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Germline polymorphisms and the risk of therapy-related myeloid neoplasms

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ABSTRACT

Therapy-related myeloid neoplasms (t-MNs) are one of the lethal complications from cytotoxic chemotherapy/radiation therapy. There is substantial variability in the risk of developing t-MNs among individuals who receive the same level of exposures and it has been widely suspected that germline polymorphisms may influence the risk and account for the variability. As the number of cancer survivors increases, effectively identifying an individual with a high risk of developing t-MNs is crucial. Here, we review the previous studies that investigated the association between germline polymorphisms and the risk of t-MNs. Through this process, we also discuss inconsistencies among the results that stem from the difficulties in conducting an appropriate study to link germline polymorphisms with a disease like t-MN that is rare and has a strong association with external exposures.

1. Introduction

Therapy-related myeloid neoplasms (t-MNs) are defined by the World Health Organization as acute myeloid leukemia (t-AML) or myelodysplastic syndrome (t-MDS) occurring in patients who have received chemo/radiotherapy for cancer or autoimmune condition [1]. T-MNs account for 10–20% of all myeloid neoplasms and have a poor prognosis: median overall survival (OS) is 8–10 months, and 5-year OS is 10–20% [2–4]. Unfavorable cytogenetics, a high prevalence of *TP53* mutations, concurrent primary malignancies in some cases, and reduced response to conventional chemotherapy all contribute to these dismal outcomes and differentiate t-MNs from their de novo counterparts [2,5]. Furthermore, analysis of the Surveillance Epidemiology and End Results (SEER-18) database indicates that the incidence of t-MNs in the United States has quadrupled from 2001 to 2014 [6]. Although OS has improved over the same timeframe due to improved therapeutics [6], a limited understanding of t-MN pathogenesis has hindered clinicians' ability to predict or prevent disease.

T-MNs typically develop 3–8 years after exposure to initial treatment [2], though incidence and time to onset differ by the type of anticancer therapy initially used. T-MNs typically occur more frequently in patients who receive alkylating agents (e.g., cyclophosphamide) and topoisomerase II inhibitors (e.g., etoposide) compared to antimetabolites or taxanes [7,8]. Other well-known risk factors for t-MNs include older age, higher total chemotherapy doses, high-dose chemotherapy followed by autologous stem cell transplant, and use of growth stimulators such as granulocyte colony-stimulating factor [9–12]. However, overall fewer than 10% of treated patients ultimately develop t-MNs and the risk of t-MNs varies significantly even among patients with the same level of treatment exposure. These data support the hypothesis that there is inherited genetic predisposition to develop t-MNs.

Here, we review previous studies that investigated the association between germline variants and t-MN development. We review

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Table 1
Summary of studies that investigated association between germline polymorphisms and therapy-related myeloid neoplasms.

