Commentary

The prospective correlation between GGN and CAG repeat polymorphisms of androgen receptors and testicular cancer

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Worldwide testicular cancer (TC) is a contributing factor towards male infertility at reproductive age. A gradual increase had been observed in TC especially in Western countries. Prevalence of TC was found to be more common in Caucasian populations as compared to Africans and Asians due to variation among genetic makeup of individuals that varies their susceptibility to anomalies like cryptorchidism, hydroceles and inguinal hernias (1). Risk of tumor development was increased 4–10 folds in men with familial history of germ cell TC (2). There were more than thirty thousand human genes and various genetic biomarkers for a particular gene, so potential to identify a huge number of genetic polymorphisms for TC was immense. Genetic changes and their effects were usually moderate and only epidemiological studies were not enough to meet the demand of scientific community (3).

TC cases associated with gene polymorphisms reported by various studies were explained by endocrine regulation. These genes encode the androgen and estrogen receptors which were directly involved in regulation of testicular functions. Therefore, alterations induced by varied length of CAG and GGN repeats might had affected the hormonal metabolism leading to tumor growth in addition to other reproductive dysfunctions. It had been found that length polymorphism in estrogen receptors are linked to azoospermia (4) and increased risk of development of seminoma and metastasis (5). Variations in trinucleotide repeats of androgen receptor (AR) gene result in changing the transactivation of the androgen receptor which was involved in developing different types of endocrine cancers (6). This hypothesis was further supported by the fact that shorter CAG and GGN repeats were associated with increased risk of seminoma due to an increased AR transactivation. Chances of TC were also increased due to imbalance between estrogen and androgen levels (7). This was traced back to altered genes which affected the action of sex hormones thus increasing the cancer susceptibility. Similarly various genes of testosterone pathway can exert similar effects if get mutated due to extrinsic or intrinsic factors (8). CAG and GGN repeat length may indicate the progression of the TC (9). Patients with longer CAG and shorter GGN repeat length represent the advanced stage of cancer. Significance of CAG and GGN repeat length for increased susceptibility to TC cannot be currently justified due to poor knowledge of its physiological basis. However, it was suggested that this repeat polymorphism may lead to AR receptor insensitivity resulting in excess of free hormones which may promote the development of TC. In addition, presence of higher number of CAG repeats was positively correlated to the advanced stages of testicular tumor at the time of diagnosis (10,11). Elevated levels of endocrine disruptors in environment may be considered as a primary culprit in this regard.

In the last fourteen years, only few studies were available representing this association. Rajpert-De Meyts *et al.* [2002] for the first time revealed the relationship between androgen receptors CAG repeats polymorphism, testicular germ cell cancer and its progression in a case control study among Danish population but with a limited sample size (6). Later on, correlation between GGN and CAG repeats and TC pathogenesis was demonstrated among Swedish men. Both of the studies illustrated no

significant association between AR GGN and CAG repeats and TC. CAG repeats transcending 25 were common in TC patients without seminoma constituent and its length was also linked with metastasis at the time of diagnosis. Gonadotrophins also seem to be correlated with the development and progression of disease (6,9). Similar results were reported in another study from Norwegian population demonstrating that AR GGN and CAG repeats were not statistically associated with TC (8,10,11). CAG >25 were more prevalent among non- seminoma TC patients whereas contrasting results were also available (8,9). High risk of TC was reported in Italian men with AR mutations and some CAG repeat polymorphisms (12). Irrespective of certain shortcomings, available studies demonstrated a predictive role of the CAG and GGN repeat polymorphism in development of TC among various populations. Current researches in the related fields of andrology, molecular genetics, endocrinology and physiology further support this hypothesis by providing an explanation of these epidemiological results (10,11).

As contrasting results were reported in literature, a meta-analysis provides precise outcome associations not available through individual reports. It assisted in synthesizing data and inferring results from diverse genetic epidemiological studies. Therefore Jiang *et al.*, [2016] conducted the first meta-analysis on association of CAG and GGN repeat polymorphisms of AR in TC. GGN repeats of AR were significantly associated with TC. Furthermore, shorter GGN repeats were also significantly associated with TC development in the mid latitude and seminoma groups. Whereas, no association was observed between CAG repeat polymorphism and TC. In order to elaborate the findings, data was summarized into different sub groups and showed that CAG repeats length with >25 were associated with testicular carcinomas increased risk in the mid-latitude subgroup whereas inverse relationship was observed in the high-latitude subgroup (in harsh environmental conditions). These results indicated that latitude contributed towards the effect of CAG repeat polymorphism on TC risk. Long CAG repeats may be protective against TC at high altitude. Exposure to different environmental conditions may exert contrasting effects on male reproductive system (13). Even though there was a close genetic relation between populations of the Scandinavian countries however, risk of TC was double in Denmark and Norway in comparison with Sweden. Slight fluctuations in environment and life style might be the reason behind these genetic differences. In addition, weak statistical power may have caused the inconsistency of results. Another reason for contrasting results may be attributed to the differences among inclusion/exclusion criteria, study design, length of CAG and GGN repeat and ethnical backgrounds (9-13).

The experimental data which could provide the valid evidence for the involvement of AR repeat polymorphism in TC progression is still deficient. These investigations give evidence to draw conclusions regarding the significance of CAG and GGN repeat polymorphism of androgen receptors as promoters of TC in different populations of the world. On the contrary, there are several flaws which lessen the credibility of the results obtained from current meta-analysis. These include small sample size of available studies, weak statistical power and importantly, inclusion of only Caucasian population. Therefore, this analysis encourages the geneticists to further explore with an integrated approach i.e., more studies with greater sample size and appropriate laboratory techniques to elaborate the results. A well-designed, systematically conducted meta-analysis with elaborated risk factors and statistical tools are mandatory to achieve coherent results. Despite the ambiguity in the interpretation of this correlation, it interests many scientists and oncologists because single gene disruption cannot lead to the development of a disease unless a series of sequential genetic and environmental changes are linked with it. Therefore, it is required to explore the role of various genes and their interactions in the TC development. It will also assist in hormonally-mediated cure and prevention of the disease.

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Footnote

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