HLA Haplotype DRB1*07:01-DQA1*02:01-DQB1*02:02 Predicts Pegaspargase Hypersensitivity

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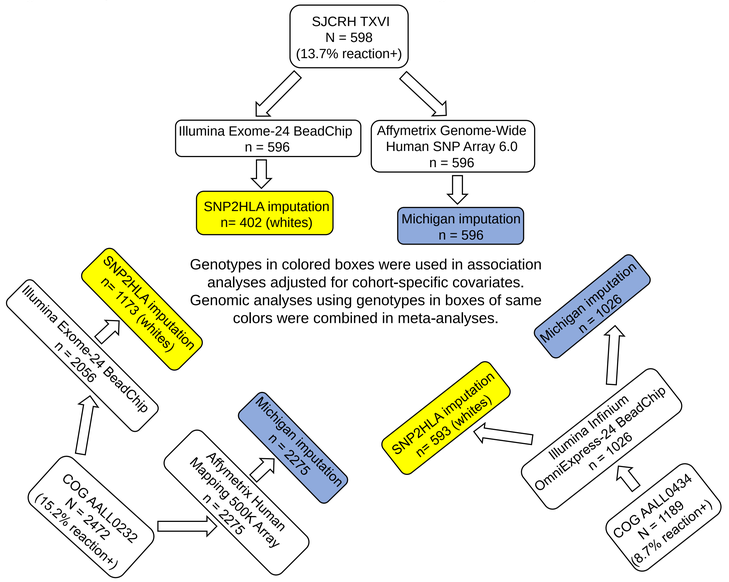
BACKGROUND

Asparaginase is a critical component of pediatric acute lymphoblastic leukemia (ALL) and lymphoma treatment. Hypersensitivity reaction is the primary adverse effect of both polyethylene-glycol conjugated (pegaspargase) and native E. coli asparaginase (L-ASP). Although IgG antibodies against both preparations of asparaginase have been detected and associated with hypersensitivity reactions, our recent study showed that polyethylene glycol (PEG), and not asparaginase, was the major antigen that caused hypersensitivity reactions in patients treated with pegaspargase (PMID 31188727). A prior study of cohorts treated with either L-ASP or pegaspargase showed that HLA-DRB1*07:01 was associated with hypersensitivity (PMID 24970932); whether this is true for reactions after pegaspargase only is not known.

METHODS

This study included three cohorts of pediatric leukemia patients who received pegaspargase as part of their frontline treatment: St. Jude Children's Research Hospital's Total XVI (TXVI, n = 598, B- and T-lineage ALL), Children's Oncology Group AALL0232 (n = 2472, B-ALL only) and AALL0434 (n = 1189, T-ALL only). Hypersensitivity reaction data were retrieved as part of the toxicity reports of each protocol. Reactions were graded according to CTCAE v3. Patients with pegaspargase hypersensitivity reactions of grade 2 or higher were treated as reaction positive (reaction+). The rest were treated as reaction negative (reaction-). Germline DNA was genotyped in subsets of each cohort using either Illumina or Affymetrix SNP-chip platforms. Genetic ancestry was inferred using iAdmix, percent ancestry was used to assign patients to race groups: whites were defined as having > 90% European (CEU/FIN/GBR/IBS/TSI) ancestry, blacks as having > 70% African (YRI/ACB/ASW/ESN/GWD/LWK/MSL) ancestry, Hispanics as having American (CLM/MXL/PEL/PUR) ancestry > 10% and greater than their African ancestry percentage, Asians as having > 90% East Asian (CHB/JPT/CDX/CHS/KHV) or South Asian (BEB/GIH/PJL/ITU/STU) ancestry, and others as those whose ancestry was outside the above boundaries. HLA alleles were imputed using SNP2HLA from Illumina array genotype for whites. Genetic variants not genotyped directly were imputed using the Michigan Imputation Server. Analyses between genetic variants and hypersensitivity were performed in each cohort first using cohort-specific covariates and then combined using meta-analyses.



RESULTS

Association between patient- and treatment-related variables and hypersensitivity reactions to pegaspargase therapy in TXVI, AALL0232, and AALL0434.