Authors	Year published	Reference No.	Tested gene/SNPs	Cases	Disease Control	Healthy Control	Short summary of findings
Felix et al.	1998	[17]	*CYP3A4*1B*	t-AML/t-MDS and t-ALL (N = 30)	de novo AML and ALL (N = 99)		*CYP3A4**1B might be protective for t-AML/MDS/ALL (3% vs. 19%, OR 0.09 95% CI 0.01–0.87), (P = 0.026)
Larson et al.	1999	[18]	*NQO1 (C609T)*	t-AML (N = 56)	de novo MDS (N = 30), AML (N = 9), CML (N = 9)		*NQO1* heterozygous/homozygous variants increased in t-AML (P = 0.036)
Naoe et al.	2000	[19]	*NQO1 (609T), CYP3A4*1B, GSTM1 and GSTT1 deletion*	t-AML/t-MDS (N = 58)	De novo AML (N = 411)	Healthy controls (N = 150)	Homozygous *NQO1* C609T had increased association with t-AML (OR 2.62, 95% CI 2.16–3.08)
Woo et al.	2000	[20]	*GSTM1* and *GSTT1* deletion	t-AML/t-MDS after childhood ALL (N = 57)	ALL patients without t-AML/t-MDS (N = 201)		No correlation with *GSTM1* and/or *GSTT1* null genotype and t-MDS/t-AML
Allan e al.	2001	[21]	*GSTM1* and *GSTT1* deletion, *GSTP1* codon 105	t-AML (N = 89)	De novo AML (N = 420)	Healthy controls (N = 1022)	*GSTP1* codon 105 hetero/homo allele is associated with the risk of t-AML (OR 2.66, 95% CI, 1.39–5.09).
Blanco et al.	2002	[22]	*CYP3A4*1B (A288G), CYP3A5*3, NQO1 (C609T)*	t-AML/t-MDS after pediatric ALL (N = 53)	Pediatric ALL without t-AML/t-MDS (N = 224)		No association with any of the genotype by itself and t-AML/t-MDS
Seedhouse et al.	2002	[30]	*XRCC1* Arg399Gln, *XRCC3* Thr241met, *XPD* Lys751Gln, *NQO1* (C609T)	t-AML (N = 34)		Healthy controls (N = 178)	*XRCC1* Gln/Gln (OR 0.28 95%CI, 0.09–0.866, P = 0.03) or Arg/Gln + Gln/Gln (OR 0.44 95% CI 0.20–0.93, P = 0.03) protective for t-AML/t-MDS
Worrillow et al.	2003	[36]	*hMSH2*	t-AML (N = 91)	De novo AML (N = 20)	Healthy controls (N = 837)	hMSH TC allele was associated with t-AML (OR 3.81, 95% CI: 1.26–11.48)
Allan et al.	2004	[37]	*XPD* Lys751Gln	t-AML (N = 91)	De novo AML (n = 420)	Healthy controls (N = 729)	*XPD* Gln751Gln is associated with chemotherapy-induced t-AML (OR 2.22 95% CI, 1.04–4.74)
Seedhouse et al.	2004	[35]	*RAD51, XRCC3, GSTM1*	t-AML (N = 51)	De novo AML (N = 216)	Healthy controls (N = 186)	*RAD51* variant x XRCC3 variant OR 8.11 (2.22–29.68) P = 0.002 for t-AML/t-MDS
Rund et al.	2005	[23]	*CYP3A41*B, MDR1 C3435T, NQO1 C609T*	t-AML/t-MDS (N = 96)		Healthy Controls: N different for each genotyping	*CYP3A4**1B protective for t-AML (2.2% vs. 15%, P < 0.025)
Jawad et al.	2006	[38]	*HLX1 P365T, HLX1 3″UTR C/T SNP, RAD51* 135 G/C	t-AML (N = 42)		Healthy controls (N = 189)	*RAD51* 135 G/C variant + *HLX1* 3″UTR C/T variant OR 9.5 (2.22–40.64), P = 0.002 for t-AML compared to healthy control
Ellis et al.	2007	[42]	*MDM2 SNP309, TP53 Arg72Pro*	Discovery: t-AML/t-MDS (N = 80) Validation: t-AML/t-MDS (N = 91)	De novo AML (N = 721)	Healthy controls (N = 2392)	None of the genotype itself was associated with t-AML risk. *MDM2* TT x TP53 Arg/Arg genotype and *MDM2* SNP309 G allele x *TP53* Arg72Pro allele was associated with increased risk of t-AML
Guillem et al.	2007	[31]	*NQO1, MTHFR, XRCC1, ERCC5, GSTP1, XPC, XRCC3, NBS3*	t-MDS/t-AML (N = 44)	Breast or hematological cancers without t-MDS/t-AML for 7 years (N = 46)	Healthy controls (N = 80)	No SNPs associated with t-AML/t-MDS in global comparison. In a cohort of breast cancer patients, *MTHFR* 677T and 1298A haplotype had an association with t-AML/t-MDS. In a cohort of hematologic malignancies, *MTHFR* 677C and 1298C haplotype protective of t-AML/t-MDS

(*continued on next page*)

Table 1 (*continued*)

