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Lay Version Progress Report for: Evaluation of non-synonymous coding single nucleotide polymorphisms (SNPs) in relation to glioblastoma multiforme prognosis and etiology

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The only proven causes of gliomas, high dose therapeutic radiation and some rare inherited conditions, do not account for very many cases of this heterogeneous group of brain tumors. Years of studies of glioma have demonstrated that familial aggregation above that expected by chance and a wide-variety of occupational, dietary and other environmental exposures may contribute to glioma risk. Furthermore, several studies have now demonstrated that people who develop glioma are less likely to have histories of allergies than people who have not developed glioma. These findings taken together with knowledge gained from studies of other types of cancer suggest that gliomas might arise from a combination of developmental errors and environmental exposures in combination with inherited variation in response to environmental exposures and in immune function. Etiologic studies of glioma try to discover, describe, and explain the variety of inherited, developmental, and environmental factors that play a role in causing glioma by comparing these factors in people with and without the disease. Understanding the etiology of gliomas might eventually help to identify people who are at high-risk for the disease or might aid in developing preventive strategies.

Some of these factors, in combination with molecular errors and abnormal chromosomal numbers or arrangements in the tumor, might influence how aggressive the tumor is and the extent to which a patient responds to treatment. Determining prognosis involves estimating the probability that a patient will survive after diagnosis and other aspects such as whether the tumor will recur after treatment or progress to a more aggressive type of tumor. Age, extent of surgery and radiation therapy are the strongest, most well-established factors known to influence glioblastoma prognosis. Finding other factors that influence prognosis would help clinicians provide better information to their patients and might help in development of more effective therapies.

With rapidly expanding knowledge and technologies, it is now possible to characterize inherited variation in very large numbers of genes and therefore, to examine this variation in relation to glioma etiology and prognosis. DNA is organized as a double-helix with complementary base-

pairs, C (cytosine) pairs with G (guanine) and A (adenine) pairs with T (thymine). Different genes are coded on the two of complementary strands and some DNA doesn't code for any genes at all. Alternative bases at an address on one strand of the DNA is defined as a "single nucleotide polymorphism" (SNP). Polymorphism means variation in genotypes; genotype means the bases that occur at a particular address in the DNA. For example, some people might have a C on one strand paired with a G on the other strand at one location in the DNA whereas other people might have an A on one strand paired with a T on the other strand at the same location. On first strand, the SNP for the address would C or A. Since each person has two copies of each address in their genome (with the exception of addresses on the X-chromosomes for which women have two copies whereas men only have one), the genotype at any given address is the two base combinations at that address—in the example above, a person's genotype for the SNP coded by the first strand could be either CC, CA or AA. Millions of SNPs have now been documented throughout the human genome. Some SNPs have no known function because they are in parts of DNA that don't code for genes. Although some SNPs within genes alter the proteins coded by the gene, many do not.

With funding from the National Cancer Institute, our research team has been studying glioma etiology in the San Francisco Bay Area since 1991. Together with clinicians at UCSF, we began studying glioma prognosis as part of the UCSF Brain Tumor SPORE (Specialized Program of Research Excellence) in 2002. In the past, we selected a small number of genes that we thought might be relevant to causing glioma and compared SNPs in those genes in people with glioma and people without glioma. In 2004, the National Brain Tumor Foundation and Accelerate Brain Cancer Cure gave us additional funding to begin to explore large numbers of SNPs in relation to glioma survival and etiology.

Because so many SNPs do not change the proteins coded by the genes and such silent changes are less likely than non-silent changes to affect cellular functions, we chose to begin the search by only examining SNPs that change proteins. These are called non-synonymous coding SNPs. ParAllele, a company in South San Francisco, has developed chips that can be used to genotype large numbers of SNPs for each person.

Using DNA specimens from people in our studies, we have now genotyped close to 10,000 non-synonymous coding SNPs for 112 adults with glioblastoma and 112 people without any history of brain tumor who are of similar age, gender and ethnicity as the patients. There are tremendous statistical challenges involved in making sense of such a great volume of data and the technologies and information used to choose the best SNPs are also rapidly evolving. Thus far, we found that for about 1200 addresses genotyped, there was no variation in the 224 subjects we studied.

Furthermore, for about 1700 addresses, less than 5% of the subjects had one base while 95% or more of the subjects had an alternative base; for these SNPs, there will not be enough variation in genotypes for meaningful analysis. This leaves approximately 7000 SNPs for statistical analyses. For each of these, we are (1) comparing the genotypes of people with and without glioblastoma, (2) comparing the length of survival of glioblastoma with patients with different genotypes, and (3) comparing the average ages at diagnosis of glioblastoma among people with different genotypes. Because of the relatively small numbers of subjects in this study, we consider it a pilot study that will provide us with useful information for planning larger studies that might determine inherited factors important in causing glioma and in glioma prognosis.