A Survey of Cancer Somatic Mutations in the HLA Region

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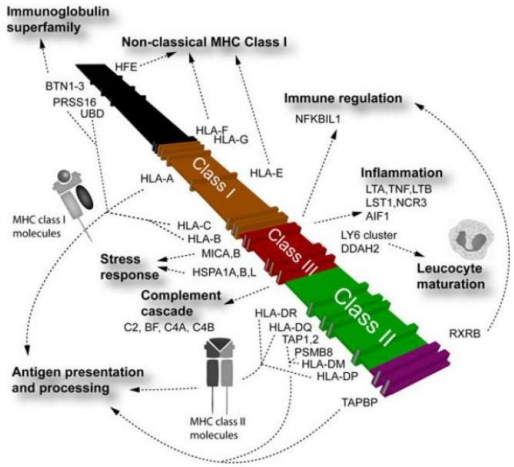
BACKGROUND

Are there cancer susceptibility genes in the HLA region?

If there are, are they HLA genes or non-HLA genes?

By what mechanism, is HLA-linked cancer susceptibility mediated?



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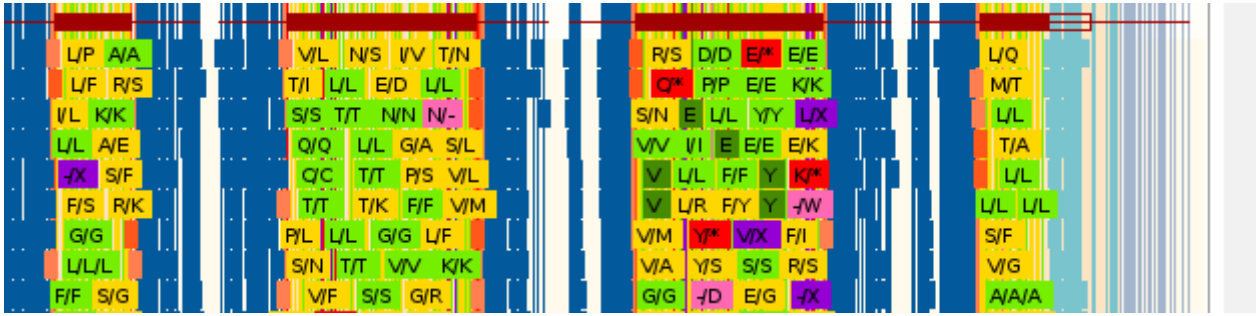
AIM

To gain insight into the involvement of HLA region sequence variants in cancer susceptibility by screening the occurrence of natural polymorphisms in cancer genomes.



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METHODS

We screened germline variants of the HLA region (chr6:28.5 to 34.5Mb; hg19) to examine their occurrence in cancer genomes as somatic mutations.

We obtained the germline variants from Ensembl (n~285K), and screened the COSMIC database for their presence in cancer genomes using SNPnexus.

SNPnexus

COSMIC
Catalogue of somatic mutations in cancer

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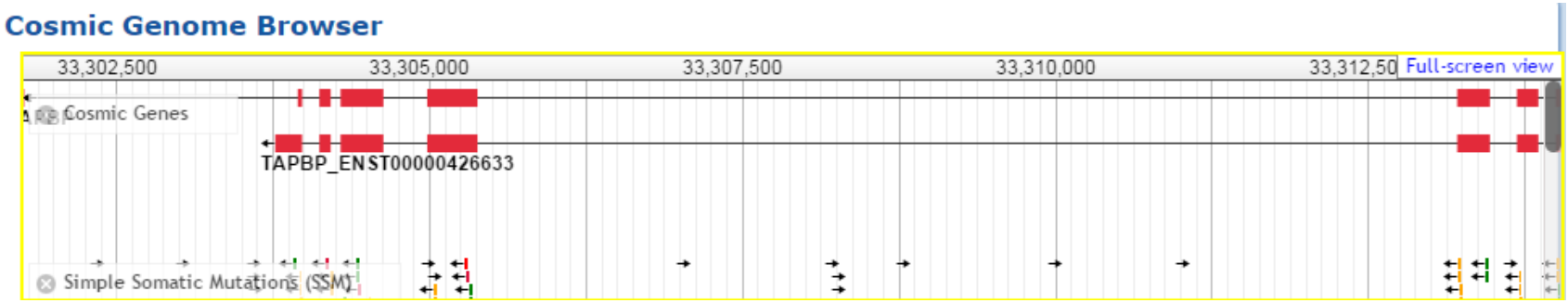
RESULTS

660 of ~285K germline SNPs are detected in 747 cancer samples as somatic mutations.