Authors	Year published	Reference No.	Tested gene/SNPs	Cases	Disease Control	Healthy Control	Short summary of findings
Bolufer et al.	2007	[25]	*CYP1A1*2A, CYP2E1*5B, CYP3A4*1B, deletion of GSTT1 and GSTM1, NQO1 (C609T), MTHFR (C677T), TYMS 2R/3R*	t-AML/t-MDS (N = 78)		Healthy Controls (N = 454)	None of the genotype by itself had a statistical association with t-AML. Having at least one of the *CYP1A*2*, deletion of *GSTT1* and *NQO1* C609T variant allele had increased association with t-AML (OR 1.94, 95% CI 1.1–3.4, P = 0.02).
Worrillow et al.	2008	[39]	*MLH1* rs1800734	t-AML (N = 96)	De novo AML (N = 420)	Healthy controls (N = 952)	*MLH1* 93 status with GA or AA is associated with t-AML/t-MDS after alkylating agents. No association with the global comparison.
Knight et al.	2009	[16]	Affymetrix 10K SNP array (11, 560 SNPs, 9,771 autosomal SNPs)	Discovery: t-MNs (N = 80) Validation t-MNs (N = 70)		Discovery: healthy controls (N = 150) Validation: cancer-free controls (N = 95)	rs1394384 (OR = 0.3, 95% CI 0.2–0.6), rs1381392 (OR = 2.1, 95% CI, 1.3–3.4), rs1199098 (OR = 0.5, 95%CI, 0.3–0.8) were associated with chr omosome 5/7 abnormal t-MNs
Ding et al.	2012	[26]	*GSTM1, GSTP1, GSTT1, NQO1, CYP1A1, CYP3A4, MTHFR, TP53, MDM2, MLH1, MSH2, XPD, RAD51, XRCC1, XRCC2, XRCC3, XRCC4, LAMC2, NMNAT2, SCGE, PEG10, FRAP1, PTPRT*	t-MNs after HL/NHL (N = 49)	HL/NHL patients without t-MNs (N = 49)		*TP53* P72R combined with *MTHFR* C677T or *TP53* P72R x *MTHFR* A1298C is associated with t-AML/t-MDS
Schultz et al.	2012	[45]	*TP53, BRCA1, BRCA2, BARD1, CHEK2*	t-MNs (N = 53)			Retrospective analysis of t-MN patients. 17% of the cohort carried germline mutations in *BRCA1*, *BRCA2*, *BARD1*, or *TP53*.
Dubois et al.	2013	[40]	Custom SNP array of 384 SNPs in DNA repair, drug metabolism, transport, signal transduction, and oncogenesis related genes	Discovery: t-MDS (N = 20) Validation: t-MDS (N = 19)	Discovery: de novo MDS (N = 39) Validation: de novo MDS (N = 24)		*MGMT* rs2308321 and rs2308327 were associated with t-MDS over de novo
Fabiani et al.	2014	[27]	*CYP3A4, NQO1, GSTA1, GSTM1, GSTP1, GSTT1, RAD51, XRCC3, BCL2L10*	t-MNs (N = 111)	De novo MNs (N = 109)	Healthy controls (N = 259)	*BCL2L10* Leu/Arg (OR 0.5, 95% CI: 0.29–0.85), P = 0.010 or Leu/Arg or Arg/Arg (OR 0.5, 95% CI: 0.30–0.83, P = 0.007)
Voso et al.	2015	[41]	14 Fanconi pathway genes: *FANCD1, FANCJ, FANC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, FANCM, FANCN, PALB2*	t-MNs (N = 37)	De novo AML (N = 24)		No difference in confirmed -germline FANC gene polymorphisms between de novo AML and t-MNs
Churpek et al.	2016	[44]	*APC, ATM, ATR, BABM1, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRCC36, BRIP1, CDH1, CDK4, CDKN2, CHEK1, CHEK2, FAM175A, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PRSS1, PTEN, RAD50, RAD51,RAD51B, RAD51C, RBBP8, RET, SMAD4, STK11, TP53, TP53BP1, UIMC1, VHL, XRCC2, XRCC3*	t-MNs after breast cancer (N = 47)			Retrospective analysis of t-MN patients. 20% of the cohort carried germline mutations in *BRCA1*, *BRCA2*, *TP53*, *CHEK2*, and *PALB2*.
Cabezas et al.	2019	[43]	*TP53* Arg72Pro and *MDM2*	t-AML/t-MDS (N = 45)	Acute leukemia who did not develop t-MNs (N = 45)		*MDM2* T/G + G/G vs T/T OR 3.75 95% CI: 1.51–9.31, P = 0.0003. *MDM2* T/G vs. T/T OR 3.09, 95% CI: 1.14–8.35, G/G vs. T/T: OR 5.60 95% CI: 1.58–19.87, P = 0.0009

the methodology and study design of the previous studies and how they evolved. We discuss the challenges of designing a study investigating the connection between germline variants and t-MN development. Because the focus of this edition is t-MNs, we do not cover germline variants that are known to predispose individuals to myeloid neoplasms in general, which have been extensively reviewed elsewhere [13–15]. It is very likely that such variants are also associated with an increased risk for t-MNs.

