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Inherited *GATA3* variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse

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URLs

dbGaP database: <http://www.ncbi.nlm.nih.gov/gap>

HapMap: <http://hapmap.ncbi.nlm.nih.gov>

R: <http://www.r-project.org>

Haploview: <http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview>

STRUCTURE: http://pritch.bsd.uchicago.edu/structure_software/release_versions/v2.3.3/html/structure.html

Zoom Locus: <http://csg.sph.umich.edu/locuszoom>

GSEA: <http://www.broadinstitute.org/gsea/index.jsp>

Epigenome Browser: <http://epigenomegateway.wustl.edu/browser>

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Jointly supervised research: J.J.Y.; Conceived and designed the experiments: V.P.A., S.P.H., C.L.W., C.G.M and J.J.Y.; Performed the experiments: V.P.A., K.G.R., R.C.H., J.G.F., S.E., I-M.C., G.N., E.G.B., D.G.T. and C.N.V.; Performed statistical analysis: V.P.A., J.J.Y., R.C.H., W.Y., C.C., D.P., Y.F., M.D., C.S. and G.N.; Analyzed the data: V.P.A., K.G.R., R.C.H., W.Y., H.X., S.E., J.Y.S.L., I-M.C., Y.F., M.J.B., C.S., G.N., E.G.B., D.T., F.A.K., C.N.V., M-L.L., M.D., D.B., C-H.P., W.E.E., M.V.R., S.P.H., C.L.W. and C.G.M.; Contributed to reagents/materials/analysis tools: R.C.H., J.G.F., J.Y.S.L., Y.F., E.G.B., F.A.K., C.N.V., N.J.W., B.M.C., E.R., B.W., F.Y., W.L.C., E.L., W.P.B., M-L.L., M.D., S.P.H., C.L.W. and C.G.M.; Wrote the paper: V.P.A and J.J.Y.

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The authors declare do not have any relevant competing interest and full disclosures are provided in the Supplementary Note.

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Abstract

Recent genomic profiling of childhood acute lymphoblastic leukemia (ALL) identified a novel high-risk subtype with a gene expression signature resembling Philadelphia chromosome-positive ALL and a poor prognosis (Ph-like ALL). However, the role of inherited genetic variation in Ph-like ALL pathogenesis remains unknown. In a genome-wide association study (GWAS) of 511 ALL cases and 6,661 non-ALL controls, we identified a single susceptibility locus for Ph-like ALL (*GATA3*, rs3824662, $P=2.17\times 10^{-14}$, odds ratio [OR]=3.85, for Ph-like ALL vs. non-ALL; $P=1.05\times 10^{-8}$, OR=3.25, for Ph-like ALL vs. non-Ph-like ALL) that was independently validated.

The rs3824662 risk allele was associated with somatic lesions underlying Ph-like ALL (i.e., *CRLF2* rearrangement, *JAK* mutation, and *IKZF1* deletion) and directly influenced *GATA3* transcription. Finally, *GATA3* SNP genotype was also associated with early treatment response and the risk of ALL relapse. Our results provide insights into interactions between host and tumor genomes and their importance in ALL pathogenesis and prognosis.

Progressive intensification and risk-adapted chemotherapy have improved the 5-year survival rate of childhood ALL to over 85% in most developed countries¹. However, prognosis remains poor for approximately 20% of patients with high-risk features (e.g., older age and higher leukocyte count at diagnosis, Philadelphia chromosome-positive [Ph+] ALL)²⁻⁵.

Recent genomic profiling studies have revealed the remarkable heterogeneity of childhood ALL with more granular classification of molecular subtypes. Up to 15% of childhood B-lineage ALL cases exhibit a gene expression signature similar to that of Ph+ ALL⁶⁻⁹. Defined by this common expression profile, the “Ph-like” ALL subtype has a range of structural genetic alterations in the tumor genome that activate lymphoid development, cytokine receptor, and kinase signaling pathways. Ph-like ALL commonly harbors somatic *IKZF1* deletion or mutation^{6,9}. Up to 50% of Ph-like ALL cases carry *CRLF2* rearrangements, with concurrent *JAK* mutations in approximately half of *CRLF2*-related cases^{8,10}. Ph-like ALL cases without *CRLF2* alterations harbor a range of genomic lesions targeting cytokine receptors and tyrosine kinases⁷. Importantly, Ph-like ALL is associated with a high risk of relapse^{6,8,11}.

GWAS have identified germline single nucleotide polymorphisms (SNPs) in *ARID5B*, *IKZF1*, *CEBPE*, *PIP4K2A*, and *CDKN2A/CDKN2B* that strongly influence susceptibility to childhood ALL¹²⁻¹⁵. In fact, children carrying the *ARID5B* variants not only are more likely to develop ALL in general, but are at a particularly high risk of having hyperdiploid ALL^{14,16,17}, implying interactions between inherited and acquired genetic variations during leukemogenesis. Similarly in myeloproliferative neoplasms, germline variation at the *JAK2* locus was linked to somatic *JAK2*^{V617F} mutation¹⁸⁻²⁰. Together, these observations indicate that both germline and somatic genetic variations play critical roles in tumor pathogenesis.