1	SNP	Mutation ID	Tumor Sample ID	Site	Symbol
18	rs1064944	1443637	TCGA-AZ-5403-01	large_intestine	HLA-DQA1
19	rs1064944	1443637	TCGA-CK-4948-01	large_intestine	HLA-DQA1
20	rs1064944	1443637	TCGA-CM-4743-01	large_intestine	HLA-DQA1
21	rs1064944	1443637	TCGA-CM-5341-01	large_intestine	HLA-DQA1
22	rs1064944	1443637	TCGA-CM-5348-01	large_intestine	HLA-DQA1
23	rs1064944	1443637	TCGA-DC-6157-01	large_intestine	HLA-DQA1
24	rs1064944	1443637	TCGA-DY-A1DC-01	large_intestine	HLA-DQA1
25	rs1064944	1443637	TCGA-G4-6304-01	large_intestine	HLA-DQA1



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RESULTS

Most (n=248) of the 660 SNPs detected as cancer somatic mutations were missense SNPs, with 36 located in the HLA-A, -B, -C, -DRA/DRB1, or -DQA1/DQB1 genes.

When all missense, nonsense and frameshift mutations were considered, HLA-A had the highest number of them followed by MUC21 and HLA-C.

HLA-A	33
MUC21	23
HLA-C	20
HLA-DRB1	18
TNXB	15
ITPR3	14

RESULTS

Only few were assessed as possibly damaging by PolyPhen or SIFT.

Overall, 28.6% of the SNPs were highly deleterious (in the top one percentile in the genome), and likely to be driver mutations as assessed by CADD scores (>20; overall median=13.7, as compared to median CADD score of 7.0 for missense mutations).

RESULTS

Genes with recurrent mutations and highest mean CADD scores did notinclude classical HLA genes high on the list.

Gene	n	Mean CADD	Min CADD
SCAND3	6	23.7	8.8
EHMT2	3	22.3	21.1
TAPBP	5	22.2	9.7
DHX16	6	22.2	12.7
VARS/VARS2	15	22.6	6.1
DDR1	9	21.5	11.6
MSH5	5	21.3	19.3
PSMB8/PSMB9	5	20.2	15.7
.....	.	...	...
HLA-A	16	11.8	0.32
HLA-DRB1	16	8.4	0.001
HLA-C	8	8.5	0.002

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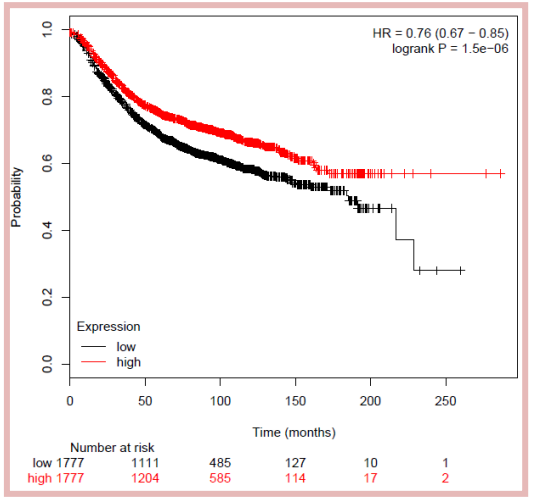
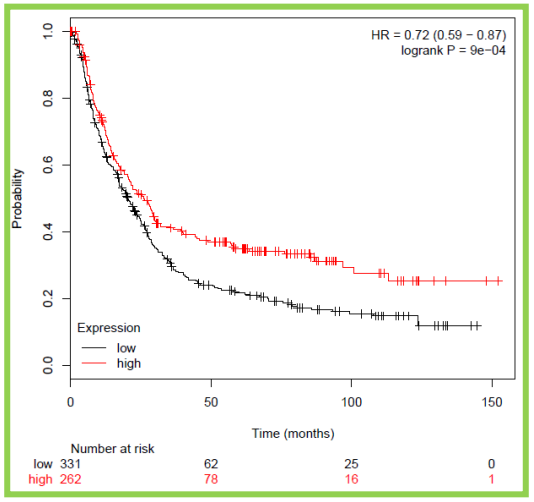
RESULTS