2. Previous studies investigating germline polymorphisms and t-MNs

Table 1 summarizes the previous association studies of germline polymorphisms and t-MNs. Notably, to date, there is only one study that performed unbiased genome-wide association study [GWAS] [16], and all other studies tested the association with a handful of genes that were selected based on particular hypotheses. Furthermore, while almost all studies chose a case-control design, there is a variability in the control cohort. Most studies used healthy population or de novo counterparts as control, and only a few studies used controls sharing the same extrinsic risks (i.e., cancer patients who were treated with chemotherapy/radiation therapy and did not develop t-MNs). These differences make the interpretation of the link between germline variants and t-MNs difficult.

3. Studies designed by particular hypotheses

Earlier studies hypothesized that t-MN risk is associated with variability in drug metabolisms and analyzed the association between t-MNs and polymorphisms in drug metabolism genes [17–23]. These included genes involved in cytochrome P450 enzymes (*CYP3A4* and *CYP3A5*), *NQO1*, *GSTT1*, and *GSTM1*. This was a plausible hypothesis because the risk of t-MNs is high with the exposure to particular classes of drugs, such as alkylators and topoisomerase II inhibitors. For example, CYP3A4 metabolizes etoposide (topoisomerase II inhibitor) to epipodophyllotoxin catechol and then to a quinone derivative, which potentially causes DNA adducts [24]. *CYP3A4* A290G variant (also known as *CYP3A4**1B [rs2740574]) affects 5' promoter region of the gene and has been suggested to downregulate CYP3A4 [17], which was hypothesized to reduce quinone level and thus protective for t-MN development. Two case-control studies (one with de novo leukemia as control and the other with the healthy population as control) suggested that *CYP3A1**1B was protective for t-AML/t-MDS [17,23]; however, this association was not verified in other studies [19,22,25–27].

The quinone derivative produced by CYP450 enzymes is catalyzed by NAD(P)H: quinone oxidoreductase (NQO1) [28]. *NQO1* C609T variant (rs1800566) has been shown to result in increased degradation of the translated protein leading to dysfunctional NQO1, and the homozygous variant was predicted to eliminate its function [29]. Therefore, it was hypothesized that heterozygous or homozygous *NQO1* C609T variant will result in an increased level of quinone and increases the risk of t-MNs. Many studies investigated the association, however demonstrating mixed results. Studies by Larson et al. and Naoe et al. both showed that individuals with homozygous *NQO1* C609T had increased likelihood to develop t-MNs [18,19]. However other studies did not confirm this association [22,23,27,30,31.]].

Another detoxifying enzyme glutathione S-transferase (GST) has been a subject of investigation because GSTs catalyze the conjugation of electrophilic compounds to glutathione and alkylating agents are known substrates of GSTs [32]. *GSTT1* and *GSTM1* encode two classes of GST enzymes and deletion of these genes is relatively common in the general population [33,34]. Seven studies analyzed the association between deleted genotypes of *GSTT1/GSTM1* and t-MNs but none found a statistical correlation [19–21,25–27,35].

The next class of genes investigated for the association with t-MNs was DNA damage repair pathway genes [26,30,31,35–41]. The most frequently investigated genes in this class include *XRCC1*, *XRCC3*, *XPD*, and *RAD51*, which are involved in base excision repair (*XRCC1*), homologous double-strand break (*XRCC3* and *XPD*), and nucleotide excision repair (*XPD*) [30]. Polymorphism in codon 399 of *XRCC1*, codon 241 of *XRCC3*, and lysine 751-glutamine of *XPD*, and codon 135 of *RAD51* were tested for the association with t-MNs; however, none of the variants have shown a consistent association with t-MNs [26,27,30,31,35,37].

Furthermore, three studies investigated the association between *TP53* Arg72Pro and *MDM2* SNP309 T/G (rs2279744) polymorphisms and t-MNs [26,42,43]. However, the results were somewhat inconsistent.

Lastly, Churpek et al. performed a retrospective analysis of t-MN patients with a history of breast cancer and analyzed the prevalence of breast cancer susceptibility gene mutations (42 genes). They found that approximately 20% of t-MNs with a history of breast cancer carried germline mutations in one of the breast cancer susceptibility genes (*BRCA1/2*, *TP53*, *PALB2*, and *CHEK2*) [44]. Similar results were also reported by Schulz et al., in which 17% of their t-MN cohort carried one of the familial cancer susceptibility gene mutations (*BRCA1/2*, *BARD1*, and *TP53*) [45]. These results suggest that patients with familial cancer susceptibility gene mutations are also at risk of t-MNs.