To this end, we conducted a GWAS of Ph-like ALL to identify germline genetic variants related to susceptibility to this ALL subtype, and to evaluate their association with somatic lesions underlying Ph-like ALL and with the risk of relapse.

In the discovery GWAS, we compared genotype frequency at 718,890 SNPs between 75 children with Ph-like ALL from the Children’s Oncology Group (COG) AALL0232 cohort and 6,661 non-ALL controls (Supplementary Fig.1). After adjusting for genetic ancestry, two SNPs at 10p14 within the *GATA3* gene reached genome-wide significance: rs3824662 ($P=2.17\times 10^{-14}$, OR=3.85 [95%CI, 2.71 to 5.47]) and rs3781093 ($P=4.94\times 10^{-12}$, OR=3.45 [2.42 to 4.93], Table 1 and Fig. 1). These two SNPs were in strong linkage disequilibrium (LD, $r^2=0.94$, $D'=1$ in HapMap CEU, Supplementary Fig. 2), representing a single susceptibility locus. The A allele at rs3824662 and the C allele at rs3781093 were over-represented in Ph-like ALL, conferring increased disease risk across ethnicity (Table 1 and

Supplementary Fig. 3). We next performed a second GWAS comparing children in the COG AALL0232 cohort who had the Ph-like expression profile (N=75) with those who did not have the Ph-like profile (“non-Ph-like”, N=436). After adjusting for genetic ancestry, the same *GATA3* SNPs, rs3824662 and rs3781093, exhibited the strongest association across the genome ($P=1.05\times 10^{-8}$, OR=3.25 [2.16 to 4.89], and $P=2.62\times 10^{-7}$, OR=2.89 [1.92 to 4.34], respectively, Table 1 and Supplementary Figs. 3 and 4). Imputation of genotypes at 37,493 additional SNPs at this locus (chr10: 60,523 to 10,060,447) did not reveal any variants with a stronger association with Ph-like ALL than the original GWAS hits (Supplementary Fig. 5).

To validate the association of *GATA3* SNPs with Ph-like ALL, we then genotyped rs3824662 and rs3781093 in 171 children with B-ALL enrolled in the COG P9906 study and in an independent cohort of 5,755 non-ALL controls. In this replication analysis, risk alleles at both *GATA3* SNPs were consistently over-represented in Ph-like ALL (N=32) compared to non-ALL controls: rs3824662 ($P=3.69\times 10^{-5}$, OR=3.14, [1.18 to 5.44]), and rs3781093 ($P=0.0001$, OR=2.95 [1.68 to 5.16]), or compared to non-Ph-like ALL (N=139): rs3824662 ($P=0.01$, OR=2.16 [1.18 to 3.97]) and rs3781093 ($P=0.004$, OR=2.55 [1.33 to 4.88], Table 1).

To explore the functions of these germline *GATA3* variants, we first examined the relationships between rs3824662 SNP genotype and *GATA3* mRNA expression. In lymphoblastoid cell lines, rs3824662 A allele was associated with significantly increased *GATA3* mRNA level (HapMap YRI, N=56, $P=0.034$, Fig. 2A; CEU and MEX, Supplementary Fig. 6). Consistently, the A allele was also linked to higher levels of DNase hypersensitivity at this locus (HapMap YRI, N=67, $P=9.5\times 10^{-8}$, Fig. 2B), indicating its influence on local chromatin accessibility and transcriptional activity. Association of germline *GATA3* SNP genotype and *GATA3* expression was confirmed in ALL blasts in both COG AALL0232 and COG P9906 cohorts (N=511, $P=9.2\times 10^{-8}$ and N=173, $P=3.6\times 10^{-6}$, respectively, Supplementary Fig. 7). Interestingly, ectopic overexpression of *GATA3* in ALL cell lines consistently led to global changes in gene expression pattern, with a highly significant enrichment of genes within the Ph-like ALL expression signature (UOCB1 cell line, $P=0.0004$; Nalm6 cell line, $P=0.001$, Supplementary Fig. 8).