The HLA region genes most deleteriously mutated in cancer consisted of antigen processing pathway genes TAP1/TAP2/TAPBP and PSMB8/PSMB9, and cancer-related genes MSH5 and DDR1.

Of these, TAPBP expression showed a correlation with breast and gastric cancer survival in the Kaplan-Meier Plotter (*P*<9E-04).





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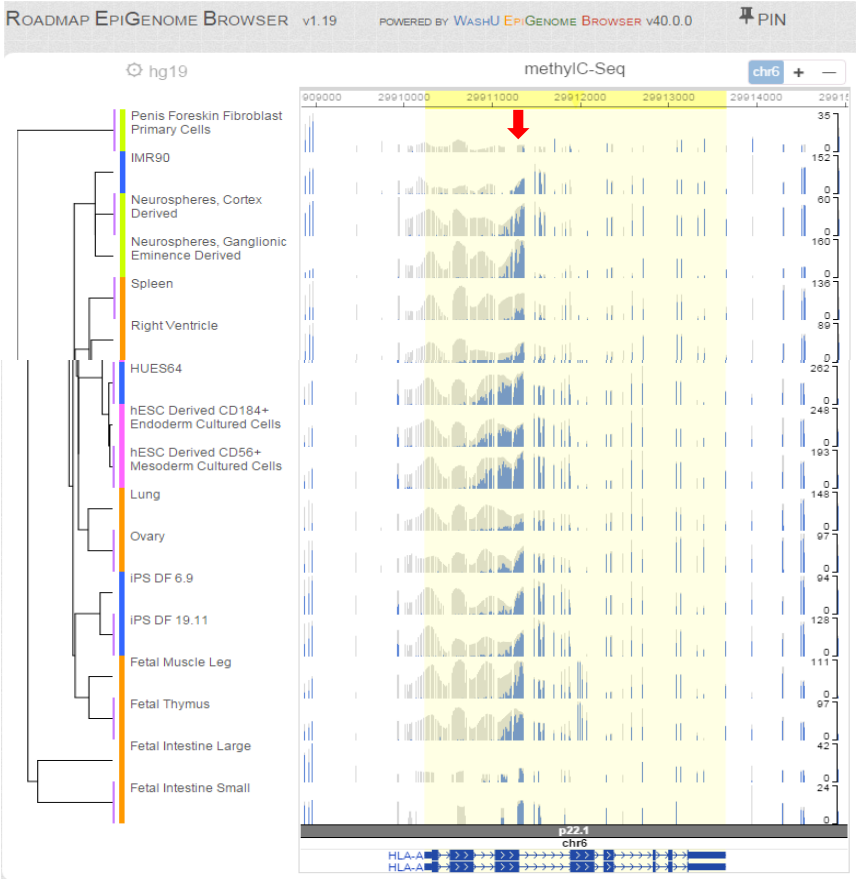
RESULTS

32 SNPs were contained within the CpG island cg00082981 located within HLA-A.



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RESULTS

HLA-A was also the classical HLA gene with the highest number of mutations along with -DRB1, with HLA-A mutations ranking more deleterious.

	HLA-A	HLA-DRB1
Number of total mutations	53	30
Number of ms/ns/fs mutations	33	18
Mean CADD score	11.8	8.4

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RESULTS

None of the 660 SNPs were in the GWAS catalog for a cancer association.

GRASP analysis revealed associations with lung, cervical, and nasopharyngeal cancer (*P*<5x10E-08). At the statistical threshold of *P*<10E-04, there were further lung and breast cancer associations.

