

Genetic Variations in *GRIA1* on Chromosome 5q33 Related to Asparaginase Hypersensitivity

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The genetic variations that result in allergy to asparaginase are as yet undetermined. We interrogated more than 500,000 single-nucleotide polymorphisms (SNPs) in 485 children with acute lymphoblastic leukemia (ALL), 322 in a discovery cohort, and 163 in a validation cohort. In the top 100 SNPs associated with allergy in the discovery cohort, chromosome 5 was overrepresented as compared with other chromosomes ($P = 0.00032$), hosting 10 SNPs annotated to genes. Among these 10 SNPs, one SNP (rs4958381), in *GRIA1* on chromosome 5q33, was replicated in the validation cohort ($P = 1.8 \times 10^{-5}$, 2.9×10^{-3} , and 3.5×10^{-7} in the discovery, validation, and combined cohorts, respectively). Four additional SNPs annotated to *GRIA1* were also significantly associated with allergy ($P < 0.05$) in both cohorts. Chromosome 5q33 has previously been associated with asthma and atopy. These data contribute to the growing body of evidence that there is an inherited component to predisposition to drug allergy.

Asparaginase is an effective antileukemia agent that has been used to treat childhood acute lymphoblastic leukemia (ALL).^{1–3} Commercial formulations consist of asparaginase isolated from *Escherichia coli* or *Erwinia chrysanthemi*. Because asparaginase is a foreign protein, hypersensitivity reactions are common, occurring in up to 45% of patients.^{4–14} Factors that may affect the incidence of allergy include the number of asparaginase injections, readministration after a hiatus, and concurrent chemotherapy.^{5,10,11,15–17} These reactions typically necessitate discontinuation of the primary formulation of asparaginase (usually *E. coli*) and subsequent substitution with another asparaginase formulation (usually *E. chrysanthemi*). However, many patients react adversely to both formulations. Also, asparaginase hypersensitivity may attenuate its enzymatic activity and consequently its antileukemic effect.^{8,18,19}

Although numerous investigations of genetic predisposition to drug hypersensitivity have been reported, the vast majority of such studies have been negative.²⁰ Two of the most notable exceptions are the links between hypersensitivity reactions to carbamazepine and to abacavir and human leukocyte antigen polymorphisms.^{20–24} Reactions to asparaginase occur much more commonly than do reactions to agents such as abacavir and carbamazepine, and it was not known whether there is a genetic basis to interindividual differences in asparaginase

hypersensitivity. Our objective, using a genome-wide approach, was to identify germline genetic variations that contribute to the risk of allergy to asparaginase in children with newly diagnosed ALL.

RESULTS

Of 498 patients, 204 (41%) developed allergic reactions to asparaginase. The majority (84%) of the allergic reactions were grade 2, 15% were grade 3, and only 1 (0.5%) was grade 4 (see **Supplementary Table S1** online). The genotype data were available for 485 patients, and these data were included in the analysis.

Of the clinical variables, including sex, age at diagnosis, racial ancestry, and risk arm, American-Indian ancestry ($P = 0.016$) was associated with a lower risk of allergy, and assignment to the low-risk treatment arm ($P = 0.041$) was associated with a higher risk of allergy. These features remained as independent risk factors in a multivariate model ($P = 0.014$ and 0.028 , respectively) (**Table 1**).

We analyzed the association between 364,033 germline single-nucleotide polymorphism (SNP) genotypes and allergy to asparaginase in the discovery cohort of 322 patients (see **Supplementary Figure S1** and **Table S2** online). From the top-ranked 100 SNPs in the discovery cohort, 55 SNPs were

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Received 9 February 2010; accepted 14 April 2010; advance online publication 30 June 2010. doi:10.1038/clpt.2010.94

Table 1 Multivariate analysis of factors associated with allergy to asparaginase

Clinical feature	Number (%)	Hazard ratio (95% CI)	P value
<i>Age at diagnosis</i>			
≤10 Years old	361 (74)	—	
>10 Years old	124 (26)	1.14 (0.78–1.67)	0.51
<i>Sex (male vs. female)</i>			
Female	216 (45)	—	
Male	269 (55)	1.20 (0.89–1.61)	0.24
<i>Risk arm (low risk vs. standard/high risk)^a</i>			
Standard/high risk	249 (51)	—	
Low risk	236 (49)	1.45 (1.04–2.03)	0.028
<i>Racial ancestry^b</i>			
White		—	
Black		0.74 (0.45–1.22)	0.25
Asian		0.35 (0.05–2.41)	0.29
American Indian ^c		0.20 (0.06–0.72)	0.014

^aAlso significant in univariate analysis ($P = 0.041$, hazard ratio = 1.36). ^bDetermined by the STRUcTURE program. ^cAlso significant in univariate analysis ($P = 0.016$, hazard ratio = 0.20).

within genes, and chromosome 5 was host to 10 of these in-gene SNPs (Figure 1a and see Supplementary Table S2 online). After normalizing for the number of SNPs interrogated on the Affymetrix SNP chip, there was a significant overrepresentation of chromosome 5 (Figure 1b) ($P = 0.00032$). Interestingly, all 10 SNPs on chromosome 5 (Table 2) were located at the 5q33 region, which has been associated with asthma and atopy.^{25–30}

We tested in the validation cohort whether these 10 polymorphisms were associated with allergy to asparaginase. Only one SNP (rs4958381), located in *GRIA1*, was significantly associated with allergy to asparaginase ($P = 2.9 \times 10^{-3}$) (Tables 2 and 3). In the combined cohort, the SNP genotypes at rs4958381 were significantly associated with asparaginase allergy ($P = 3.5 \times 10^{-7}$). Focusing on *GRIA1*, there were 11 additional SNPs in *GRIA1* that were significantly associated with asparaginase allergy ($P < 0.05$) in the discovery cohort, 4 of which (rs10070447, rs6890057, rs4958676, and rs6889909) were significantly associated in the validation cohort (Table 3 and Supplementary Figure S2 online). In the combined cohort, 9 SNPs in *GRIA1* were significantly associated with asparaginase allergy ($P < 0.05$, Table 3 and see Supplementary Table S3 online). Figure 2 shows the example of rs4958381; there was a monotonic relationship between the number of copies of the A allele and the risk of allergy to asparaginase in patients on the low-risk and standard/high-risk treatment arms. Overall, the cumulative incidence of asparaginase allergy was 74, 44, and 32% in patients with the AA, AG, and GG genotypes, respectively. There was no association between these genotypes and the severity of allergy to asparaginase ($\geq$ grade 2 vs. $<$ grade 2, $P = 0.61$, by logistic regression analysis).