Recurrent genomic lesions targeting lymphoid development, cytokine receptor, and tyrosine kinase signaling are a hallmark of Ph-like ALL. In both COG AALL0232 and COG P9906, the *GATA3* SNP rs3824662 was associated with *CRLF2* lesion, *JAK* mutation, and *IKZF1* deletion, which was also validated in a third cohort of 781 children enrolled on the COG P9905 protocol (Table 2). The A risk allele at rs3824662 was further enriched among patients with multiple “Ph-like ALL related” somatic lesions. In COG AALL0232, the frequency of the rs3824662 A allele was highest (73%) in ALL cases with *CRLF2* lesion, *JAK* mutation, and *IKZF1* deletion simultaneously, followed by patients with one or two of lesions (40%), and lowest (29%) among patients without any of the three lesions ($P=6.09\times 10^{-5}$, Fig. 3). This correlation was also validated in the COG P9906 cohort ($P=0.0005$) and in the COG P9905 cohort ($P=7.6\times 10^{-5}$, Fig. 3). Within Ph-like ALL, there was a trend that rs3824662 A allele was over-represented in cases with *CRLF2* lesions ($P=0.05$, Supplementary Fig. 9). However, the association of rs3824662 with Ph-likeness

remained significant within ALL cases that were negative for *CRLF2* alterations ($P=8.8\times 10^{-5}$, Supplementary Fig. 9), *JAK* mutation ($P=2.1\times 10^{-5}$), or *IKZF1* deletion ($P=0.001$), and in a multivariate model after adjusting for all three lesions ($P=0.001$).

Given the poor prognosis of Ph-like ALL, we next examined the relationships between *GATA3* SNP genotypes and ALL relapse. In the COG P9906 cohort, the *GATA3* allele linked to Ph-like ALL was also associated with a higher risk of relapse after adjusting for genetic ancestry (rs3824662, $N=215$, $P=0.002$, Fig. 4A). While rs3824662 was strongly related to early treatment response (i.e., minimal residual disease [MRD] at the end of induction therapy, $N=193$, $P=9.8\times 10^{-5}$, Fig. 4B), it remained prognostic even within patients who were MRD negative ($N=132$, $P=0.028$). To further define the prognostic value of the *GATA3* SNP, we tested the association of rs3824662 with relapse in the COG P9905 protocol. In this cohort, genotype at rs3824662 was significantly associated with relapse, with each copy of A allele linked to 1.43-fold increase (95% CI, 1.10 to 1.86) in the risk of disease recurrence ($N=781$, $P=0.007$, Fig. 4C). Also, the A allele at rs3824662 was associated with a higher MRD level at the end of induction therapy ($N=710$, $P=0.039$, Fig. 4D), and there was a trend for it to be linked to higher relapse risk within patients negative for MRD in the COG P9905 cohort ($N=566$, $P=0.094$).

While association of rs3824662 with Ph-like ALL was consistent across ethnicity (Supplementary Fig. 3), the risk allele frequency varied significantly among different ethnic groups. Among worldwide populations, the rs3824662 allele related to Ph-like ALL and relapse was markedly more common in Guatemalans with high Native American (NA) genetic ancestry and US Hispanics than individuals of European descent (52%, 40%, and 14%, respectively, Supplementary Fig. 10), consistent with the racial disparities in ALL treatment outcomes²¹.

The majority of children with ALL can be cured with individualized combination chemotherapy, and treatment outcome continues to improve as new molecular prognostic markers are incorporated to achieve more precise risk classification². Until recently, little is known about why a child develops a specific subtype of ALL in the first place and whether inherited genetic variations that predispose to a subtype also influence prognosis^{12,14,16}. Therefore, the goal of this GWAS was to discover the genetic basis of the susceptibility to Ph-like ALL and to better understand the biology of this important high-risk subtype. The discovery of *GATA3* variants associated with Ph-like ALL and related genomic lesions points to potentially novel mechanisms of ALL etiology and also previously unrecognized function of *GATA3* in leukemogenesis. *GATA3* belongs to a group of transcription factors characterized by 2 highly-conserved zinc fingers that mediate binding to the (A/G)GATA(A/G) sequence and protein-protein interactions²². Stage-specific transcription of *GATA3* has been extensively characterized during T cell development and differentiation²³. *GATA3* is critical for the generation of early T-lineage progenitor cells²⁴ and somatic loss-of-function mutations in *GATA3* are enriched in early T-cell precursor ALL²⁵. Inherited genetic variation in *GATA3* has also been linked to the susceptibility to Hodgkin lymphoma²⁶, although they are not related to rs3824662 or rs3781093 ($r^2<0.1$ in HapMap CEU). Other members of *GATA* family are critical for different stages of hematopoietic

development, and germline or somatic mutations in these genes can lead to a variety of hematologic disorders^{27,28}.