TXVI	n	reaction+‖	reaction-‖	P_{uni}*	P_{multi}†
age at diagnosis (year)					
	598	7.4 ± 4.8	7.3 ± 4.9	0.77	-
sex					
male	350	48 (13.7%)	302 (86.3%)	1.0	-
female	248	34 (13.7%)	214 (86.3%)		
ancestry‡					
black	81	11 (13.6%)	70 (86.4%)	-	
white	402	63 (15.7%)	339 (84.3%)	0.62	
Hispanic	63	5 (7.9%)	58 (92.1%)	0.33	-
Asian	8	0 (0.0%)	8 (100.0%)	0.29	
other	42	3 (8.8%)	39 (91.2%)	0.33	
ALL lineage					
B	494	74 (15.0%)	420 (85.0%)	0.049	0.94
T	104	8 (7.7%)	96 (92.3%)		
risk arm					
LR	260	36 (13.8%)	224 (86.2%)	1.0	-
SHR	338	46 (13.6%)	292 (86.4%)		
Down syndrome					
absent	585	82 (14.0%)	503 (86.0%)	0.30	0.16
present	13	0 (0.0%)	13 (100.0%)		
Number of intrathecal injection during remission induction§¶					
	551	3.1 ± 1.7	4.2 ± 1.9	$4.7x10^{-6}$	$2.6x10^{-5}$
Number of pegaspargase doses during remission induction§					
	551	1.3 ± 0.47	1.3 ± 0.45	0.37	-

AALL0232	n	reaction+‖	reaction-‖	P_{uni}*
age at diagnosis (year)				
	2472	11.1 ± 5.4	10.7 ± 5.7	0.26
sex				
male	1352	225 (16.6%)	1127 (83.4%)	0.025
female	1120	150 (13.4%)	970 (86.6%)	
ancestry‡				
black	115	18 (15.7%)	97 (84.3%)	-
white	1295	203 (15.7%)	1092 (84.3%)	1.0
Hispanic	577	85 (14.7%)	492 (85.3%)	0.80
Asian	67	6 (9.0%)	61 (91.0%)	0.23
Other	221	37 (16.7%)	184 (83.3%)	0.79
CNS status				
Non-CNS3	2417	371 (15.3%)	2046 (84.7%)	0.10
CNS3	55	4 (7.3%)	51 (92.7%)	
Length of induction				
Not extended	2397	368 (15.4%)	2029 (84.6%)	0.15
extended	75	7 (9.3%)	68 (90.7%)	
Number of Delayed Intensification				
0	234	31 (13.2%)	203 (86.8%)	0.47
1	1802	289 (16.0%)	1513 (84.0%)	
2	436	55 (12.6%)	381 (87.4%)	
Induction glucocorticoid				
Dexamethasone	960	228 (15.1%)	1284 (84.9%)	0.88
Prednisolone	1512	147 (15.3%)	813 (84.7%)	
Methotrexate regimen				
Capizzi	1210	195 (16.1%)	1015 (83.9%)	0.20
High dose	1262	180 (14.3%)	1082 (85.7%)	

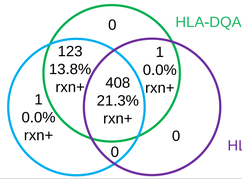
AALL0434	n	reaction+‖	reaction-‖	P_{uni}*
age at diagnosis (year)				
	1189	9.9 ± 5.3	10.4 ± 4.7	0.36
sex				
male	892	78 (8.7%)	814 (91.3%)	0.20
female	297	19 (6.4%)	278 (93.6%)	
ancestry‡				
black	114	12 (10.5%)	102 (89.5%)	-
white	593	40 (6.7%)	553 (93.3%)	0.19
Hispanic	158	19 (12.0%)	139 (88.0%)	0.66
Asian	37	1 (2.7%)	36 (97.3%)	0.14
Other	124	17 (13.7%)	107 (86.3%)	0.38
CNS status**				
Non-CNS3	1084	86 (7.9%)	998 (92.1%)	0.32
CNS3	102	11 (10.8%)	86 (89.2%)	
risk arm*				
Low Risk	109	12 (11.0%)	97 (89%)	-
Intermediate Risk	808	70 (8.7%)	738 (91.3%)	0.40
High Risk	229	13 (5.7%)	216 (94.3%)	0.094
M3 Marrow	43	2 (4.7%)	41 (95.3%)	0.20
Nelarabine regimen				
Nelarabine+	366	25 (6.8%)	341 (93.2%)	0.27
Nelarabine-	823	72 (8.7%)	751 (91.3%)	
Methotrexate regimen				
Capizzi	519	40 (7.7%)	479 (92.3%)	0.62
High dose	670	57 (8.5%)	613 (91.5%)	

*P_{uni} values were generated from general linear regression.
†P_{multi} values were generated from multiple logistic regression among patients who received pegaspargase after remission induction and were evaluable post-induction.
‡Genetically determined with iAdmix. P values for each ancestry group was generated using blacks as the reference ancestry.
§Analyses of association between these variables and reaction was restricted to patients who received pegaspargase after remission induction and were evaluable post-induction.
‖Numbers in these columns represent the number (percentage within row) of patients for categorical variables, or mean ± standard deviation for continuous variables (age at diagnosis, number of intrathecal injections and pegaspargase doses during remission induction).
¶Number of intrathecal injection and pegaspargase were not included in analyses on AALL0232 and AALL0434 due to their lack of variation.