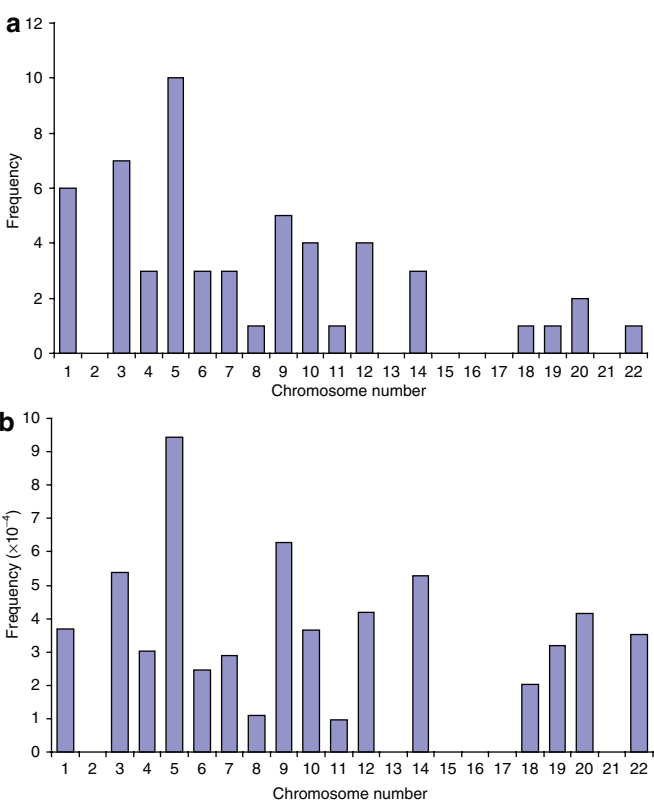


Figure 1 The number of in-gene SNPs ($n = 55$) in each chromosome among the top 100 SNPs associated with asparaginase allergy in the discovery cohort (a) unadjusted and (b) after normalization for the number of SNPs interrogated on each chromosome on the Affymetrix SNP chip. SNP, single-nucleotide polymorphism.

DISCUSSION

Asparaginase is an effective drug in the treatment of ALL. A major toxicity of L-asparaginase is allergy, which may attenuate the pharmacological effect of the drug. In this study, we used a genome-wide interrogation that identified germline genetic variations in *GRIA1*, located at 5q33, that were associated with asparaginase allergy in both discovery and validation cohorts. The 5q33 locus has previously been associated with asthma and atopy.^{25–30}

Clinical symptoms of allergy to asparaginase include localized pain, fever, skin rash, urticaria, respiratory distress, and anaphylaxis. In this study, 172 patients (84%) had grade 2 reactions, 31 (15%) had grade 3 reactions, and only 1 (0.5%) had a grade 4 reaction. Many of the asparaginase allergic reactions are typical of type I hypersensitivity, which is also a hallmark of asthma. In this study, we found that SNPs on chromosome 5q33 were overrepresented with respect to association with asparaginase allergy (Figure 1). Chromosome 5q31–33 contains a cluster of cytokine and other immune-related genes such as interleukin-4, interleukin-13, and interleukin-5; this region has been mapped as a susceptibility locus for several inflammatory and autoimmune diseases, including asthma.^{25–30} Our findings support the hypothesis that drug allergy and asthma share a range of genes that might cause these reactions.³¹

Table 2 In-gene SNPs from chromosome 5 ($n = 10$) from the top 100 SNPs associated with asparaginase allergy in the discovery and validation cohorts

SNP ^a	Chromosome	Location ^b	Gene	Alleles ^c	Frequency of risk alleles	Discovery cohort ($n = 322$)		Validation cohort ($n = 163$)	
						<i>P</i> value ^d	Hazard ratio (95% CI) ^e	<i>P</i> value ^d	Hazard ratio (95% CI) ^e
rs4958351	5	153150567	<i>GRIA1</i>	G/A	0.27	1.8×10^{-5}	1.72 (1.35–2.21)	0.0029	1.93 (1.25–2.98)
rs11167667	5	153634138	<i>GALNT10</i>	T/C	0.58	2.1×10^{-5}	1.81 (1.38–2.38)	0.29	0.82 (0.57–1.18)
rs12523441	5	153634860	<i>GALNT10</i>	T/C	0.58	2.1×10^{-5}	1.81 (1.38–2.38)	0.29	0.82 (0.57–1.18)
rs707184	5	153466019	<i>C5orf3,MFAP3</i>	T/C	0.37	3.5×10^{-5}	1.77 (1.35–2.31)	0.35	1.19 (0.82–1.71)
rs7737215	5	153625371	<i>GALNT10</i>	C/T	0.54	7.2×10^{-5}	1.69 (1.31–2.18)	0.40	0.85 (0.59–1.24)
rs7717132	5	150634674	<i>SLC36A3</i>	G/T	0.46	6.1×10^{-5}	1.61 (1.27–2.03)	0.39	1.16 (0.82–1.64)
rs10875583	5	153593909	<i>GALNT10</i>	C/G	0.57	9.7×10^{-5}	1.72 (1.32–2.24)	0.23	0.80 (0.56–1.15)
rs1438588	5	153425143	<i>C5orf3,MFAP3</i>	G/A	0.35	7.7×10^{-5}	1.65 (1.29–2.11)	0.22	1.25 (0.87–1.79)
rs6890748	5	153668293	<i>GALNT10</i>	G/A	0.39	9.7×10^{-5}	1.66 (1.29–2.13)	0.047	0.71 (0.51–0.99)
rs6863455	5	153665437	<i>GALNT10</i>	G/A	0.64	1.1×10^{-4}	1.7 (1.3–2.23)	0.22	0.81 (0.57–1.14)

CI, confidence interval; SNP, single-nucleotide polymorphism.

^ars numbers according to the National Center for Biotechnology Information SNP database. ^bPhysical location of an SNP based on March 2006 human genome assembly (hg18).

^cAlleles were listed with the second allele as the risk allele. ^d*P* values from Gray's test. ^eFor example, patients in the discovery cohort who harbor an additional copy of the risk allele (A allele) of the SNP rs4958351 are 1.72 times more likely to have an allergic reaction as compared with those without the risk allele.

GRIA1 encodes a subunit of the AMPA (α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptor, a tetrameric ligand-gated ion channel that transmits glutamatergic signals in the brain. The same polymorphisms of *GRIA1* that we found to be associated with asparaginase allergy are also associated with schizophrenia and bipolar disease.^{32,33} All the genetic variations we identified in *GRIA1* were in intronic sequences. Interestingly, intronic polymorphisms in the glutamate receptor subunit *GluR2* are the ones that direct RNA editing of the *GluR2* coding sequence;³⁴ this suggests that there is a mechanism through which intronic variations could affect gene function. Furthermore, it has recently been shown that glutamate has a role not only as a neurotransmitter but also as an immunomodulator.^{35,36} To our knowledge, this is the first direct link to be reported between *GRIA1* polymorphisms and an immune-related phenotype.