In strong LD in European, Hispanic, and Asian populations ($r^2=0.94$, 0.90 , and 0.97 in HapMap CEU, MEX, and CHB/JPT, respectively), rs3824662 and rs3781093 both achieved genome-wide significance in the discovery GWAS with similar association with Ph-like ALL (Supplementary Figs. 2, 3, and 11). However, rs3781093 became non-significant in multivariate analysis conditioning on rs3824662 (Supplementary Table 1). In African subjects in which these 2 SNPs are poorly linked ($r^2=0.006$ in the HapMap YRI), the A allele at rs3824662 remained over-represented in Ph-like ALL whereas rs3781093 no longer showed any evidence of association with Ph-like ALL (Supplementary Fig. 11). Also, rs3781093 was not associated with *GATA3* expression nor with local DNase hypersensitivity in HapMap YRI samples, whereas consistent evidence points to rs3824662 as a potential expression quantitative trait locus across ancestry in HapMap populations (Supplementary Figs. 6 and 12). In fact, rs3824662 was the top SNP influencing DNase hypersensitivity at this locus in the YRI population (Supplementary Fig. 12). Further examination of the ENCODE data suggested possible enhancer activities within the region encompassing rs3824662 in lymphoblastoid cell lines, based on histone methylation marks and PU.1 and P300 binding (Supplementary Fig. 13). Although functional studies are warranted to determine the exact causal variant(s) at this locus and molecular mechanisms by which *GATA3* variants influence Ph-like ALL leukemogenesis, these lines of evidence consistently point to rs3824662 as a potentially functional variation with possibly direct contribution to the GWAS signal.

The *GATA3* allele linked to Ph-like ALL was also associated with an increased risk of relapse in the COG P9906 cohort, which was validated in the COG P9905 cohort (Fig. 4). However, in the COG P9906 cohort, the *GATA3* SNP was not prognostic after adjusting for Ph-likeness, arguing that the association with relapse might be largely driven by its relationship with Ph-like ALL. *GATA3* SNP genotype was also related to *CRLF2* rearrangement, *JAK* mutation, and *IKZF1* deletion, but remained associated with Ph-like ALL after adjusting for these genomic lesions. To explore this further, we attempted to build a classification model for Ph-like ALL on the basis of *GATA3* germline SNPs, somatic lesions in *CRLF2*, *JAK*, and *IKZF1*, and genetic ancestry in 682 patients in COG AALL0232 and COG P9906, using classification and regression tree methods (CART²⁹). In this analysis (Supplementary Fig. 14), *CRLF2*, *IKZF1*, rs3824662, and NA genetic ancestry were independent predictors of Ph-like ALL, and rs3824662 was associated with Ph-likeness regardless of *CRLF2* status. Interestingly, NA genetic ancestry remained significant after stratifying on the *GATA3* SNP, indicative of additional ancestry-related germline variants that are associated with Ph-like ALL. There was also significant over-representation of the rs3824662 risk alleles in non-Ph-like ALL compared with non-ALL control ($P=0.0008$ and 0.00035 in the discovery GWAS and replication cohorts, respectively), suggesting effects of this variant on ALL susceptibility in general.

In conclusion, our genome-wide germline SNP analysis identified genetic variations in the *GATA3* gene that influence susceptibility to Ph-like ALL and the risk of relapse. These

findings highlight the intricate interactions between host and tumor genomes and their importance in the pathogenesis and prognosis of cancer in general.

ONLINE METHODS

Subjects and genotyping

The ALL cases investigated comprised children with newly-diagnosed B-precursor ALL who were treated on the Children's Oncology Group (COG) trials AALL0232, P9905³² and P9906¹⁰ (Supplementary Table 2), and non-ALL controls included 12,416 subjects^{14,33-35}. The number of subjects included in each analysis was described in Supplementary Figs 15, 16, and 17, and in the text as appropriate. This study was approved by the Institutional Review Boards with proper informed consent.

Germline genomic DNA was extracted from peripheral blood or bone marrow samples obtained during clinical remission for children with ALL. Genotyping was done for COG AALL0232 and COG P9905 cohorts and for non-ALL controls using the Affymetrix Human SNP Array 6.0. Quality control was performed for samples and SNPs according to call rate and minor allele frequency (Supplementary Fig. 1). Theta (allele signal intensity) plots were constructed using Affymetrix Genotyping Console for rs3824662 and rs3781093 (Supplementary Fig. 18). *GATA3* SNPs (rs3824662 and rs3781093) were genotyped in the COG P9906 cohort and in the Guatemalan samples by Sanger sequencing (Supplementary Table 3).

Genetic ancestry was determined by using STRUCTURE^{21,36} and was used to define ethnicity (Supplementary Note).

Ph-like ALL and GWAS

Ph-like ALL was identified in the COG ALL0232 cohort and in the COG P9906 cohort on the basis of unsupervised hierarchical clustering analysis of global gene expression profile, as described previously^{7,9,37}.