SNP ID	P value	Phenotype	Chr	Pos	In Gene	PMID
rs3749971	1.50E-09	Lung cancer	6	29374998	(OR12D3)	22899653
rs29230	1.30E-12	Nasopharyngeal carcinoma	6	29608616	(GABBR1)	20512145
rs7750641	2.40E-11	Lung cancer	6	31161533	(TCF19)	22899653
rs7750641	7.00E-05	Lung cancer	6	31161533	(TCF19)	18978790
rs1129640	1.50E-08	Cervical cancer	6	31538847	(DDX39B)	23482656
rs3130618	1.70E-06	Lung cancer	6	31664357	(GPANK1)	19836008
rs3134942	7.20E-08	Lung cancer	6	32200994	(NOTCH4)	19836008
rs144861747	1.20E-04	Breast cancer	6	32980608	(BRD2)	23555315

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RESULTS

HLA Region Genes in Cancer Gene Databases

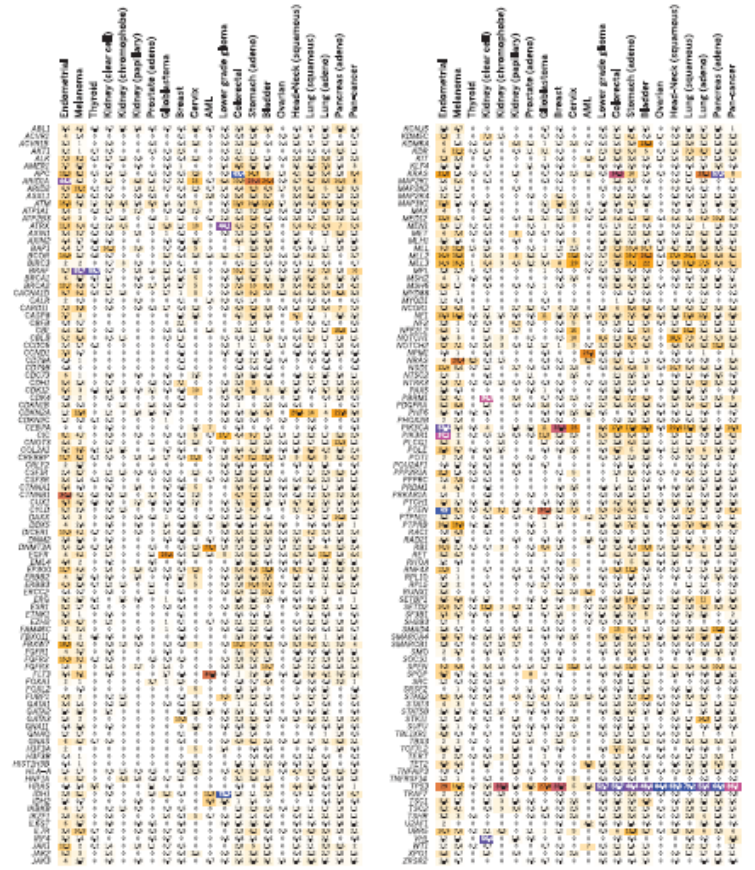

Fig. 2. Frequency of mutations in recurrently mutated cancer genes across tumor types. This reference table summarizes the percentage of patients carrying a nonsynonymous coding substitution or small indel in each gene. Data are from TCGA and are visualized as in (60). Different colors emphasize the frequency of mutations. The list of 198 cancer genes corresponds to all genes in the curated list of 174 mutated genes from the COSMIC database (version 73) (26) and any Cancer Gene Census database gene found recurrently mutated in (59).

