36)	5.6%	0	2.8%	0	5.6%	0	2.9%	16.7%
CRC (N=254)	6.3%	2.0%	2.0%	0	0.4%	0	4.0%	13.0%
Pancreatic (N=62)	4.8%	1.6%	3.2%	0	0	1.7%	3.3%	12.9%
NSCLC (N=234)	8.2%	0	1.7%	0	0	1.4%	2.6%	11.9%
Neuroendocrine (N=35)	2.9%	0	0	0	0	0	5.7%	8.6%
Esophageal (N=26)	3.8%	0	0	0	0	0	4.0%	7.7%
Overall (N=1029)	5.0%	1.6%	1.6%	0	0.8%	0.8%	6.3%	15.2%

Background:

Homologous recombination is a high-fidelity, error-free pathway for double stranded DNA repair that involves multiple critical proteins involved in break recognition, end resection, RAD51 loading and strand invasion, etc (figure). When defects occur in HR, double-stranded DNA break repair relies on an error-prone mechanism NHEJ (non-homologous end joining) and can lead to genetic instability. Emerging clinical data have shown that PARP-inhibitors that can lead to synthetic lethality in HR-impaired tumors and DNA-damaging agents including platinums have improved clinical activity in patients carrying defects on the HR pathway.



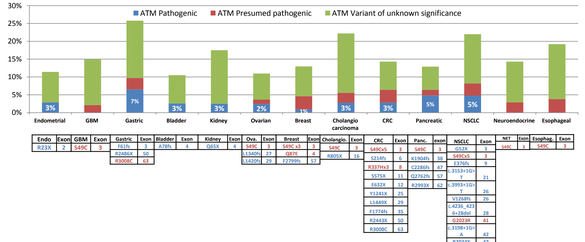
Walsh et.al. 2015

Results:

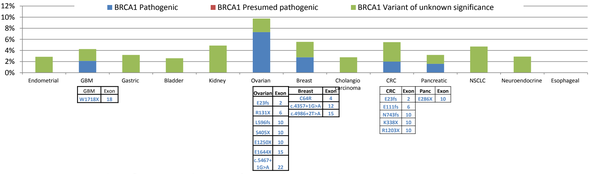
1. Number (N) of tumors from 13 cancer types included in the analysis.

Cancer type	Endometrial	GBM	Gastric	Bladder	Kidney	Ovarian	Breast	Cholangio carcinoma	CRC	Pancreatic	NSCLC	Neuroendocrine	Esophageal
N	35	47	31	38	41	82	108	36	254	62	234	35	26

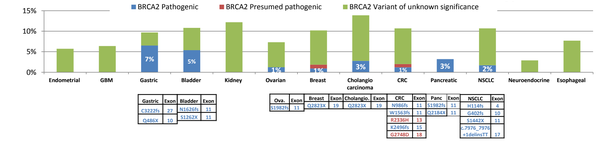
2. ATM mutation frequencies in 13 cancer types. Protein changes that are pathogenic or presumed pathogenic are listed for each cancer type.



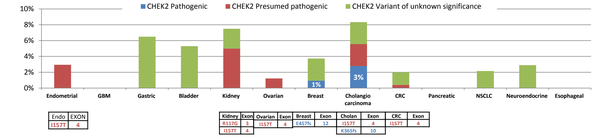
3. BRCA1 mutation frequencies. Pathogenic mutations were seen in 5 cancer types.



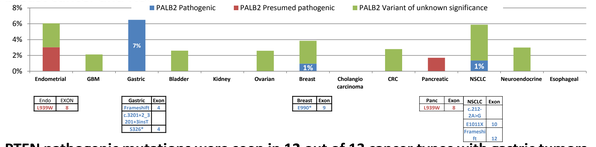
4. BRCA2 mutation frequencies. Pathogenic mutations were seen 8 cancer types.