The discovery GWAS of Ph-like ALL comprised 511 ALL cases enrolled on the COG AALL0232 protocol and 6,661 non-ALL controls from the dbGaP MESA dataset. We performed two association tests to identify germline SNPs related to Ph-like ALL: we compared the genotype frequency at each SNP 1) in Ph-like ALL (N=75) vs. non-ALL controls (N=6,661) and 2) in Ph-like ALL (N=75) vs. ALL cases without Ph-like profile ("non-Ph-like ALL", N=436). Association was evaluated with logistic regression under an additive model with genetic ancestry as covariates. Population stratification was assessed by the construction of a quantile-quantile (Q-Q) plot (Supplementary Fig. 19). SNPs that reached $P < 5 \times 10^{-8}$ in the discovery GWAS were tested in an independent replication cohort: 171 ALL cases from the COG P9906 protocol and 5,755 non-ALL controls. Association with Ph-like ALL was evaluated by logistic regression with genetic ancestries as covariates by comparing 1) Ph-like ALL (N=32) vs. non-ALL controls (N=5,755) and 2) Ph-like ALL (N=32) vs. non-Ph-like ALL (N=139). Independently, the Ph-like phenotype was also identified by the recognition of outliers by sampling ends (ROSE) algorithm (Supplementary

Fig. 20). *GATA3* SNPs (rs3824662 and rs3781093) and expression were also evaluated in a separate cohort of patients with Ph+ ALL (Supplementary Note and Supplementary Fig. 21).

Functional characterization of *GATA3* SNPs was performed by examining the association of SNP genotype with *GATA3* expression, local DNase hypersensitivity, and global gene expression in ALL (Supplementary Note, Supplementary Table 4, Fig. 2, Supplementary Figs. 6,7, 12, 22, and 23), partly using previously published data sets^{30,31,38}. Associations of *GATA3* SNPs with *CRLF2*, *JAK*, and *IKZF1* somatic lesions were evaluated in the COG AALL0232, COG P9906, and COG P9905 cohorts, and with relapse in the COG P9906 and COG P9905 cohorts (Supplementary Note). Germline SNPs within the *JAK2* gene were tested for association with somatic *JAK2* mutation in ALL (Supplementary Table 5). R 2.15.1 statistical software was used for all analyses unless indicated otherwise (Supplementary Note). Statistical tests were chosen as appropriate and according to the phenotype distribution (e.g., normally or binomially distributed for continuous or categorical variables, respectively).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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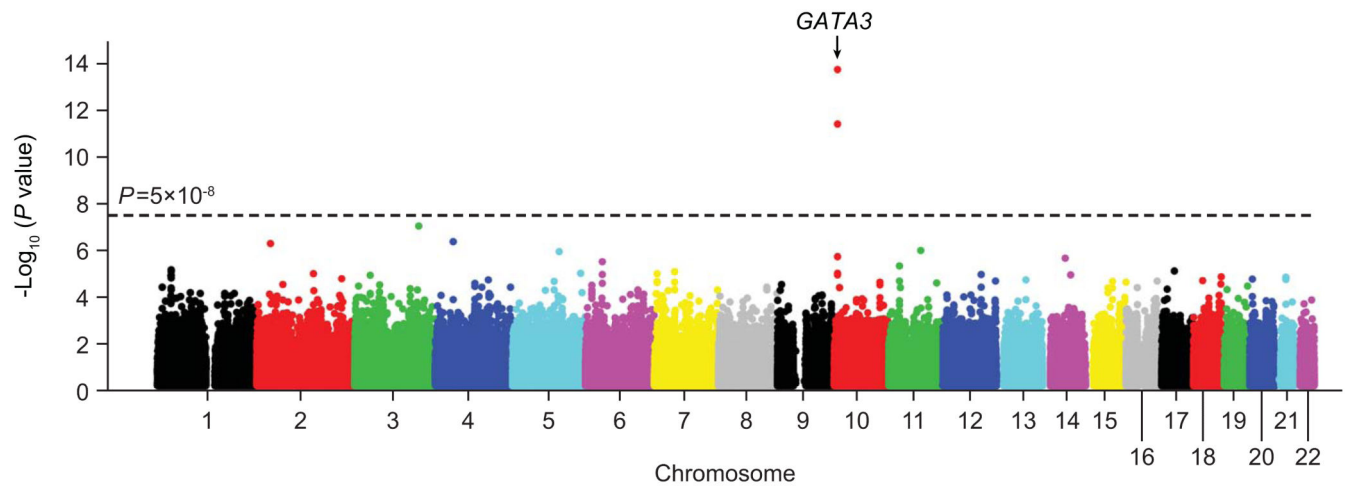


Figure 1. Genome wide association study (GWAS) of the susceptibility of Ph-like ALL

The association between genotype and Ph-like ALL was evaluated using logistic regression model for 718,890 SNPs in 75 Ph-like ALL and 6,661 non-ALL controls. P -values ($-\log_{10} P$, y axis) were plotted against respective chromosomal position of each SNP (x axis). The blue horizontal line indicates the genome-wide significant threshold ($P < 5 \times 10^{-8}$). Gene symbol was indicated for the *GATA3* locus at 10p14.