Forty-one percent of the 498 patients who were treated with the Total Therapy XV protocol had a hypersensitivity reaction to asparaginase, which is consistent with the reported frequency in children (up to 45%).^{4–14} The incidence of allergic reactions was very low within the first 100 days after treatment was initiated (Figure 2), consistent with exposure to a relatively small number of doses, but reactions could have been attenuated by immunosuppression associated with early concomitant chemotherapy,^{5,10,15–17} particularly with steroids. The majority of the reactions occurred during continuation or reinduction therapy. Interestingly, the rate of occurrence of reactions differed between the low-risk arm and the standard/high-risk arms; this difference may be related to the intermittent use of asparaginase in the low-risk arm, in contrast to the weekly administration of asparaginase in the standard/high-risk arms (see **Supplementary Table S4** online). Our findings support the theory that the risk of hypersensitivity reactions may increase with readministration after an interval of at least 1 month.^{14,15}

We found that the frequency of asparaginase allergy was significantly associated with racial ancestry (Table 1), consistent with a previous report that white children had a higher frequency of allergic reactions than either black or Hispanic children.³⁷ Our catchment area is racially and ethnically diverse, and for this study we used genomic variation to define the racial backgrounds of all the patients. It has been suggested that variations in *HLA* genes or other immunoregulatory factors contribute to asparaginase allergy.³⁷ Genetic variations in *HLA-B*5701* have indeed been shown to be significantly associated with hypersensitivity to a medication unrelated to asparaginase, namely, abacavir;^{22–24} in addition, there are some data indicating that race-related differences also play a part in *HLA-B*5701*-related hypersensitivity to abacavir.^{38,39} Interestingly, the prevalence of asthma has been shown to be higher among black children and children from certain Hispanic ethnic subgroups than among white children.^{40–42} In genetic studies of asthma, some genetic variations were found to be associated with certain population subgroups,^{43–46} indicating that the genetic risk factors in allergic diseases can vary with race and ethnicity.

In conclusion, we identified genetic variations in the glutamate receptor *GRIA1* on chromosome 5q33 that were associated with risk of allergy to asparaginase. These findings add to previous reports indicating a role for 5q genes in immune responses, and they contribute to the data showing the importance of inherited variation in risk of drug allergy.

METHODS

Patients and treatment regimen. Of the 498 patients treated with St Jude Children's Research Hospital treatment protocol Total Therapy XV for newly diagnosed childhood ALL, we included all those who were evaluable for allergy to asparaginase and who had evaluable DNA ($n = 485$). The study was approved by the institutional review board. Informed consent from the parent or guardian and age-appropriate assent from the patient were obtained at the time of study enrollment. Risk assignment (low, standard, or high risk) and the treatment

Table 3 The *P* values for 12 SNPs in *GRIA1* associated with asparaginase allergy (*P* < 0.05) in the discovery cohort

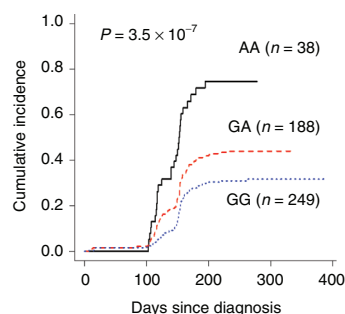
SNP ^a	Location ^b	Alleles ^c	Frequency of risk allele	Discovery cohort		Validation cohort		Combined cohort	
				<i>P</i> value ^d	Hazard ratio (95% CI) ^e	<i>P</i> value ^d	Hazard ratio (95% CI) ^e	<i>P</i> value ^d	Hazard ratio (95% CI) ^e
rs4958351	153150567	G/A	0.27	1.8×10^{-5}	1.72 (1.35–2.21)	0.0029	1.93 (1.25–2.98)	3.5×10^{-7}	1.75 (1.41–2.17)
rs10070447	153159007	C/T	0.27	1.3×10^{-4}	1.59 (1.25–2.02)	0.0023	1.96 (1.27–3.01)	2.0×10^{-6}	1.66 (1.35–2.05)
rs6890057	153103681	C/T	0.17	4.3×10^{-4}	1.64 (1.24–2.15)	0.0035	1.80 (1.21–2.68)	2.1×10^{-5}	1.63 (1.30–2.05)
rs4958676	153132470	G/A	0.17	0.0014	1.57 (1.19–2.08)	0.0066	1.66 (1.15–2.40)	9.2×10^{-5}	1.56 (1.25–1.95)
rs6889909	153103626	C/T	0.18	0.0020	1.53 (1.17–2.00)	0.016	1.58 (1.09–2.29)	2.3×10^{-4}	1.51 (1.21–1.87)
rs11167640	153112499	C/T	0.74	0.0025	1.72 (1.21–2.45)	0.84	1.04 (0.71–1.52)	0.014	1.39 (1.07–1.81)
rs10072570	153159960	G/A	0.22	0.0038	1.47 (1.13–1.91)	0.21	1.32 (0.85–2.05)	0.0035	1.40 (1.12–1.75)
rs4424038	153100457	G/A	0.73	0.0056	1.62 (1.15–2.28)	0.27	0.83 (0.59–1.16)	0.125	1.21 (0.95–1.55)
rs13354399	153169624	G/A	0.22	0.0069	1.41 (1.10–1.80)	0.21	1.32 (0.85–2.05)	0.0055	1.36 (1.09–1.69)
rs17356099	153123241	T/C	0.06	0.017	1.85 (1.12–3.07)	0.43	1.37 (0.63–3.01)	0.019	1.66 (1.09–2.54)
rs7711124	153123087	C/G	0.65	0.021	1.40 (1.05–1.86)	0.90	0.98 (0.66–1.45)	0.084	1.22 (0.97–1.53)
rs7708391	153127393	A/G	0.65	0.022	1.39 (1.05–1.85)	0.85	0.96 (0.64–1.44)	0.089	1.22 (0.97–1.53)

Also listed are the *P* values and hazard ratios of the 12 SNPs in the validation and combined cohorts.

CI, confidence interval; SNP, single-nucleotide polymorphism.

^ars numbers according to the National Center for Biotechnology Information SNP database. ^bPhysical location of an SNP based on March 2006 human genome assembly (hg18).

^cAlleles are listed with the risk allele as the second allele. ^d*P* values from Gray's test. ^eFor example, patients in the discovery cohort who harbor an additional copy of the risk allele (A allele) of the SNP rs4958351 are 1.72 times more likely to have an allergic reaction as compared with those without the risk allele.

**Figure 2** The cumulative incidence of allergy to asparaginase was compared using Gray's test (stratified for treatment arms) for each genotype at rs4958381 in *GRIA1* in the combined (entire) cohort.

regimen have been described previously.⁴⁷ In brief, the remission induction therapy consisted of prednisone daily for 28 days, weekly doses of vincristine for 4 weeks, weekly doses of daunorubicin for 2 weeks, native *E. coli* asparaginase (Elspar, 10,000 IU/m²) three times a week (six doses), and triple intrathecal therapy. Additional asparaginase (Elspar, three doses, 10,000 IU/m²) was administered based on minimal residual disease status on day 19. Subsequent induction therapy consisted of cyclophosphamide, mercaptopurine, and cytarabine. Consolidation therapy consisted of high-dose methotrexate, mercaptopurine, and triple intrathecal therapy. Asparaginase treatment differed markedly by risk arm in the first 20 weeks of continuation therapy (see **Supplementary Table S4** online). Standard/high-risk cases received asparaginase (25,000 IU/m²) once a week during weeks 1–20; low-risk cases received asparaginase (10,000 IU/m²) three times weekly only during each of the reinduction phases of the treatment (weeks 7–9 and weeks 17–20).