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	Endometrial	Melanoma	Thyroid	Kidney (clear cell)	Kidney (chromophobe)	Kidney (papillary)	Prostate (adeno)	Glioblastoma	Breast	Cervix	AML	Lower grade glioma	Colorectal	Stomach (adeno)	Bladder	Ovarian	Head-Neck (squamous)	Lung (squamous)	Lung (adeno)	Pancreas (adeno)	Pan-cancer
ABL1	3.6	4.1	0.2	0.7	1.5	1.8	0.5	0.7	0.6	2.5	0.7	0.5	2.3	3.6	3.8	0	0.3	1.7	1.2	5.3	1.4
ACVR1	4	1.4	0	0	0	0	0	0	0.1	0	0	0.5	0.8	1.8	0	0.9	1.6	0	1.3	0	0.7
ACVR1B	3.2	1	0	0.9	0	0	0.5	0	0.6	2.5	0	0.9	2.3	3.9	0.6	0.4	1.3	1.7	1.7	1.8	1.2
AKT1	3.2	1	0.7	0.5	0	0	0.5	0.3	2.5	0	0	0.5	2.1	1.1	0	0	0.6	0.6	0.6	3.5	1.1
ALK	7.3	8.1	0.2	1.7	1.5	0.9	0	0.3	0.4	2.5	0	0.5	4.1	3.9	1.3	0.4	2.8	2.2	5.8	1.8	2.5
AMER1	7.7	5.7	0	0.7	0	0.9	0	0.3	1	0	0	1.4	8.5	5.7	1.9	0	3.1	4.5	7.3	1.8	3
APC	13.3	8.1	0.5	1.4	1.5	0	0.5	0.3	0.5	7.5	0	0.9	69.4	14.3	5	1.3	4.1	3.9	5.4	1.8	8.4
ARID1A	44.8	4.1	0	3.1	0	4.5	1.6	0.7	2.1	15	0.7	6.4	10.9	29.4	26.4	0.9	4.7	6.7	8.5	10.5	8
HLA–A	1.6	1.7	0	0.9	1.5	0.9	0.5	0	0.5	2.5	0	0.5	4.7	3.9	5	0.4	4.7	3.9	1.9	3.5	1.8
HNF1A	4	3.7	0	0	4.5	1.8	0.5	0.7	1.2	0	0	0	3.1	3.6	1.3	0	0	1.7	0.8	1.8	1.3
HRAS	0.4	1.4	3.5	0.2	0	0	1.1	0	0	0	0	0	0.3	0	4.4	0	4.4	2.8	0.2	1.8	1
IDH1	2.8	5.1	0	0.5	0	0	1.6	5.2	0.3	0	11.3	75.9	1.8	1.1	2.5	0	0.9	1.1	0.6	1.8	4.7
IDH2	1.6	0.7	0	0	0	0.9	0	0	0	0	9.9	3.6	1	1.4	0	0	0	0	0.4	1.8	0.8
IKBKB	4	1.7	0	0.2	1.5	0.9	0	0.3	0.5	0	0	0	1.3	2.9	2.5	0.4	1.9	1.1	1.7	1.8	1.1
IKZF1	2.8	4.4	0	0.5	0	0	0	1.4	0.3	5	0.7	0.5	1.6	1.4	0.6	0	0.6	1.1	2.1	1.8	1.1
IL6ST	6	3.7	0	0.9	0	0.9	0.5	0	0.8	0	0	0.9	1.6	2.5	1.9	0	0.6	0.6	0.6	1.8	1.2
IL7R	3.6	10.5	0.7	0.2	0	0.9	0.5	0.7	0.5	0	0	0	2.3	6.1	0.6	0.9	0.9	4.5	3.9	1.8	2.1
IRF4	3.2	1.4	0.2	0	0	0	0.5	0.7	0	0	0	0.5	0.8	1.4	0.6	0	0.6	1.1	2.1	0	0.8
JAK1	12.1	2	0.2	1.4	0	1.8	1.1	0.7	0.5	0	0	0	2.8	5	1.9	0	1.6	1.1	3.3	3.5	2
JAK2	5.2	3	0	1.4	0	0	0	0.7	0.6	2.5	0	0.9	2.1	3.6	1.9	0	0.6	2.2	2.7	1.8	1.5
JAK3	4	2.7	0	0.9	0	0.9	0	0.7	0.6	0	0.7	0.5	2.6	3.6	3.1	1.3	1.6	3.4	1.5	1.8	1.5
TP53	29	14.5	0.7	2.6	33.3	1.8	8.5	27.8	33.2	5	5.6	52.7	56.7	48.4	48.4	84.8	69.3	79.2	51.6	64.9	36.1