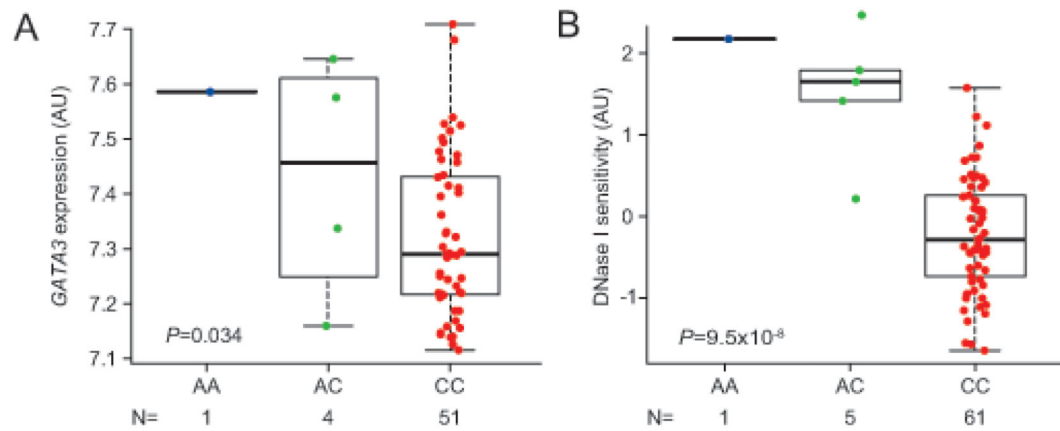


Figure 2. rs3824662 as a cis-acting regulatory element of *GATA3* transcription

GATA3 SNP rs3824662 risk allele (the A allele) was associated with higher *GATA3* mRNA in 56 unrelated lymphoblastoid cell lines from HapMap population (YRI) (A), and was related to increased DNase hypersensitivity (higher transcription activity) in 67 unrelated HapMap cell lines (YRI). *GATA3* expression and DNase hypersensitivity at this locus were obtained from previously published datasets^{30,31}. (B). Genotype-expression association and genotype-DNase hypersensitivity association was evaluated using a linear regression model, adjusting genetic ancestry as appropriate. AU, arbitrary unit. Boxes include data between the twenty-fifth and the seventy-fifth percentiles.