Phenotyping of allergy to asparaginase. Hypersensitivity reactions to asparaginase were characterized by local manifestations at the injection site as well as systemic manifestations (erythema, swelling, urticaria, rash, pruritus, tachypnea, and wheezing). Asparaginase allergy was graded (grade 1, 2, 3, or 4) using the National Cancer Institute Common Toxicity

Criteria, version 2.0. The phenotype of interest was the first episode of allergy to asparaginase (the allergy was always to native *E. coli*).

Genotyping and quality control. DNA was extracted from normal peripheral blood leukocytes, digested with restriction enzymes, amplified, labeled, and hybridized to the Affymetrix GeneChip Human Mapping 500K sets or SNP 6.0 (Affymetrix, Santa Clara, CA) as described.⁴⁸ SNPs with call rates <95% or alleles with frequencies of <5% were filtered out.

SNP genotypes were coded according to the number of B alleles in the genotype call, with the AA, AB, and BB genotype calls coded as 0, 1, and 2, respectively. SNPs were annotated to genes if they were within 5 kb of the transcription start site and transcription 3' end.

Genome-wide analysis for asparaginase allergy. We assigned all the patients into two cohorts—discovery and validation cohorts—by using a balanced stratified approach,⁴⁹ balancing age, sex, treatment arm, race, and the presence of allergy to asparaginase. The discovery cohort comprised 67% of the patients, and the validation cohort comprised the other 33% (see **Supplementary Table S5** online). Using this approach, given our sample size, we performed *post hoc* power calculations to estimate our power to detect a polymorphism associated with the risk of allergy (details in **Supplementary Table S6** online); for example, with a hazard ratio of 1.8 and a minor allele frequency of 0.27, power is estimated at 99.7% in the discovery cohort and 67% in the validation cohort, at an α -level of 0.005. Population racial ancestries were estimated using STRUCTURE⁵⁰ on the basis of SNP genotypes, with HapMap phase II samples and publicly available genotype data of American Indians⁵¹ as reference populations. Racial ancestries were included as covariates, treated as continuous values (percentages of European, African, Asian, and American-Indian ancestries) in the association analysis between genotypes and asparaginase allergy.

First, we used Gray's test to compute the statistical significance for each SNP genotype's association with asparaginase allergy in the discovery cohort, stratifying for risk arm and adjusting for racial ancestry. Among the top significant SNPs (ranked by *P* value), we examined whether there was overrepresentation of any chromosomes by dividing the number of in-gene SNPs from the top 100 ranked SNPs by the number of in-gene SNPs on each chromosome interrogated by the Affymetrix SNP chip. Second, we tested the significance of the genotypes of SNPs of interest

from the discovery cohort in the validation cohort. Third, we used Gray's test to assess the statistical significance of the associations between the cumulative incidence of asparaginase allergy and the SNPs of interest in the combined cohort. Time at risk was censored at the end of reinduction II treatment (last asparaginase exposure) or at the date of allergic reaction. Data from patients who underwent bone marrow transplant or were off study before they reached reinduction II were censored at their off-study date. Data from patients who experienced a relapse of the disease or died were censored at the time of that event, which was treated as a competing event in the estimation of cumulative incidence.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/cpt>

ACKNOWLEDGMENTS

This study was supported by National Cancer Institute grant CA 21765, the NIH/NIGMS Pharmacogenetics Research Network and Database (<http://pharmgkb.org>; U01 GM61393 and U01 GM61374), and the American Lebanese Syrian Associated Charities. We thank our protocol co-investigators and the clinical and research staff, particularly Pamela McGill, Natalie Lowery, Sean Freeman, Emily Baum, and Nancy Kornegay, as well as the patients and their families for their participation. We also thank the staff at St Jude's Hartwell Center for Bioinformatics and Biotechnology.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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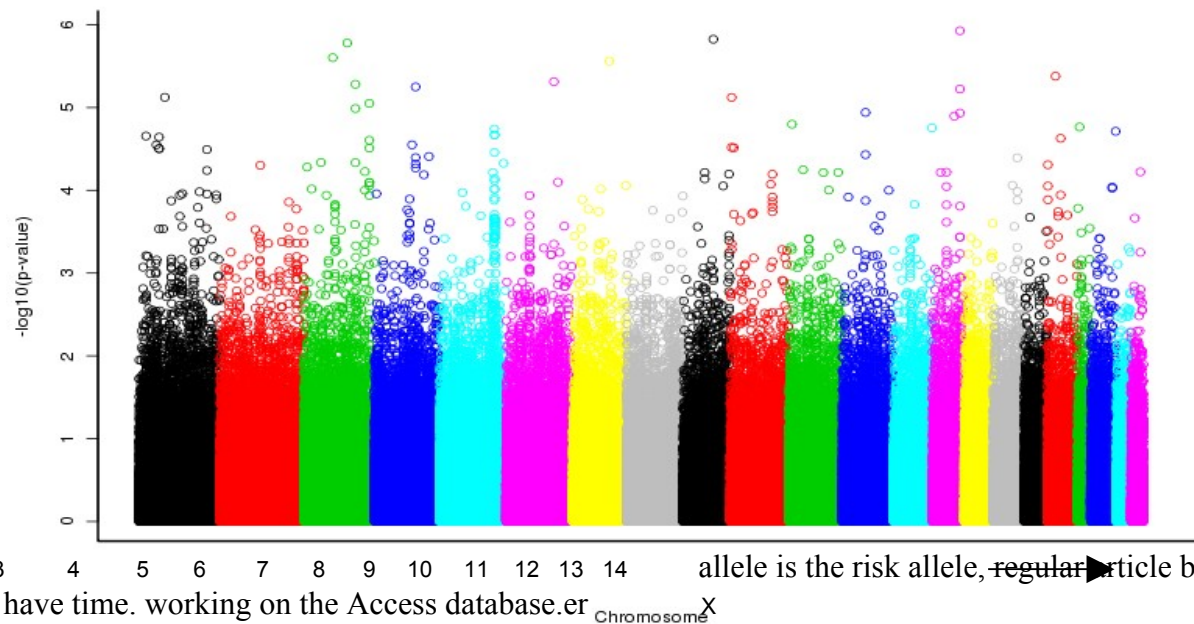


Figure S1. *P*-values (shown as $-\log_{10}$) for the association of 364,033 single-nucleotide polymorphism genotypes and asparaginase allergy in the discovery cohort (n = 322) are plotted from chromosomes 1 to X. Colors discriminate chromosomes.