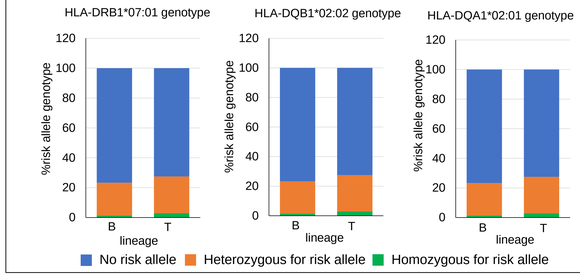
The three risk HLA alleles were in the same haplotype in whites.

Of 2168 evaluable whites, 533 harbored at least one copy of at least one of the three high risk alleles (HLA-DRB1*07:01, HLA-DQA1*02:01, HLA-DQB1*02:02); of these 19.5% had a reaction. Of those 1635 patients who carried none of the three high risk alleles, 11.4% had a reaction.

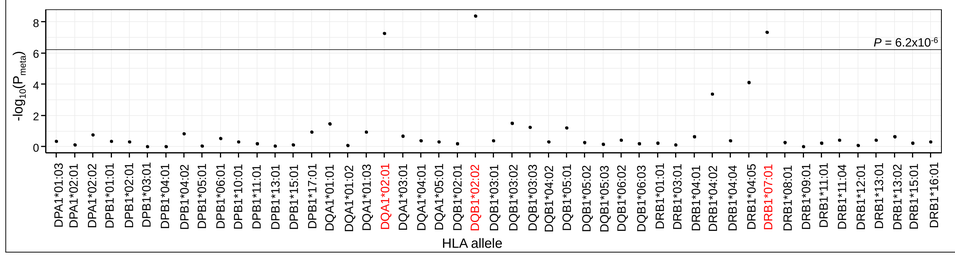
Number of allele carriers and risk of reaction are shown in corresponding areas.



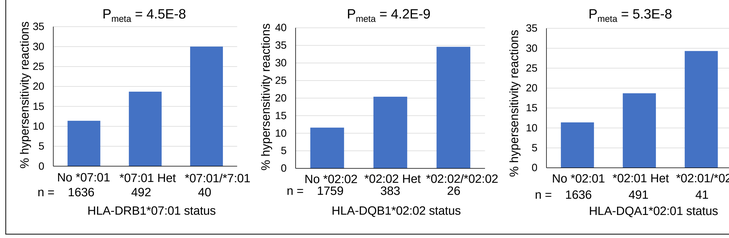
Frequency of risk HLA alleles was not lower in T-ALL (n = 659) than B-ALL (n = 1507), as reported in an L-ASP hypersensitivity study (PMID 28596278).



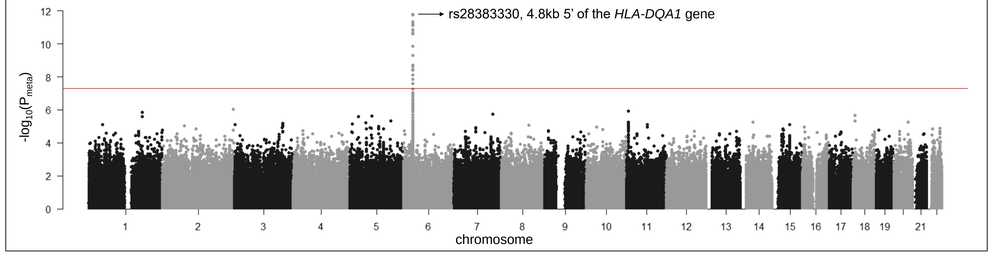
Three HLA class II alleles were significantly associated with hypersensitivity reactions to pegaspargase among whites (n = 2168).



The effect of risk HLA alleles on reaction was additive.



All genetic variants associated with hypersensitivity reactions to pegaspargase among all evaluable patients (n = 3897) with genome-wide significance ($P < 5x10^{-8}$) fell in the HLA loci on chromosome 6.



CONCLUSIONS

Pegaspargase and L-ASP differ in their risk of causing hypersensitivity reactions, the severity of the reactions, and the major reaction-causing epitopes. Herein, we associated the HLA-DRB1*07:01-HLA-DQA1*02:01-HLA-DQB1*02:02 haplotype with hypersensitivity reactions to pegaspargase among pediatric ALL patients. A previous study on a different cohort treated with L-ASP showed that the same HLA haplotype was associated with L-ASP hypersensitivity (PMID 28596278). Taken together, hypersensitivity to L-ASP and pegaspargase share the same HLA risk alleles in spite of the differences in epitopes.

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