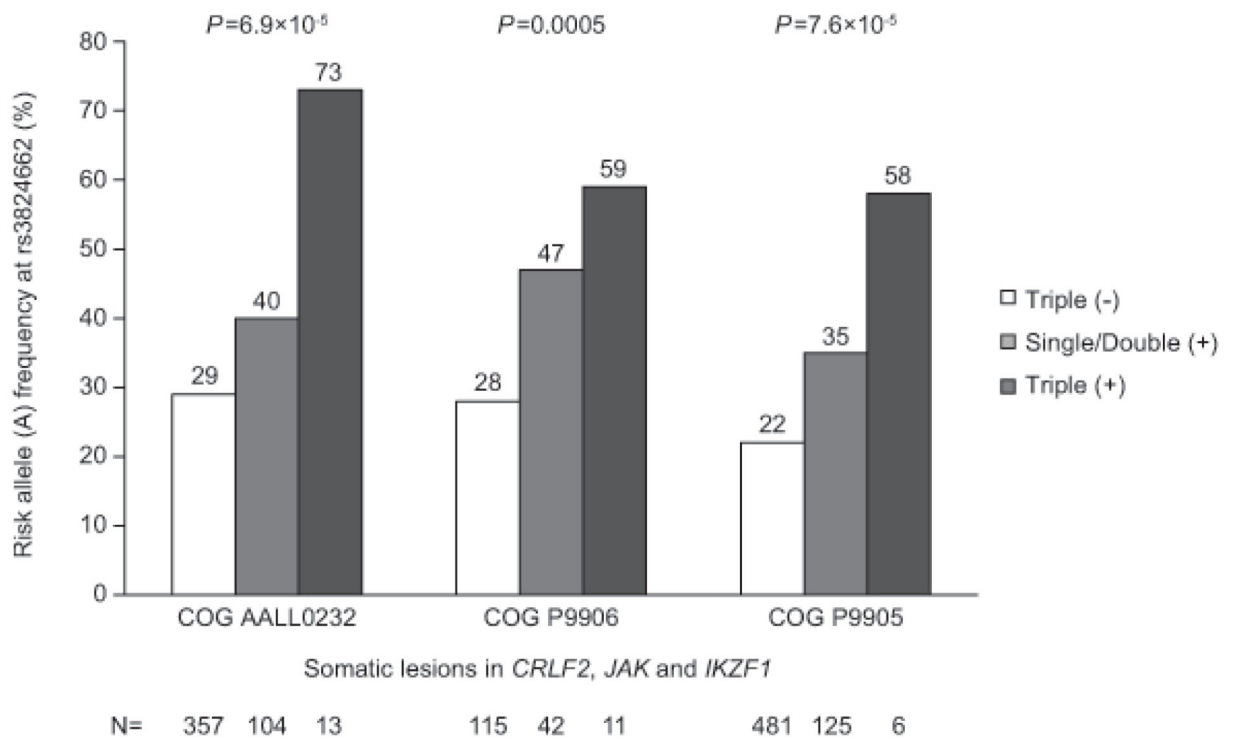


Figure 3. *GATA3* SNP rs3824662 risk allele frequency and the constellation of multiple “Ph-like ALL related” genomic lesions (*CRLF2* lesion, *JAK* mutation, and *IKZF1* deletion)
 Patients in COG AALL0232, COG P9906, and COG P9905 cohorts were grouped as triple positive, double positive, single positive and triple negative based on their status for somatic *CRLF2* lesion, *JAK* mutation, and *IKZF1* deletion. Risk (A) allele frequency at rs3824662 was highest in patients carrying all three lesions and lowest in patients carrying no lesions at these three genes, with a positive correlation between A allele frequency and the cumulative number of lesions in three cohorts ($P=6.9 \times 10^{-5}$, $P=0.0005$ and $P=7.6 \times 10^{-5}$, respectively), as determined by the ordinal regression test adjusting genetic ancestry.

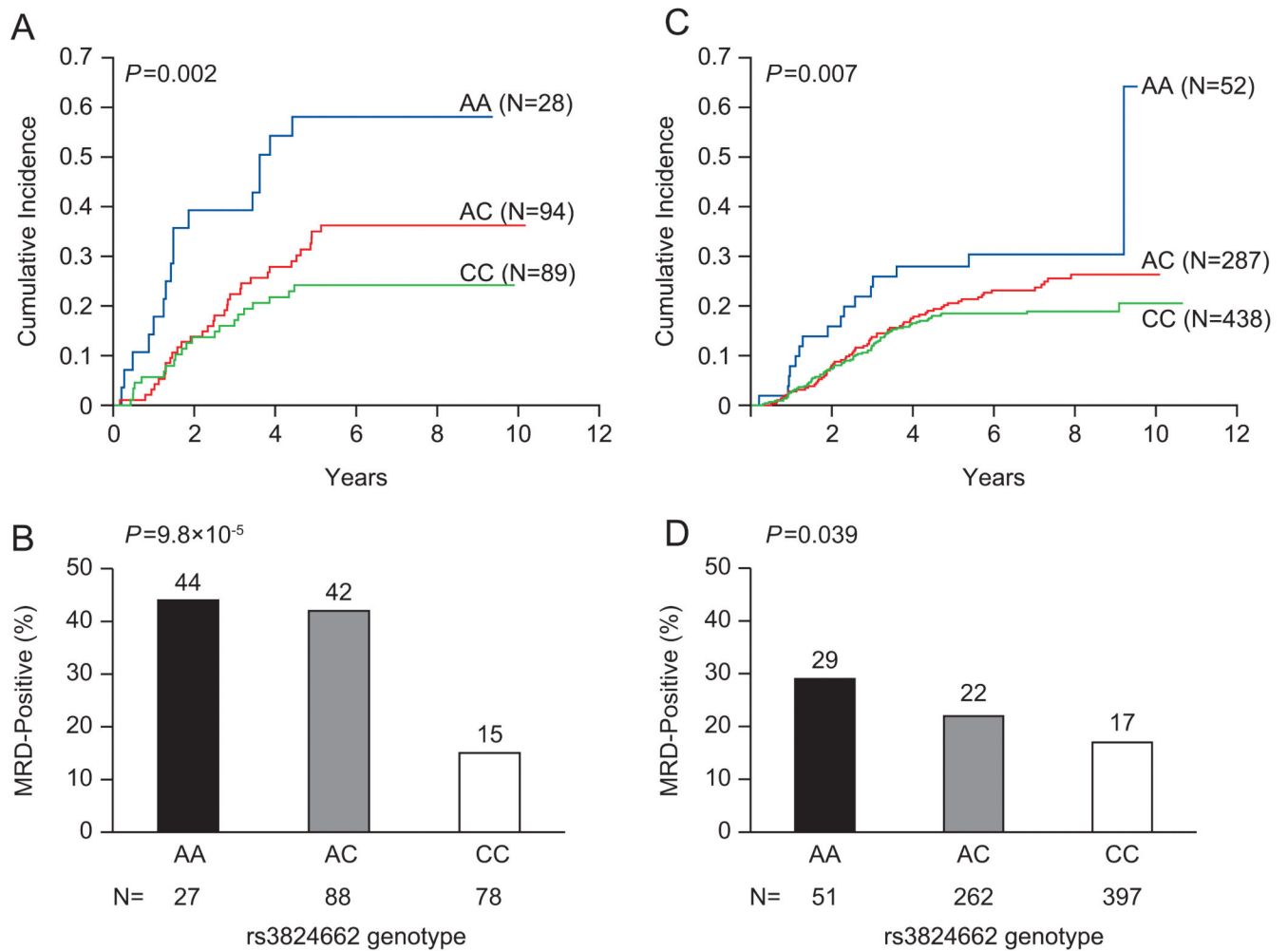


Figure 4. Genotype at GATA3 SNP rs3824662 and ALL treatment response

The cumulative incidence of relapse was compared by genotype at rs3824662 in the COG P9906 (A) and COG P9905 (B), with P value estimated by hazard regression test including ancestry as covariate. Early treatment response measured by minimal residual disease (MRD) at the end of induction was also related to genotype at rs3824662 in both COG P9906 (C) and COG P9905 (D), with P value estimated by Spearman Rank test. For both relapse and MRD, the allele linked to Ph-like ALL was also associated with worse treatment response.

