The TP53 Pro72Arg SNP in de novo acute myeloid leukemia

In a recent issue of Haematologica, Lucena-Araujo and co-workers report that the germline variation rs1042522 in TP53, which encodes either proline (72Pro) or arginine (72Arg), influences the risk of de novo acute myeloid leukemia (AML) development and overall survival (OS).[1] This stems from a case-control study of patients and healthy volunteers from Brazil. In comparing the frequency of the rs1042522 genotype in 198 AML cases and 224 age- and sex-matched controls with no history of hematological disease, the homozygous 72Pro status was reported to be associated with 2.06 increased AML risk. Genotyping was performed by the polymerase chain reaction restriction fragment length polymorphism (RFLP) method. Peripheral blood was used as DNA source material in healthy volunteers, but the source was not specified for the patients. Importantly, no deviation from Hardy-Weinberg equilibrium (HWE) was detected in patients or controls groups. Univariate survival analysis (n= 119, 63%), after exclusion of patients who did not receive conventional chemotherapy, revealed a 41% decreased risk of death from AML (hazard ratio [HR] 0.59, 95% CI 0.37 to 0.95) for patients with homozygous 72Pro resulting in a significantly higher calculated 5-year OS rate (42%) compared to the other genotypes (12%; P=0.031). This survival benefit was not apparent in multivariate analysis where also established risk factors like age and cytogenetic risk groups failed to show significant associations. The median follow up for the entire cohort was 135 days.

Following an analysis of the TP53 Pro72Arg SNP in patients with therapy-related AML,[2] we have very recently performed a case-control study of 215 de novo AML patients and 3759 controls from Austria and Germany.[3] Constitutional DNA from buccal swabs or saliva was used for genotyping of rs1042522 by the TaqMan SNP Genotyping Assay whereby more than 10% of each patient cohort were also genotyped by direct sequencing. No deviation from HWE was detected in any group, and median follow up for all patients was 427 days for overall survival (OS), and 344 days for relapse free survival (RFS). We did not find any evidence to support rs1042522 as a risk factor of de novo AML development and survival; the latter could be assessed in 186 patients who were treated by standard induction and consolidation therapy, including allogeneic stem cell transplantation, according to European LeukemiaNet (ELN) risk groups. Known risk factors such as age and ELN risk groups, but not rs1042522 status, were found to influence survival in univariate and multivariable analyses comparable to previous published studies.

How can these obviously conflicting results be explained? There are major differences between both studies which we think must be addressed. Most importantly, the difference with respect to the risk of AML is due to the genetic background of the study populations, which is mixed in the Brazilian study according to Bezerra et al., whereas almost only Caucasians participated in our study. Consequently, genotype frequencies are highly significantly different between both cohorts (Table 1). It is possible that other, yet unknown genetic and environmental modifiers linked to certain population backgrounds, might further modulate the risk of AML caused by rs1042522. Evidence for such a population-specific risk can be found in a recent meta-analysis of 32 case-control studies involving 8,586 cases and 10,275 controls, which revealed an increased risk of colorectal cancer for Asian individuals with homozygous TP53 72Pro, but not for the overall population.[4]

Table 1. Distribution *TP53* rs1042522 genotypes in cases and controls.

Cohort	Pro/Pro (%)	Pro/Arg (%)	Arg/Arg (%)	*P* (χ^2)
AML (Austria, Germany)	20 (9.3)	78 (36.3)	117 (54.4)	0.000001
AML (Brazil)	43 (22.8)	89 (47.1)	57 (30.2)	
Controls (Brazil)	28 (12.5)	107 (47.8)	89 (39.7)	0.000015
Controls (Austria, Germany)	249 (6.6)	1482 (39.4)	2028 (54.0)	

Other issues that should be considered in the survival analyses are patient sample size and follow up. As described above, a substantial percentage of patients were excluded from survival analysis in the study of Bezerra et al., which increases the chance of sample bias and type I error, and median follow up was shorter than a year masking late events. Indeed, although the difference in OS between homozygous 72Pro and the other genotypes was modestly significant, other known strong risk factors such as age and cytogenetics were not significantly associated with OS.

From a technical point of view, one must note that RFLP was used for genotyping the Brazilian cohorts but no other methods, such as direct sequencing, were applied for validation of the results. Furthermore, DNA source material was not specified for the patient population. Although the authors have stated that chromosome 17p abnormalities were not observed upon karyotyping in their AML cohort, submicroscopic alterations at 17p, the locus of TP53, may, nevertheless, have skewed their results if diagnostic material were used for genotyping.[5]

In conclusion, the comparison of these two analyses on the role of the TP53 Pro72Arg SNP with respect to AML risk and survival following intensive treatments again reveal the ongoing challenges of genetic association studies. Importantly, consideration of the genetic background of populations analyzed remains a major issue with respect to interpretation and potential application of their results.

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