Indian scientists identify genes behind oral cancer

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A team of Indian scientists has identified new genes and new biological pathways that are specific to driving oral cancer associated predominantly with smokeless tobacco consumption in India. Further detailed study on these discoveries may lead to finding better therapies for oral cancer, the researchers point out. The findings have been published on Monday in the journal *Nature Communications*.

The Indian group is part of the International Cancer Genome Consortium (ICGC), an initiative started in 2009, to understand the genomic basis of 50 different types of cancer with clinical and societal importance around the globe.

The Indian component is being conducted collaboratively by the National Institute of Biomedical Genomics (NIBMG), Kalyani, West Bengal, and the Tata Memorial Centre (TMC), Mumbai. This is the first set of results to come out of the India Project, which has been noted as an important contribution to cancer genomics.

Oral cancer is the eighth most common cancer worldwide and is the leading cancer among males in India. Unlike in the West, where 65 per cent of oral cancers are tongue cancer, in India, oral cancer predominantly (60 per cent) is of the lining of the mouth, lower gum and other mucosal regions of the oral cavity, termed the Oral Squamous Cell Carcinoma of the gingivo-buccal region (OSCC-GB). Tobacco chewing is a major cause of OSCC-GB, which accounts for over half of the oral cancers in India.

Cancer is known to be associated with changes in the DNA contained in the cells of the tumour tissues. However, these genetic changes — triggered by lifestyle or other environmental factors such as exposure to tobacco, chemicals and radiation — occur only in non-reproductive cells and are called somatic alterations. But, as Dr. Partha Majumder of the NIBMG, who led the research, explains, most somatic alterations do not cause the abnormal growth, which results in cancer. Gene alterations that do provide this growth advantage to cancerous cells over normal cells are called driver mutations. Though past studies have identified several genes associated with oral cancer, these have not been systematically catalogued. More pertinently, as the paper says, “Oral cavity comprises sub-sites with distinct biological features. It is therefore likely that genes driving cancers in these sub-sites may be different.”
The study included 110 subjects suffering from OSCC-GB, about half of who were between the age of 40 and 50, and nearly all were tobacco users. Eighty-eight per cent of the patients were male and 94 per cent were in advanced stages of cancer. Fifty patients, who had not undergone any treatment, were identified for investigation into the genetics of OSCC-GB and the data on the remaining 60 were used to test the validity of the discoveries.

Using the technique of massively-parallel DNA sequencing, blood and tumour DNA of each patient were screened for all genes — about 20,000 — in the human genome. On an average, 85 somatic alterations were found on each patient. But, as mentioned above, only some of these are potential drivers.

The study found 10 significantly mutated genes that were associated with OSCC-GB. These are TP53, FAT1, CASP8, NOTCH1, HRAS, USP9X, MLL4, UNC13C, ARID2 and TRPM3. Of these, the first five have been implicated earlier in the cancer called, the Head and Neck Squamous Cell Carcinoma (HNSCC), of which OSCC-GB is a subtype. The remaining five are new, which seem to be specific to OSCC-GB. These new genes were found to be altered in 10-22 per cent of the patients.

Any alteration in a ‘tumour suppressor gene’ means that it cannot perform its normal function of tumour suppression, which can lead to cancer. Sixty-two per cent of patients exhibited mutations in TP53, a very important tumour suppressor gene. In fact, four of the five genes identified earlier are tumour suppresser genes, according to Dr. Majumder. Likewise, three of the five new genes – USP9X, MLL4 and ARID2 – are also involved in tumour suppression, the first directly and the other two indirectly.

While MLL4 acts in concert with TP53, and increases its expression, both MLL4 and ARID2 are involved in regulating key biological processes in the cell, such as programmed cell death, inefficiency of which can cause cancer. The authors note that TRPM3 may also be indirectly involved in tumour suppression. “Overall,” says the paper, “tumour suppresser genes, compared with oncogenes [cancer causing genes], are predominantly involved in oral cancer; this fact may have therapeutic implications.”

The remaining two new genes — UNC13C and TRPM3 — are involved in biochemical pathways associated with neurotransmitter release and, according to the authors, alterations in these could be related to predisposition to tobacco addiction, which enhances the risk of oral cancer.

The study also found that patients who had alterations in MLL4 were found to have a significantly longer disease-free survival period (about 21 months) after treatment as compared to 13 months otherwise. This observation too will have therapeutic implications but needs further validation, says the study.

“The characterisation of a large sample of the OSCC-GB subtype provides a unique contribution to the literature on characterisation of HNSCCs,” Dr. Carolyn Hutter of the National Human Genome Research Institute (NHGRI), USA, observed in an e-mail message.