Supplemental Figure S2.

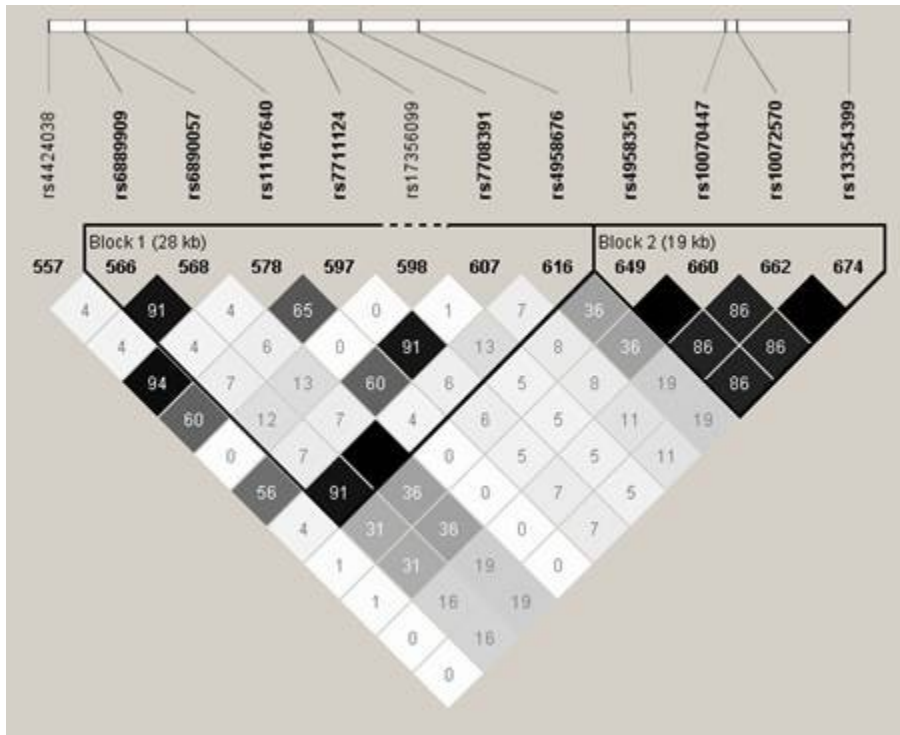


Figure S2. Linkage disequilibrium among the 12 SNPs in *GRI1* that were associated with risk of asparaginase allergy. Numbers in boxes represent the correlation (r^2) between any two SNPs in HapMap CEU cell lines; solid black boxes indicate perfect correlation, solid white boxes represent no correlation

Supplemental Table S1. The frequency of asparaginase allergy by grade in each ancestral group

NCI toxicity grading for asparaginase allergy				
Race *	Grade 0/1	Grade 2	Grade 3/4	Total
White	174 (56.1%)	116 (37.4%)	20 (6.5%)	310
Black	48 (65.8%)	21 (28.8%)	4 (5.5%)	73
Hispanics	54 (77.1%)	12 (17.1%)	4 (5.7%)	70
Asian	4 (66.7%)	2 (33.3%)	0 (0%)	6
Other	17 (65.3%)	8 (30.8%)	1 (3.8%)	26
Total	297	159	29	485

*Race was inferred by the program STRUCTURE using HapMap Phase 2 data as the reference.

Supplemental Table S2. Top 100 SNPs associated with asparaginase allergy in the discovery cohort

SNP	dbSNP ID	Chr	Location	Gene	Allele [#]	P value	Frequency of the Risk Allele*					
							All	White	Black	Hispanic	Asian	Other
SNP_A-2111352	rs9671457	14	94086589		T/C	1.18E-06	0.72	0.72	0.66	0.78	0.83	0.67
SNP_A-2287164	rs419574	9	97194636	KIAA1529	A/G	1.50E-06	0.05	0.06	0.03	0.05	0.08	0.04
SNP_A-2303483	rs16829569	3	120429487	B4GALT4,UPK1B	G/A	1.66E-06	0.08	0.05	0.06	0.25	0.00	0.00
SNP_A-4209521	rs17689208	3	69932637	MITF	C/T	2.50E-06	0.05	0.06	0.01	0.06	0.08	0.02
SNP_A-4237602	rs11762802	7	106749118	COG5	T/C	2.75E-06	0.06	0.08	0.01	0.03	0.00	0.00
SNP_A-2224789	rs7232668	18	22286916	KCTD1	A/G	4.18E-06	0.07	0.02	0.21	0.16	0.00	0.06
SNP_A-1871792	rs594401	6	124905860	TCBA1	A/C	4.87E-06	0.21	0.25	0.10	0.20	0.33	0.15
SNP_A-4261144	rs868767	3	142860020	LOC646730	A/G	5.24E-06	0.17	0.13	0.10	0.40	0.42	0.19
SNP_A-2207321	rs6534127	4	120267285		G/A	5.63E-06	0.47	0.50	0.36	0.46	0.33	0.42
SNP_A-2248662	rs2854946	14	94118132	SERPINA5	C/G	5.98E-06	0.21	0.23	0.21	0.16	0.17	0.12
SNP_A-2215007	rs9437407	1	76527545	ST6GALNAC3	C/T	7.53E-06	0.10	0.05	0.30	0.14	0.42	0.10
SNP_A-4257690	rs2388399	10	2782892		A/G	7.55E-06	0.08	0.01	0.45	0.01	0.00	0.10
SNP_A-2051957	rs12629404	3	186378157		A/G	8.92E-06	0.80	0.85	0.57	0.85	0.58	0.78
SNP_A-2201584	rs868768	3	142860222	LOC646730	C/T	1.03E-05	0.17	0.13	0.10	0.41	0.50	0.20
SNP_A-1889905	rs4763039	12	61512591	PPM1H	A/C	1.15E-05	0.08	0.04	0.27	0.02	0.00	0.12
SNP_A-2063843	rs17109616	14	79159469	NRXN3	A/G	1.27E-05	0.07	0.02	0.31	0.06	0.40	0.02
SNP_A-4280068	rs11041882	11	8305413		C/T	1.59E-05	0.15	0.15	0.14	0.16	0.08	0.14
SNP_A-1814016	rs318699	19	11362240	RGL3	G/A	1.72E-05	0.30	0.36	0.09	0.27	0.50	0.23
SNP_A-1811394	rs2317446	13	112322678		C/A	1.76E-05	0.07	0.04	0.15	0.09	0.08	0.08
SNP_A-2100887	rs4958351	5	153150567	GRIA1	G/A	1.82E-05	0.28	0.31	0.26	0.20	0.08	0.23
SNP_A-2076161	rs6142900	20	59966932		A/G	1.94E-05	0.06	0.03	0.12	0.07	0.67	0.10
SNP_A-2136536	rs12523441	5	153634860	GALNT10	T/C	2.14E-05	0.59	0.57	0.89	0.35	0.33	0.65
SNP_A-2169100	rs11167667	5	153634138	GALNT10	T/C	2.14E-05	0.59	0.57	0.89	0.35	0.33	0.65
SNP_A-2224058	rs1256334	1	21764321	ALPL	G/A	2.21E-05	0.13	0.16	0.04	0.10	0.00	0.19
SNP_A-1898422	rs4501865	1	61709161		G/A	2.28E-05	0.16	0.11	0.25	0.25	0.42	0.17
SNP_A-2263574	rs16973345	18	36269528		A/G	2.36E-05	0.09	0.08	0.12	0.08	0.33	0.08
SNP_A-2039835	rs2048253	3	186372596		G/A	2.48E-05	0.75	0.85	0.45	0.73	0.17	0.65
SNP_A-1923587	rs17039065	4	109604852	FLJ37673	C/T	2.82E-05	0.14	0.12	0.14	0.22	0.42	0.14