Table 1
Association of GATA3 SNPs with Ph-like ALL in the discovery GWAS and replication cohorts¹

Chr	Position ²	SNP	Alleles ³	Cohort ⁴	Risk allele frequency (total number of subjects)			Ph-like ALL vs. non-ALL		Ph-like ALL vs. non-Ph-like ALL	
					Ph-like ALL	non-Ph-like ALL	non-ALL ⁵	P-value ⁵	OR (95% CI) ⁵	P-value ⁵	OR (95% CI) ⁵
10	8144214	rs3824662	A/C	Discovery	58% (75)	29% (436)	20% (6,661) ⁻¹⁴	2.17×10	3.85 (2.71-5.47)	1.05×10 ⁻⁸	3.25 (2.16-4.89)
				Replication	50% (32)	30% (139)	18% (5,755)	3.69×10 ⁻⁵	3.14 (1.18-5.44)	0.01	2.16 (1.18-3.97)
10	8141933	rs3781093	C/T	Discovery	52% (75)	26% (436)	22% (6,661)	4.94×10 ⁻¹²	3.45 (2.42-4.93)	2.62×10 ⁻⁷	2.89 (1.92-4.34)
				Replication	46% (32)	25% (139)	18% (5,755)	0.0001	2.95 (1.68-5.16)	0.004	2.55 (1.33-4.88)

Abbreviations: Chr, chromosome; OR, odds ratio; CI, confidence interval.

¹ Association of SNP genotype and Ph-like ALL was evaluated by comparing allele frequency between Ph-like ALL and non-ALL, also between Ph-like ALL and non-Ph-like ALL, after adjusting for genetic ancestry.

² Chromosomal locations are based on hg18.

³ Bold indicates risk allele for Ph-like ALL.

⁴ Discovery cohort: COG AALL0232, Replication cohort: COG P9906.

⁵ P-values were estimated by the logistic regression test and OR represents the increase in risk of developing Ph-like ALL for each copy of the risk allele compared with subjects who don't carry the risk allele.

Table 2

Association of *GATA3* SNP rs3824662 with somatic lesions in *CRLF2*, *JAK* and *IKZF1*¹

Genomic lesions	COG AALL0232				COG P9906				COG P9905			
	Subjects with lesion (RAF)	Subjects without lesion (RAF)	P-value ²	OR (95% CI) ²	Subjects with lesion (RAF)	Subjects without lesion (RAF)	P-value ²	OR (95% CI) ²	Subjects with lesion (RAF)	Subjects without lesion (RAF)	P-value ²	OR (95% CI) ²
<i>CRLF2</i> genomic lesion	39 (62%)	472 (30%)	9.64×10 ⁻⁷	3.68 (2.18-6.23)	23 (50%)	150 (32%)	0.08	1.87 (0.99-3.87)	66 (34%)	711 (24%)	0.009	1.70 (1.13-2.57)
<i>JAK</i> mutation	23 (67%)	488 (31%)	2.06×10 ⁻⁵	4.31 (2.18-8.52)	18 (58%)	155 (32%)	0.008	2.89 (1.29-6.44)	21 (38%)	610 (25%)	0.05	1.89 (0.96-3.71)
<i>IKZF1</i> deletion	84 (45%)	371 (30%)	0.00026	1.97 (1.36-2.86)	45 (50%)	122 (30%)	0.002	2.30 (1.23-3.96)	89 (37%)	519 (23%)	0.0002	1.94 (1.35-2.78)

Abbreviations; RAF, risk allele frequency (i.e., allele A at rs3824662); OR, odds ratio; CI, confidence interval.

¹ Association of SNP genotype with *CRLF2* genomic lesions (either *IGH@-CRLF2* or *P2RY8-CRLF2*), *JAK* mutation (*JAK1*, *JAK2* or *JAK3*) or *IKZF1* deletion was evaluated by comparing allele frequency between ALL cases with vs. without the specific lesion or mutation, after adjusting for genetic ancestry.

² P-values were estimated by logistic regression test and OR represents the increase in the likelihood of *CRLF2*, *JAK* or *IKZF1* somatic lesions/mutations for each copy of the A allele compared with subjects who don't carry the A allele at this SNP.