Network: Obesity and Related Disorders

Project: Population Genetics and Molecular Evolution of Candidate Genes for Obesity

Mark Stoneking - Max Planck Instute for Evolutinar Anthroplogy, Leipzig - stoneking@eva.mpg.de

Introduction

The goal of this project is to analyze the population genetics and molecular evolution of candidate genes/mutations for obesity, in order to elucidate the evolutionary mechanisms that have influenced the history and spread of these genes/mutations. For example, there is a high frequency in European populations of a mutation that causes the persistence of lactase activity (and, hence, the ability to digest milk) into adulthood. Population genetic analyses indicate that the high frequency of this mutation in dairying populations was due to strong selection, thereby indicating that the ability to digest milk into adulthood was an important factor in the evolutionary history of these populations. Similar analyses of candidate mutations that predispose for obesity would indicate if such mutations were also increased in frequency due to selection.

Why should there have been selection for mutations that lead to obesity? One hypothesis for the high prevalence of obesity in some human populations (in particular, Polynesians) is the "thrifty gene" hypothesis, which postulates that during the long open-ocean voyages between Polynesian islands, there was strong selection for an efficient metabolism, to make maximal use of limited nutritional resources. Polynesians on "Western" diets suffer from a variety of obesity-related disorders, especially diabetes, hypertension, heart diseases, and certain types of cancer, although the genetic basis for these disorders remains unknown. Thus, it may be the case that selection for an efficient metabolism under one set of circumstances (i.e., limited nutritional resources) led to an increased frequency of mutations that that then lead to obesity under a different set of circumstances (i.e., the modern high fat, high calorie diet). A high incidence of obesity today thus may be an evolutionary legacy.

In order to test the thrifty gene hypothesis, candidate mutations will be genotyped in Polynesians and other human populations, to determine if the frequency of particular candidate mutations is elevated in Polynesians. Population genetic analyses will reveal if selection has indeed influenced the frequency of particular candidate mutations. In additino, re-sequencing of candidate genes for obesity will be carried out in non-human primates, to determine if recent selection in humans has influenced the molecular evolution of these genes. By understanding the evolutionary forces that have influenced the origin and spread of candidate mutations for obesity, we will thereby gain a fuller understanding of the underlying causes of obesity.

Results/Project Status

A collection of 1000 DNA samples from around the world (the CEPH Human Diversity Panel) was sent to Dr. Anke Hinney and Dr. Johannes Hebebrand for analysis of mutations in the MC4R gene, a candidate gene for obesity. Several novel mutations were found which might influence MC4R function; functional analyses of these mutations are underway. Preliminary population genetic analyses are being conducted, and we are also currently sequencing the MC4R gene in several non-human primates. These population genetic and molecular evolution analyses should enable us to elucidate if selection has been operating on the genetic variation present in the MC4R gene.

We have also begun screening a sample of Polynesians for variation in the MC4R gene and in other candidate genes for obesity and diabetes. In addition to this candidate gene approach, we are also using genomic approaches to identify genes that have been subject to selection during the history of Polynesians. The idea is to screen a large number of marker loci, spaced throughout the genome, in samples of Polynesians and their ancestors (Melanesians and Southeast Asians). Marker loci tht show unusually large genetic distances between Polynesians and their ancestors are possible indicators of genomic regions that have been subject to recent selection in Polynesians. A screen of about 400 microsatellite loci (by the group of Dr. Peter Nürnberg) in Polynesians, New Guineans, and East Asians will soon be completed, and in collaboration with Prof. Dr. Manfred Kayser at the Erasmus MC University Medical Centre in Rotterdam, we are currently screening these same samples for 100,000 SNP markers. The data from these screens will be used to search for marker loci that show unusually large genetic distances between Polynesians and their ancestral populations, which in turn will be further investigated for indications of selection in Polynesians.

Outlook

New advances in both genomic methodologies and population genetic analyses make the detection of selection in human populations more realistic. We thus anticipate that by the end of this project, we should have a better understanding of the role of our evolutionary past in shaping how and why obesity has become such a prevalent health problem in human populations today.