SNP_A-2022770	rs4926698	1	56101184		G/T	2.83E-05	0.48	0.47	0.41	0.63	0.50	0.44
SNP_A-1882585	rs1931859	10	2782489		A/C	3.03E-05	0.08	0.01	0.44	0.01	0.00	0.10
SNP_A-1956428	rs7917326	10	6397443	LOC399715	C/T	3.06E-05	0.15	0.11	0.14	0.34	0.92	0.10
SNP_A-2282321	rs2377371	3	186371883		A/C	3.09E-05	0.75	0.85	0.45	0.73	0.17	0.68
SNP_A-1854093	rs6676020	1	61724756		G/C	3.14E-05	0.29	0.19	0.43	0.54	0.67	0.25
SNP_A-2107974	rs4915746	1	61725162		G/A	3.14E-05	0.29	0.19	0.43	0.54	0.67	0.25
SNP_A-4195103	rs1339358	1	215050518	ESRRG	G/A	3.22E-05	0.07	0.05	0.06	0.14	0.25	0.06
SNP_A-4211362	rs707184	5	153466019	C5orf3,MFAP3	T/C	3.50E-05	0.40	0.42	0.37	0.33	0.17	0.42
SNP_A-4240101	rs7311342	12	61516180	PPM1H	C/T	3.71E-05	0.07	0.04	0.25	0.02	0.00	0.10
SNP_A-1838606	rs17257818	X	100774838	ARMCX3	T/C	3.80E-05	0.09	0.13	0.02	0.02	0.20	0.08
SNP_A-1979647	rs4691753	4	162537436	FSTL5	C/T	3.90E-05	0.11	0.11	0.08	0.14	0.13	0.14
SNP_A-4210485	rs1459061	4	120269210		G/A	4.03E-05	0.45	0.48	0.36	0.46	0.33	0.40
SNP_A-2172164	rs12929743	16	77251379		G/C	4.05E-05	0.19	0.20	0.21	0.14	0.17	0.19
SNP_A-2081279	rs9637536	3	38775877	SCN10A	G/A	4.61E-05	0.15	0.16	0.12	0.16	0.00	0.17
SNP_A-1974596	rs2030186	3	142833593		C/T	4.64E-05	0.23	0.18	0.19	0.45	0.50	0.23
SNP_A-2044458	rs17076923	5	173543990		T/C	4.71E-05	0.09	0.10	0.06	0.07	0.25	0.02
SNP_A-1978680	rs1459060	4	120269246		C/A	4.81E-05	0.54	0.50	0.75	0.49	0.33	0.58
SNP_A-4200520	rs1812571	18	1208635		A/C	4.91E-05	0.49	0.53	0.35	0.44	0.50	0.50
SNP_A-1819098	rs12623828	2	112180830		T/C	4.99E-05	0.44	0.47	0.32	0.46	0.42	0.42
SNP_A-2059251	rs7635047	3	5567056		A/G	5.24E-05	0.09	0.13	0.00	0.03	0.17	0.06
SNP_A-1978678	rs1459062	4	120269106		A/G	5.37E-05	0.50	0.50	0.57	0.46	0.33	0.48
SNP_A-1925774	rs10767942	11	32478583		T/C	5.66E-05	0.26	0.21	0.32	0.39	0.92	0.29
SNP_A-4198927	rs2813675	1	215053556	ESRRG	T/C	5.76E-05	0.10	0.08	0.10	0.17	0.42	0.12
SNP_A-4298675	rs7372276	3	172348544	TNIK	A/G	5.94E-05	0.12	0.09	0.31	0.09	0.00	0.15
SNP_A-1942777	rs138079	22	42570832	PNPLA5,SULT4A1	C/T	6.00E-05	0.13	0.17	0.06	0.06	0.00	0.12
SNP_A-2284554	rs856205	14	58303794	LOC729646	T/G	6.04E-05	0.08	0.10	0.01	0.06	0.00	0.10
SNP_A-2109283	rs1777081	14	42252097		A/G	6.08E-05	0.11	0.07	0.20	0.18	0.33	0.16
SNP_A-2259930	rs661021	11	126439357		A/G	6.08E-05	0.38	0.34	0.33	0.58	0.42	0.42
SNP_A-1984005	rs7717132	5	150634674	SLC36A3	G/T	6.09E-05	0.46	0.37	0.67	0.66	0.58	0.37
SNP_A-2129864	rs12339024	9	76587339	TRPM6	T/C	6.10E-05	0.37	0.40	0.37	0.23	0.25	0.42
SNP_A-4297660	rs12789145	11	94047384		T/G	6.10E-05	0.10	0.08	0.21	0.08	0.42	0.12
SNP_A-2201226	rs552148	9	135143302	ABO	C/T	6.38E-05	0.29	0.27	0.26	0.44	0.17	0.25
SNP_A-2210103	rs10736136	10	100445514	HPSE2	C/T	6.40E-05	0.40	0.35	0.53	0.50	0.75	0.39