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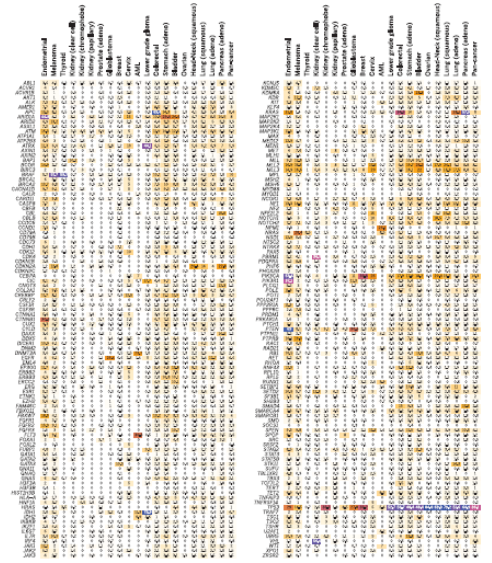

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RESULTS

HLA Region Genes in Cancer Gene Databases

COSMIC
Catalogue of somatic mutations in cancer

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Census | Breakdown | Abbreviations

The cancer Gene Census is an ongoing effort to catalogue those genes for which mutations have been causally implicated in cancer. The original census and analysis was published in Nature Reviews Cancer and supplemental analysis information related to the paper is also available.

The census is not static but rather is updated regularly/as needed. In particular we are grateful to Felix Mitelman and his colleagues in providing information on more genes involved in uncommon translocations in leukaemias and lymphomas. Currently, more than 1% of all human genes are implicated via mutation in cancer. Of these, approximately 90% have somatic mutations in cancer, 20% bear germline mutations that predispose to cancer and 10% show both somatic and germline mutations.

Show 10 entries | Search: HLA | Export: CSV TSV

Gene Symbol	Name	Entrez GeneId	Genome Location	Chr Band	Somatic	Germline	Tumour Types(Somatic)	Tumour Types(Germline)	Cancer Syndrome	Tissue Type	Molecular Genetics	Mutatio Types
CD74	CD74 molecule; major histocompatibility complex; class II invariant chain	972	5:150402584-150412749	5q32	yes		NSCLC			E	Dom	T
HLA-A	major histocompatibility complex; class I; A	3105	6:29942554-29945455	6p21.3	yes		Spitzoid tumour			E	Dom	T
ROS1	v-ros UR2 sarcoma virus oncogene homolog 1 (avian)	6098	6:117288492-117425656	6q22	yes		glioblastoma; NSCLC; Spitzoid tumour			O; E	Dom	T

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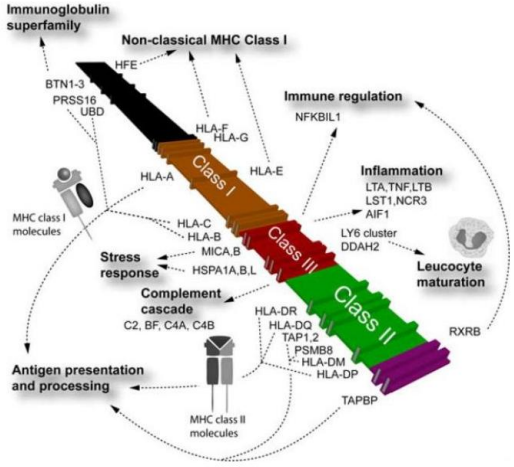
FUTURE WORK

- Include all somatic mutations from the HLA region
- Include all xMHC mutations (histone genes included)
- Consider adjustment for gene size



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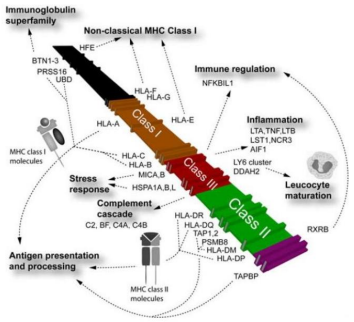
CONCLUSIONS

The survey, which assessed the relevance of germline HLA region SNPs:

- **implicated the HLA region in carcinogenesis**
- **identified HLA-A as the most relevant classical HLA gene**
- **drew attention to the non-HLA genes as candidate cancer susceptibility genes**
- **suggested alternative mechanisms for the involvement of HLA region genes in carcinogenesis**



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