4. Genome-wide association study for t-MNs

Knight et al. performed GWAS using the Affymetrix 10K SNP array and compared the SNPs distribution between t-MN cases and healthy controls [16]. The study first identified 15 SNPs that had significant enrichment with t-MN cases with $P < 0.001$ and found 3 of them having a trend toward significant enrichment in t-MN cases in the replication cohort. Two of the SNPs, rs1394384, and rs1199098 were protective against t-MNs, whereas rs1381392 was associated with increased risk of t-MNs. rs1394384 is an intronic polymorphism for *ACCN1*, a gene encoding an amiloride-sensitive cation channel [46]. rs1199098 is in linkage disequilibrium with *IPMK* gene, which encodes a multi-kinase that positively regulated AKT [47]. rs1381392 has not been associated with any known genes. Functional characterization of these SNPs has not been done. In this GWAS study, none of the earlier SNPs (drug metabolisms, DNA repair, and *TP53/MDM2*) showed association with t-MNs.

5. Challenges of identifying germline predispositions for t-MNs

Inconsistent results from the previous studies highlight the challenges of designing an adequate study to identify germline predispositions for t-MNs. First, because t-MNs are rare, it is difficult to collect a large number of cases required to have sufficient power in the study. Based on the assumption of odds ratio 2, 5% disease prevalence, 5% minor allele frequency, complete linkage disequilibrium, 1:1 case-control ratio, and a 5% error rate in the allelic test, one study suggested that 248 cases are required to test a single SNP marker [48]. When testing 500,000 SNP markers in GWAS design, the same study suggested that 1206 cases are required to ensure 80% power. Sample size could be lower if the risk allele has a stronger effect size. However, even with the assumption of odds ratio 2.5, it still requires 134 cases and 653 cases for single SNP and 500,000 SNPs, respectively. These are difficult numbers to achieve for t-MNs especially in a single center study design.

Second, collecting an appropriate control population is essential for detecting biologically significant risk alleles. Ideally, control population should share the same extrinsic risks with cases. Because t-MN patients, by definition, have a history of primary malignancy and exposure to chemotherapy/radiation therapy, the best control population is patients with similar primary malignancy who received similar chemotherapy/radiation regimens and doses.

Third, clinical heterogeneity among t-MN cases may introduce bias due to phenotype misclassification. T-MN is a clinical diagnosis and whether there is an actual biological connection between prior exposures and a given case of t-MN is not always clear. Therefore, restricting cases to phenotypically homogeneous t-MNs, such as with chromosome 5/7 abnormal and/or TP53 mutation might help to reduce the bias. Furthermore, topoisomerase II inhibitor-induced t-MNs (often involving 11q23 rearrangement) and alkylator-induced t-MNs might have a distinct mechanism of development, and the entities might need to be separately analyzed.

Lastly, a future study needs to take clonal hematopoiesis (CH) into account as another confounding factor [49]. Clonal hematopoiesis (CH) has been recently recognized as an essential risk factor for t-MNs [50,51] and it is conceivable that risk allele for t-MNs might overlap with that for CH. Two recent studies identified *TERT* rs34002450 as a risk allele for CH, and it is of interest whether the allele could also influence the risk of t-MNs [52,53].

6. Future directions

With the trend of increasing use of immunotherapy and molecularly targeted therapy in cancer treatment, it is not clear whether the incidence of t-MNs will continue to rise in long-term. However, as the number of cancer survivors increases, patients at risk for t-MNs is expected to rise. Therefore, there will be a critical need to effectively identify individuals at risk of t-MNs. So far, there are no germline polymorphisms that have consistently shown to predict the risk of t-MNs. This is because of the abovementioned challenges in designing an appropriate study to identify a true risk allele. These challenges are perhaps addressable by combining forces between multiple institutions and collect a large number of t-MN cases and well-matched controls.

Conflicts of interest

Consulting fees: Celgene, Kyowahakko Kirin, Symbio Pharmaceuticals.

Practice points

- There is substantial variability in the risk of t-MN development among cancer patients.
- Various germline polymorphisms in genes associated with drug metabolisms and DNA damage repair have been implicated in the risk of t-MNs, however, the results are inconsistent, and the polymorphisms are not ready to be used in the clinic as markers of prediction.
- Patients with known familial cancer predisposition gene mutations (e.g., *BRCA1/2* or *TP53*) have a high risk of developing t-MNs.

Research agenda

- There is a critical need to identify clinically useful markers for t-MN risk prediction.
- Large-scale unbiased GWAS with appropriate control is needed to identify novel germline polymorphisms that predict the risk of t-MNs.

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