SNP_A-1925817	rs12503342	4	148056414	TTC29	A/C	6.50E-05	0.14	0.06	0.40	0.19	0.42	0.14
SNP_A-1791289	rs7737215	5	153625371	GALNT10	C/T	7.21E-05	0.55	0.53	0.87	0.32	0.33	0.58
SNP_A-4245797	rs6560408	9	76586475	TRPM6	C/T	7.28E-05	0.37	0.41	0.32	0.23	0.25	0.42
SNP_A-2049131	rs1438588	5	153425143	C5orf3,MFAP3	G/A	7.66E-05	0.38	0.40	0.39	0.28	0.17	0.40
SNP_A-1987773	rs6926933	6	136274373	PDE7B	A/G	7.98E-05	0.25	0.21	0.50	0.17	0.00	0.31
SNP_A-2026229	rs7631503	3	186512797		A/G	8.05E-05	0.81	0.83	0.65	0.86	0.92	0.79
SNP_A-4279123	rs7431357	3	186514488		A/G	8.05E-05	0.81	0.83	0.65	0.86	0.92	0.79
SNP_A-1959401	rs10882517	10	96784724	CYP2C8	G/A	8.45E-05	0.35	0.32	0.46	0.29	0.58	0.40
SNP_A-1925357	rs17765606	16	64540948		A/G	8.70E-05	0.11	0.02	0.29	0.24	0.50	0.10
SNP_A-2229118	rs1076435	7	156971525		C/T	8.73E-05	0.56	0.52	0.71	0.54	0.75	0.65
SNP_A-2031710	rs9875687	3	186505879		C/T	8.82E-05	0.81	0.83	0.69	0.86	0.92	0.82
SNP_A-4293974	rs1928985	9	118773794	ASTN2	C/T	8.86E-05	0.06	0.01	0.34	0.01	0.00	0.06
SNP_A-1852754	rs1826507	18	1211372		C/T	8.88E-05	0.68	0.64	0.93	0.54	0.67	0.71
SNP_A-2291232	rs311818	14	58238848		A/T	9.02E-05	0.06	0.07	0.03	0.04	0.08	0.06
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SNP_A-2243504	rs13091718	3	14355778		T/C	9.64E-05	0.54	0.58	0.49	0.47	0.33	0.44
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SNP_A-4258513	rs6890748	5	153668293	GALNT10	G/A	9.65E-05	0.39	0.42	0.38	0.26	0.08	0.44
SNP_A-1816395	rs10875583	5	153593909	GALNT10	C/G	9.73E-05	0.59	0.58	0.86	0.36	0.17	0.65
SNP_A-2303199	rs17649831	11	106094921	GUCY1A2	C/G	9.95E-05	0.20	0.24	0.09	0.20	0.08	0.10
SNP_A-4263904	rs1499821	3	172207423	SLC2A2	T/C	9.99E-05	0.84	0.84	0.89	0.77	1.00	0.87
SNP_A-4243191	rs7306948	12	121911300	CCDC62,HIP1R, LOC728014,VPS37B	A/G	1.00E-04	0.08	0.08	0.09	0.08	0.08	0.06
SNP_A-4234911	rs7197903	16	77172009		C/T	1.03E-04	0.21	0.17	0.27	0.23	0.67	0.33
SNP_A-1862631	rs322899	1	197357762		T/C	1.04E-04	0.19	0.12	0.55	0.16	0.00	0.21
SNP_A-1824439	rs16892342	5	63190580		A/G	1.06E-04	0.06	0.00	0.33	0.03	0.00	0.10
SNP_A-2029526	rs4845540	1	151591835	PGLYRP4	C/A	1.10E-04	0.15	0.11	0.25	0.19	0.00	0.17
SNP_A-2219374	rs11935439	4	6738446		C/A	1.10E-04	0.54	0.54	0.51	0.62	0.42	0.42
SNP_A-4256311	rs766159	1	215053916	ESRRG	C/T	1.11E-04	0.06	0.05	0.01	0.14	0.25	0.06
SNP_A-1902791	rs16973295	18	36256729		A/G	1.14E-04	0.09	0.08	0.10	0.09	0.33	0.06
SNP_A-1959103	rs6863455	5	153665437	GALNT10	G/A	1.14E-04	0.66	0.66	0.88	0.39	0.67	0.73
SNP_A-2062667	rs2664057	1	237417351		A/G	1.14E-04	0.64	0.75	0.17	0.69	0.83	0.60
SNP_A-1937806	rs798023	1	117141325		G/A	1.15E-04	0.13	0.04	0.59	0.05	0.33	0.12

SNP_A-1953791	rs6784112	3	186381925		G/A	1.15E-04	0.74	0.83	0.44	0.73	0.20	0.69
SNP_A-1972712	rs950155	3	56895920		C/G	1.15E-04	0.62	0.58	0.68	0.69	0.92	0.58
SNP_A-2063758	rs9370092	6	52002914	PKHD1	G/A	1.15E-04	0.49	0.44	0.77	0.38	0.67	0.62
SNP_A-4291501	rs3923107	8	144327163	LY6H	A/G	1.17E-04	0.30	0.33	0.25	0.26	0.17	0.23
SNP_A-2161758	rs10845936	12	14288468	LOC644693	G/T	1.21E-04	0.13	0.12	0.10	0.19	0.08	0.10
SNP_A-2241219	rs497340	10	100423153	HPSE2	A/T	1.21E-04	0.37	0.34	0.37	0.49	0.75	0.33

Alleles were listed with the second allele as the risk allele;

*Race was inferred by the program STRUCTURE using HapMap phase 2 data and publicly available genotype data of American Indians² as reference.

Supplemental Table S3. The minor allele frequency in different racial ancestry for the 21 SNPs of interest (the 10 in Table 2 and the *GRIA1* SNPs in Table 3) identified from the discovery cohort

SNP	dbSNP ID	Chr	Location	Gene	Allele # (A/B)	P value	All	Frequ White
SNP_A-2100887	rs4958351	5	153150567	GRIA1	G/A	1.82E-05	0.28	0.31
SNP_A-2169100	rs11167667	5	153634138	GALNT10	T/C	2.14E-05	0.59	0.57
SNP_A-2136536	rs12523441	5	153634860	GALNT10	T/C	2.14E-05	0.59	0.57
SNP_A-4211362	rs707184	5	153466019	C5orf3,MFAP3	T/C	3.50E-05	0.40	0.42
SNP_A-1984005	rs7717132	5	150634674	SLC36A3	G/T	6.09E-05	0.46	0.37
SNP_A-1791289	rs7737215	5	153625371	GALNT10	C/T	7.21E-05	0.55	0.53
SNP_A-2049131	rs1438588	5	153425143	C5orf3,MFAP3	G/A	7.66E-05	0.38	0.40
SNP_A-4258513	rs6890748	5	153668293	GALNT10	G/A	9.65E-05	0.39	0.42
SNP_A-1816395	rs10875583	5	153593909	GALNT10	C/G	9.73E-05	0.59	0.58
SNP_A-1959103	rs6863455	5	153665437	GALNT10	G/A	1.14E-04	0.66	0.66
SNP_A-1948657	rs10070447	5	153159007	GRIA1	C/T	0.000132	0.28	0.31
SNP_A-2174565	rs6890057	5	153103681	GRIA1	C/T	0.000429	0.17	0.18
SNP_A-1817100	rs4958676	5	153132470	GRIA1	G/A	0.00145	0.18	0.19
SNP_A-2175465	rs6889909	5	153103626	GRIA1	C/T	0.00199	0.18	0.19
SNP_A-1883803	rs11167640	5	153112499	GRIA1	C/T	0.00252	0.74	0.79
SNP_A-2118157	rs10072570	5	153159960	GRIA1	G/A	0.00381	0.22	0.25
SNP_A-4296498	rs4424038	5	153100457	GRIA1	G/A	0.00564	0.73	0.79
SNP_A-2110153	rs13354399	5	153169624	GRIA1	G/A	0.00694	0.22	0.25
SNP_A-2219492	rs17356099	5	153123241	GRIA1	T/C	0.0171	0.05	0.05
SNP_A-2040793	rs7711124	5	153123087	GRIA1	C/G	0.0206	0.66	0.70
SNP_A-2068404	rs7708391	5	153127393	GRIA1	A/G	0.0218	0.65	0.70

B allele is the risk allele,

*Race was inferred by the program STRUCTURE using HapMap phase 2 data as reference.

