Translating genetic questions into clinical answers in acute myeloid leukemia

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The p53 tumor suppressor is central to the process by which cells sense and respond to a variety of stresses with oncogenic potential. Underscoring the importance of p53 to this process is the observation that the TP53 gene is mutated in nearly 50% of all cancers [1]. This high frequency of TP53 loss suggests that constitutional variation in TP53 could alter the tumor suppressing activity of the protein, and consequently, would be associated with an altered risk for cancer. A common single nucleotide polymorphism (SNP) in TP53 at codon 72 that encodes either an arginine (Arg) or a proline (Pro), for example, has long tempted investigators studying cancer susceptibility, first, because the allele frequency of this SNP follows a latitudinal cline suggesting it is under environmentally driven selective pressure [2], and secondly, because there are data to indicate that the Arg72 variant is more effective at inducing apoptosis and suppressing malignant transformation than is the Pro72 form [3,4]. Despite years of study in many different cancers, however, the association of this SNP with cancer remains controversial [5–10].

The association of the MDM2 SNP309 with cancer is less open for debate. MDM2 is a transcriptional target of p53, the protein product of which functions as the primary negative regulator of p53. Bond et al. [11] identified a T/G SNP in the intronic MDM2 promoter (the SNP309), and found that the G allele enhances the binding affinity of the Sp-1 transcriptional activator to the MDM2 promoter. The increased binding results in increased MDM2 transcription and lower steady-state levels of p53, thereby attenuating the p53-mediated stress response. Data from a number of groups have convincingly demonstrated that the G allele is associated with accelerated cancer development, both for a variety of sporadic cancers [5,11,12] and for patients with Li-Fraumeni syndrome [13]. Of note, the contribution to cancer susceptibility made by this SNP is not distributed equally; pre-menopausal female carriers are at greatest risk. This observation underscores the need to include biologically relevant clinical data in association studies to ensure that disease associations specific to patient subsets can be detected.

Previously, Ellis et al. [14] found that, although neither the TP53 codon 72 SNP nor MDM2 SNP309 was by itself detectably associated with therapy-related acute myeloid leukemia (t-AML), there was an interactive effect between the two variants that was associated with an increased risk for t-AML in patients of European descent treated with chemotherapy but not radiation therapy (OR = 2.05, CI 1.07–3.92, and p-value for interaction = 0.029). With regard to sporadically occurring AML, they observed a modest association between the MDM2 SNP309 G allele (OR = 1.29, CI 0.85–1.95, and p-value = 0.10) and increased risk of AML in 404 patients and 816 matched controls, all of European descent. In contrast, Phang et al. reported that the G allele was associated with a decreased risk of different forms of leukemia, including AML, in 44 patients and 160 healthy individuals, all of whom were Singaporean Chinese (OR = 0.38, CI 0.18–0.82, and p-value = 0.025) [15].

In Leukemia Research, Xiong and colleagues report the results of a case–control association study to assess the contribution of the MDM2 SNP309 and the TP53 codon 72 polymorphisms to the risk of AML in 231 Northern Chinese patients and 128 healthy controls. They found that the TP53 codon 72 variant is not associated with AML, but that the SNP309 G allele confers a significant increase in disease risk (OR = 2.38, CI 1.38–4.10, and p-value = 0.002). They report no association between the MDM2 SNP309 and gender or age of onset, however, and find no evidence for an interactive effect between the MDM2 and TP53 variants [15].

How can we explain these conflicting results concerning the role of the MDM2 SNP309 in AML? First, the case and control cohort sizes were relatively small and underpowered, in particular for the Phang and Xiong studies. This limitation increases the likelihood that true associations will be missed and that spurious associations will be detected. It also makes it difficult to estimate the true effect size of an associated variant. We note, for example, that although the odds ratios reported by Xiong et al. and Ellis et al. apparently differ, the confidence intervals overlap. Secondly, genetic or environmental interactions could modify the contribution of the variant to AML risk in different populations. Thirdly, if the MDM2 SNP309 G allele predisposes to a particular subtype of AML, then its contribution to disease may be masked by differences in the types of AML comprising the cohorts analyzed in the three studies. This concern is exacerbated in Phang et al. [16] in which different types of leukemia are lumped together. Taken together, these concerns reinforce the
need for clinical data that are as granular as possible in the largest cohort possible.

Even given well-designed and appropriately powered studies, the question that emerges from these analyses is how do these data translate clinically? The clinical value of a variant that contributes even a threefold increase in risk to a relatively rare disorder such as AML is limited. By definition, there will be many more individuals carrying the risk allele who do not develop the disease than there will be individuals who do develop the disease. Furthermore, the etiology of complex diseases is most likely due to interactions between multiple genetic factors and a variety of difficult to quantify non-genetic factors and oncogenic exposures. Currently, there is no satisfactory way to assess how these gene-by-gene or gene-by-environment interactions might alter the contribution of any single susceptibility allele to disease risk. Thus, clinicians are faced with a dilemma—to genotype or not to genotype, and if they choose to genotype, what do they do with this information?

One solution is to employ a “brute force” approach by undertaking ever larger studies at ever increasing cost. An alternative solution is to undertake smarter studies. As an example, Knight et al. [17] found that by using recurrent acquired genetic alterations (abnormalities of chromosomes 5 and/or 7) as a surrogate for alkylator-induced t-AML, they were able to define a mechanistically homogeneous patient cohort for association testing, thereby obviating the need to rely upon clinical characterizations that may appear uniform but which actually have disparate biological etiologies. By then conditioning their analysis on a potent and well-defined environmental exposure, cytotoxic therapy, they were able to potentiate their ability to detect and replicate genetic associations in t-AML even with relatively small numbers of cases and controls. Thus, they took advantage of biology to unmask gene-by-environment interactions in t-AML that would have been undetectable in an unselected cohort of t-AML patients.

In the case of de novo AML, there are multiple acquired genetic lesions that can be used to discriminate among mechanistically distinct AML subtypes. Some patients with AML have apparently normal karyotypes, while others have activating mutations of FLT3, translocations involving RARα or MLL, or a host of other lesions. The prognostic implications of each differ dramatically as do their treatment strategies. These acquired molecular abnormalities can be used to define etiologically distinct subsets of patients in which constitutional susceptibilities specific to different disease mechanisms may be discerned. How the association signals of these risk variants can be enhanced, however, remains to be determined.

The study of germline genetics in complex diseases such as AML is still in its infancy. Smarter studies are likely to be both more informative and more efficient than brute force strategies. Moving forward, the challenge will be to apply the lessons learned from t-AML to de novo AML. By incorporating AML biology into the design of genetic studies it may be possible to define biologically homogeneous patient subsets and to identify conditions or exposures that enhance the detection of genetic variants truly associated with AML. Ultimately, redefining the genetic question may be necessary before it will be possible to integrate genetics into the medical armamentarium.

Conflict of interest

None of the authors have any conflict of interest to declare.

References


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