CDKN2a and HNSCC: IRB Proposal

A. Study Purpose and Rationale

Over the last century, a significant number of cancer susceptibility genes and familial cancer syndromes have been identified. Tumor suppressor (TS) genes, such as Rb, p53, APC and BRCA1, constitute an important class of cancer susceptibility genes [1]. A germline mutation in a TS gene predisposes the carrier of the mutation to a particular cancer or set of cancers. Cancer pathogensis is mediated through the loss of the wild type allele, as described in the two-hit hypothesis by Knudson in 1971 [2].

CDKN2a, located on chromosome 9p21, is an important cancer susceptibility locus, in part because this region contains INK4a(p16), a well-known tumor suppressor gene. There are many lines of evidence for a crucial role of CDKN2a in tumor formation. For example, in head and neck squamous cell carcinoma (HNSCC), abnormalities in p16 expression are found in up to 80% of tumors [3]. Furthermore, germline mutations in CDKN2a have been identified in Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM, MIM# 155601), where patients have 10-100 moles that vary in size, outline, and color on upper trunk and limbs, frequently develop melanoma and in some families, pancreatic cancer [4].

Genetic susceptibility likely plays an important role in HNSCC carcinogenesis. Only a fraction of patients exposed to tobacco and alcohol develop cancer. There is familial aggregation of HNSCC and an increased risk of cancer among relatives of patients with HNSCC [5]. Furthermore, patients with HNSCC are more likely to develop a second primary tumor if their parents or siblings had respiratory or upper aerodigestive tract cancer [5]. The genes responsible for this increased susceptibility are not known.

The goal of this study is to determine the frequency of mutations in CDKN2a in patients who develop HNSCC without other well-known significant risk factors: smoking, alcohol, and advanced age. In turn, this will help determine whether HNSCC should be considered part of the FAMMM syndrome, and whether there is genotype-phenotype correlation between CDKN2a mutations and cancer formation. In the future, this information can be used for genetic counseling and for surveillance and prevention of cancers in a high-risk population.

B. Study Design and Statistical Analysis

The study will compare the frequency of mutations in CDKN2a in young non-smokers with HNSCC compared to the general population. Although the penetrance of melanoma phenotype in people with a CDKN2a mutations can be as low as 28% by 80 years of age [6], we assume that CDKN2a germline mutation rate in the general population is close to 0%. Aitken et. al. [7] did not identify any germline CDKN2a mutations in 200 unrelated Australian individuals. Furthermore, even among patient with melanoma but without known family

history of melanoma, the mutation rate is only ~0.2% as reported in several studies [7].

Approximately 50 individuals will be required to show a statistically significant mutation rate of ~10% among the study individuals (alpha=0.05, beta=0.8, one-sample chi-square test). The choice of 10% comes from the "Genetic Testing for Cancer Susceptibility" guidelines published by the American Society for Clinical Oncology [8, 9]. In their guidelines, the first criteria for a good genetic test requires that only individuals with a reasonable probability of having a positive test should be tested, and 10% probability has been suggested by ASCO to be a reasonable number [10].

C. Study Procedure

Recruited patients will have an interview to obtain a complete family history of cancer. Also, their genomic DNA will be collected during a routine office visit by venupuncture. Some of the genomic DNA will be sent to Myriad Genetics (CLIA) laboratories for CDKN2a analysis (MELARIS® genetic test). The rest of the DNA will be stored for future genomic analysis if consent is obtained.

D. Study Drugs

n/a

E. Medical Devices

n/a

F. Study Questionnaires / Data Collection

n/a

G. Study subjects

Inclusion criteria:

a. Tissue diagnosis of HNSCC, including larynx and nasopharynx
b. Age 18-50
c. No history of tobacco or marijuana use prior to diagnosis of cancer
d. No history of use of > 20 g of alcohol / day

H. Recruitment of Subjects

The subjects for the study will by recruited by two methods. First, pathology reports and medical records in the ENT clinic will be reviewed to identify potential candidates for the study. Patient's primary physicians will ascertain from the patient whether he/she is willing to participated in the study

and the patient will be asked to come for consent, an interview, and a blood draw.

The second method of recruitment will be prospective. ENT physicians will identify new patients eligible for the study and ask the patients if they are willing to participate in the study. If so, the patients will return for a brief interview and venupuncture.

I. Confidentialy of Study Subjects

All study data will be coded to protect patient confidentiality.

J. Potential Conflicts of Interest

none

K. Location of the Study

ENT clinics in New York Presbyterian Hospital, Cornell and Columbia campuses.

L. Potential Risks

none

M. Potential Benefits

none

N. Alternative Therapies

n/a

O. Compensation to Subjects

All of the subjects will be compensated $20 for their trip to the hospital for bloodwork and interview.

P. Costs to Subjects

none

Q. Minors as Research Subjects

n/a

R. Radiation and Radioactive Substances

n/a

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