Supplemental Table S4. First 20 weeks of continuation therapy for Total Therapy XV

Week	Treatment Arms	
	Low Risk	Standard/High Risk
1	6MP ₇₅ + DEX ₈₋₁ + VCR _{2.0}	6MP ₅₀ + DEX ₁₂ + VCR _{2.0} + DOX + ASP ₂₅
2	6MP ₇₅ + MTX	6MP ₅₀ + ASP ₂₅
3	6MP ₇₅ + MTX	6MP ₅₀ + ASP ₂₅
4	6MP ₇₅ + DEX ₈₋₁ + VCR _{2.0}	6MP ₅₀ + DEX ₁₂ + VCR _{2.0} + DOX + ASP ₂₅
5	6MP ₇₅ + MTX	6MP ₅₀ + ASP ₂₅
6	6MP ₇₅ + MTX	6MP ₅₀ + ASP ₂₅
7	DEX ₈₋₂ + VCR _{1.5} + DOX + ASP ₁₀ × 3 + IT MHA	DEX ₈₋₂ + VCR _{1.5} + DOX + ASP ₂₅ + IT MHA
8	VCR _{1.5} + DOX + ASP ₁₀ × 3	VCR _{1.5} + DOX + ASP ₂₅
9	DEX ₈₋₃ + VCR _{1.5} + ASP ₁₀ × 3	DEX ₈₋₃ + VCR _{1.5} + ASP ₂₅
10	6MP ₇₅ + MTX	6MP ₅₀ + ASP ₂₅
11	6MP ₇₅ + MTX	6MP ₅₀ + DEX ₁₂ + VCR _{2.0} + ASP ₂₅
12	6MP ₇₅ + MTX + IT MHA	6MP ₅₀ + ASP ₂₅ + IT MHA
13	6MP ₇₅ + MTX	6MP ₅₀ + ASP ₂₅
14	6MP ₇₅ + DEX ₈₋₁ + VCR _{2.0}	6MP ₅₀ + DEX ₁₂ + VCR _{2.0} + DOX + ASP ₂₅
15	6MP ₇₅ + MTX	6MP ₅₀ + ASP ₂₅
16	6MP ₇₅ + MTX	6MP ₅₀ + ASP ₂₅
17	DEX ₈₋₂ + VCR _{1.5} + DOX + ASP ₁₀ × 3 + IT MHA	DEX ₈₋₂ + VCR _{1.5} + ASP ₂₅ + IT MHA
18	VCR _{1.5} + DOX + ASP ₁₀ × 3	VCR _{1.5} + ARA-C + ASP ₂₅
19	DEX ₈₋₃ + VCR _{1.5} + ASP ₁₀ × 3	DEX ₈₋₃ + VCR _{1.5} + ASP ₂₅
20	6MP ₇₅ + MTX	No chemotherapy

Abbreviations:

ASP_{10/25}: L-asparaginase 10,000 U/m²/dose or 25,000 U/m²/dose intramuscularly

DEX_{8-1/8-2/8-3}: dexamethasone 8 mg/m²/day orally for 5, 8, or 7 days, respectively

DEX₁₂: dexamethasone 12 mg/m²/day orally for 5 days

DOX: doxorubicin 30 mg/m²/dose intravenously

IT MHA: intrathecal methotrexate, hydrocortisone, and cytarabine

6MP_{50/75}: 6-mercaptopurine 50 mg/m²/day or 75 mg/m²/day orally for 7 days

MTX: methotrexate 40 mg/m² intravenously

VCR_{2.0/1.5}: vincristine 2.0 mg/m²/dose or 1.5 mg/m²/dose intravenously (maximum 2 mg)

ARA-C: cytarabine 2 gm/ m²/dose intravenously every 12 hours for 4 day

Supplemental Table S5. Clinical features in discovery and replication cohorts

	Discovery cohort No. = 322	Replication cohort No. = 163
Age		
1 – 10 years	240 (74.5%)	121 (74.2%)
> 10 years	82 (25.5%)	42 (25.8%)
Sex		
Female	143 (44.4%)	73 (44.8%)
Male	179 (55.6%)	90 (55.2%)
Risk arm		
Low risk	157 (48.8%)	79 (48.5%)
Standard/High risk	165 (51.2%)	84 (51.5%)
Race*		
White	211 (65.5%)	99 (60.7%)
Black	40 (12.5%)	33 (20.3%)
Hispanics	46 (14.3%)	24 (14.7%)
Asian	4 (1.2%)	2 (1.2%)
Other	21 (6.5%)	5 (3.1%)
Asparaginase allergy		
No	197 (61.2%)	100 (61.4%)
Yes	125 (38.8%)	63 (38.6%)

*Race was inferred by the program STRUCTURE¹ using HapMap phase 2 data as reference.

Supplemental Table S6. Power calculations.

Power estimation was performed by randomly sampling from two empirical distributions defined by two SNPs and the study data set.

Power estimation based on 10,000 random samples

Example SNP	Cohort	Alpha level						
		0.05	0.01	0.005	0.001	0.0005	0.0001	0.00005
SNP_A-2100887 (MAF = 0.27) Hazard Ratio=1.8	Discovery (2/3)	100%	99.97%	99.7%	97.8%	95.4%	83.7%	75.7%
	Validation (1/3)	92.1%	76%	67%	44.8%	36.2%	20.7%	15.6%
SNP_A-4213370 (MAF = 0.40) Hazard Ratio=1.5	Discovery (2/3)	99.3%	90.9%	81.4%	48.9%	34.2%	11.8%	7%
	Validation (1/3)	68.2%	35.7%	24.8%	9.1%	5.7%	1.7%	1%

MAF = minor allele frequency

Power was estimated for the “effect size” (measured by hazard ratio) on allergic reaction by cumulative incidence estimates using Gray’s test stratified by ALL risk. Within each (stratified by) genotype of this SNP, we randomly sampled 2/3 from the entire cohort without replacement. We analyzed the association between SNP and allergy as described in Methods. We repeated this process 10,000 times, and computed the % of significant results out of the 10,000 rounds, and this is the power estimate.

Supplemental References

1. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics*. 2000;155:945-959.
2. Mao, X., Bigham, A.W., Mei, R., Gutierrez, G., Weiss, K.M., Brutsaert, T.D., Leon-Velarde, F., Moore, L.G., Vargas, E., McKeigue, P.M., et al. (2007). A genomewide admixture mapping panel for Hispanic/Latino populations. *Am J Hum Genet* 80, 1171-1178.