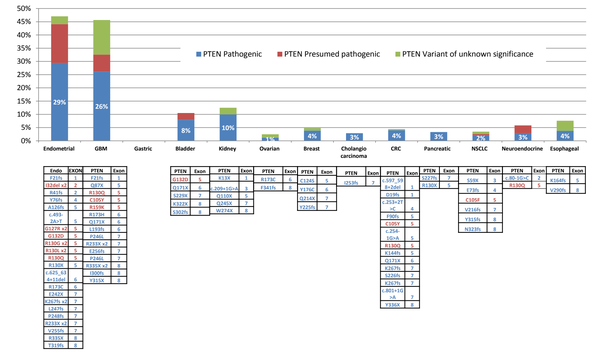
5. No pathogenic or presumed pathogenic CHEK1 mutations were seen in the cohorts studied. CHEK2 mutation frequencies are listed.



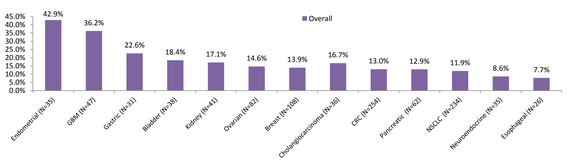
6. PALB2 pathogenic mutations are seen in over 5% of gastric tumors, and in 1% or more in breast cancer and NSCLC.



7. PTEN pathogenic mutations were seen in 12 out of 13 cancer types with gastric tumors absent of PTEN mutations.



8. Frequency of tumors carrying at least one aberration in 7 key genes in the HR pathway (pathogenic and presumed pathogenic only).



9. Case report (*adapted from Colton et.al. 2016 with permission)*

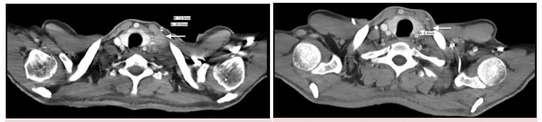


Figure 8A: Transverse CT image taken from Patient 1 before treatment. This image shows a left supraclavicular adenopathy measuring 1.4x2.0cm.

Figure 8B: Transverse CT image taken from Patient 1 after four cycles of FOLFOX. This image shows that the left supraclavicular node decreased to 0.8x0.6cm from 1.4x2.0cm.

A 53-yr old man with newly diagnosed metastatic poorly-differentiated adenocarcinoma of the stomach reported abdominal and back pain, decreased appetite, weight loss, and fatigue. Upper endoscopy showed a large gastric mass. CT scan showed extensive mesenteric lymphadenopathy and periaortic adenopathy, measuring 1.4 x 2.0 cm (figure A) and a retrocaval lymph mode measuring 3.0x1.6cm. The patient was treated with four cycles of FOLFOX. A restaging CT scan showed a significant interval decrease in disease burden, with a marked decrease in the size of the primary gastric mass and complete resolution of previously documented infiltration of adjacent fat, peritoneal nodule, and mesenteric lymphadenopathy. The left periaortic node decreased to 0.8 x 0.6 cm(figure B) and the retrocaval lymph node to 1.2 x 0.7 cm. Clinically, drastic relief of symptoms was reported.

Posthoc tumor profiling analysis by IHC and sequencing revealed intact expression of DNA repair pathway genes including ERCC1 (2+, 65%) and PTEN (1+, 100%). NextGen sequencing (Illumina NextSeq; an Agilent custom-designed SureSelect XT assay on 591 whole-gene targets) revealed a truncating mutation on PALB2 (S326*), in addition to c.3201+2_3201+3insT. No mutations were seen in other genes on the HR pathway. It's therefore likely that the PALB2 mutation in the tumor of the patient led to the loss of function of PALB2 and the observed outstanding response to oxaliplatin-based chemotherapy.

Conclusions

1. Mutations in 7 key genes in the homologous recombination pathway are detailed in 13 cancer types on a total of 1029 tumors.
2. Overall, ATM and PTEN mutations are the most prevalent among the 7 genes considered on the HR pathway.
3. Deleterious ATM mutations were seen in gastric, pancreatic, NSCLC at frequencies higher than 5%; the highest BRCA1 deleterious mutations was seen in ovarian cancer (7%) and BRCA2 in Gastric (7%) and bladder (5%); a high mutation rate of PALB2 (7%) was noted in gastric cancer.
4. A case report in gastric cancer suggests that a complete investigation of the HR pathway mutations can potentially identify outstanding responders for DNA-damaging agents including platinum.
5. Investigation into the other genes on the pathway and research into epigenetic changes of select genes will further strengthen the study.
6. Our study provides important information for clinical trials investigating activities of PARP inhibitors in various cancer types.

References

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