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Step by Step Progress Towards Genetic Knowledge of Prostate Cancer

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Dear Editor,

Cancer is a medical compendium. Scientists worldwide aspire to understand the prevalence and severity of cancer and its associated genomic variations. In recent years, there have been major advances in genomic technologies involving new generation sequencing (1, 2), large scale array tissue expression (3, 4), and multiple polymorphism/mutation screening (5), all of which have been used in genetic and cancer studies. In addition, the screening of large populations for cancer, multicenter studies, and complete genomic analyses of cancer have been undertaken in several reference centers. In view of these technological and scientific advances, are studies of single polymorphisms, restricted populations, and a single type of cancer, still relevant or valid? The report by Seidabadi et al. titled "R462Q mutation in prostate cancer specimens" addressed these questions indirectly (6).

Although the new technologies indicated above are costly and their implementation in genetic studies can be problematic in some countries, their use in diagnosis and research is nevertheless a reality (7, 8). With sufficient effort, the genetic problems associated with cancer can be systematically addressed using a step-by-step, mutation-by-mutation, and polymorphism-by-polymorphism approach. Although this process is long and demanding, the information obtained on the genetic background of cancer can be rewarding.

Prostate cancer is a high-prevalence cancer, a genetic understanding of which must consider common and rare variants, as well as the patient's ethnic background (9, 10). One potential gene associated with prostate cancer is the RNASEL (ribonuclease L; MIM #180435) gene, located in chromosomal region 1q25. Variants of this gene have been associated with hereditary prostate cancer (11, 12), whereas few studies have addressed familial and sporadic prostate cancer (9, 13).

The RNASEL gene codes for the enzyme endoribonuclease L which mediates the apoptotic and antiviral activities of interferon; this protein is a member of the interferon-regulated 2-5A tumor suppressor gene system. Viral infection in prostate cancer is a well-known problem (9) and could potentially involve the RNASEL gene, although conflicting results have been reported on this issue (14, 15).

Several polymorphisms have been described for the RNASEL gene, with one of the most important being R462Q (G1385A; rs486907), in which the variant allele showed three times less enzymatic activity than the normal enzyme. Seidabadi et al. (6) examined the association between this polymorphism and prostate cancer. For this, they enrolled 121 subjects including 51 patients with familial prostate cancer and 70 patients with non-cancerous prostate cancer. Although polymorphism data have been associated with patient's age, clinical parameters and geographical location, no such association was observed for the present polymorphism [prostate cancer: RR–82% (42), RQ–14% (7) and QQ–4% (2); patients with non-cancerous prostate: RR–87% (61) and RQ–13% (9)]. Similarly, no association was observed between this polymorphism and prostate cancer. The publication of this "negative" finding is a step in the right direction since negative results are generally difficult to publish. Indeed, many studies are not published because they contain no positive data. Publishing such studies can lower the costs of scientific studies by preventing unnecessary repetition and improving our scientific knowledge.

The study of many variants simultaneously can lead to rapid expansion of our scientific knowledge. However, generation of large amounts of information means there is an increasing need to deal with spurious data and technical limitations, and to address a problem peculiar to this genome era, namely, the question of incidental findings (8, 16). As the number of polymorphisms increases, so does the probability of encountering a positive result

or relationship, but does this necessarily reflect reality? To address this problem, corrections are sometimes introduced such that true relationships are maintained and the most "positive" results continue to be positive (17). Another question that surfaces is: are the remaining results (after appropriate corrections) negative results, or are they masked by the statistical correction? One way to deal with such complex scenarios is to restrict the population size and to study only one polymorphism and one type of cancer and relate these to several clinical data. This step-by-step approach can facilitate the identification of associations and help us to understand this complex disease.

Another aspect involves technical limitations. Although new technologies can improve our results by providing greater expertise, sensitivity and specificity, each variant analyzed introduces an additional potential error. This is a common problem. For each polymorphism included in a study, we can sum the potential errors and use multiple screening tests to identify the true variants. The highly divergent findings reported by various studies indicate that reproducibility is a major problem that only worsens when one considers "unknown variants" that emerge from new studies (15). Assessing the true importance of each variant is a problem which needs to be addressed by clinicians and scientists.

The study by Seidabadi et al. (6) used a simple technique in a simple association study to obtain a clear-cut result (a simple study design can sometimes be better). Are there limitations to this approach? Clearly there are. For any perfect study, the science would "stop" as soon as the study was published. In the present case, the major problem highlighted by the authors was that of addressing the question "what type of cancer am I dealing with and is it sporadic, familial or hereditary? This question can be addressed by considering the family history of cancer, the patient's age, affected organ, environmental factors, cancer etiology, number of cases, geographic location, treatment response, and the mutations screened in oncogene and tumor suppressor genes. The main factors historically used to determine the cancer classification, i.e. family history of cancer, patient age and affected organ, are the most problematic to deal with.

The family structure has changed because families with many members in each generation are no longer common, which makes it more difficult to determine the evolution of cancer within a family using a standard hierogram. With regard to age, the new diagnostic tools allow early diagnosis of cancer, ie, patients that would normally be diagnosed at a later age are now identified much earlier. In such cases, using age to classify the cancer could lead to erroneous conclusions. Finally, environmental factors should be considered. The general population structure has changed over the years, with urban center emerging every day. Pollution, the widespread use of medicines, the increasing consumption of manufactured products, stress and lack of physical activity are factors of increasing importance in this century. The organ affected may be dependent on an interaction with an environmental factor or activity. Is the genetic background important in this case? Does the risk polymorphism have a specific "weight" (proportional contribution to the disease) or clinical importance?

To adequately address the genetics of cancer, it is necessary to consider: (1) the clinical diagnosis, (2) family history, (3) the occurrence of polymorphisms in restricted populations, (4) technological limitations, (5) statistical information, (6) population size, (7) clinical markers, (8) the patient's expectations, (9) mutations in the "causal gene"–oncogene and tumor suppressor gene, (10) genetic counseling, (11) environmental factors, (12) the type of cancer, (13) the patient's evolution, and (14) the need for funding/financial support to perform the genetic screening. In the future, we need to consider better genetic therapies and discover the gene(s) that truly "drive" cancer. A hopeful and optimistic outlook is necessary and each step is important in improving our knowledge of cancer.

Short studies are important for demonstrating direct associations in restricted populations. Having the correct ideas is more important than the technique used. Knowledge cannot be restricted to big research centers nor should it be dominated or determined by only certain types of studies; the limitations of each study need to be recognized.

In conclusion, Seidabadi et al. (6) have clearly and concisely shown no association between prostate cancer and the R462Q polymorphism. Negative results are still results and should be reported. Such reporting is a step in the right direction. However, we still have a long way to go; but, together, the scientific community can achieve a better future.

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