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Editorial

Population Genomics and Dental Public Health

Background

Most clinicians are familiar with the child who in spite of poor oral hygiene, evidence of a diet rich in sugar and little exposure to fluoride remains caries free. In contrast, the young adult patient who maintains excellent oral hygiene, attends the dentist regularly and is highly motivated in terms of dental care, but still experiences significant destruction of their periodontal tissues is also encountered. These scenarios raise the fundamental question, to what extent is dental and oral disease governed by nature or by nurture? In other words, to what degree do genetic or environmental factors influence susceptibility to dental disease and conditions?

In early 2006, the Faculty of Public Health in the United Kingdom held a one day conference entitled "Genomics and Population Health". This event brought together geneticists, public health practitioners and government officials. The primary purpose of the meeting was to explore current developments in the field of genomics and to discuss their potential to impact on the health of the public.

The emerging fields of genetic epidemiology and public health genomics have received little attention in dental circles. The purpose of this article is to provide a brief overview of developments in this area and consider their implications for dental public health.

What is public health genomics?

Genomics is the study of genes and their function. A recent United States Centres for Disease Control and Prevention (CDC) sponsored committee has defined "public health genomics" as an emerging field, which assesses the impact of genes and their interaction with behaviour, diet and the environment on the population's health (Hernandez, 2005).

The sequencing of the human genome completed in 2003, provided for the first time, the blueprint for humankind and has raised the possibility of a much greater understanding of health and disease and their determinants. However, although the basic sequencing of the human genome is complete, many years of research and development lie ahead in determining the value and role of genomic information in the prevention and treatment of disease.

Developments in public health genomics

The US Federal Government has established an Office of Genomics and Disease Prevention within CDC and established the Human Genome Epidemiology Network, or HuGENet™. This is a global collaboration of individuals and organizations committed to the assessment of the impact of human genome variation on population health and how genetic information can be used to improve health and prevent disease.

Across the world a number of population cohort studies are underway to examine the effects of genetic variation on common traits. In the U.K., the Biobank Project will gather information on the health and lifestyles of 500,000 volunteers between 40 and 69 years of age. Following informed consent, each participant will be asked to donate a blood and urine sample, have some standard measurements (such as blood pressure) and complete a confidential lifestyle questionnaire. Over the next 20 to 30 years UK Biobank will allow researchers to use these resources to study the progression of illnesses such as cancer, heart disease, diabetes and Alzheimer's disease; however, there are no plans to study dental or oral conditions at this time.

In addition, six Genetic Knowledge Parks have been established in England and Wales as part of the Government's strategy to put Britain at the leading edge of advances in genetic technology. The Genetics Knowledge Parks are all linked to multidisciplinary centres of excellence and offer access to internationally recognised academic and clinical expertise on genetics in relation to healthcare. The Network is building the knowledge base on all aspects of human genetics, ensuring that the National Health Service is better placed to exploit the findings of genetics research.

What then is the relevance of these developments to dental and oral disease?

Genetics and oral disease

Genetic influence on disease broadly falls into one of two groups: Mendelian-inherited disorders, involving one (monogenic) or multiple (polygenic) genetic loci, and complex disorders involving the interaction of multiple genetic loci and environmental factors. Simple Mendelian disorders are characterised by a clinical phenotype that is highly correlated with the presence of a specific genotype, i.e. mutation, that alters or abolishes protein function so significantly that a "disease" phenotype results. Many syndromes have been described that include dental conditions as part of a complex pleiotropic phenotype. However, Mendelian non-syndromic dental conditions are generally inherited as single gene disorders and include for example, amelogenesis imperfecta, dentinogenesis imperfecta, tricho-dento-osseous syndrome and Papillon-Léfevre syndrome (Hart et al, 2000). Although of great impact to the affected patient and the clinician responsible for their care, from a public health perspective, the low prevalence of these conditions limit their significance. The common oral diseases that impose a substantial burden on society; dental caries,

adult periodontitis, oral cancer and craniofacial disorders such as clefting or malocclusion are much more complex genetic entities. Here, disease is not the consequence of a particular genetic variation, but rather the interaction of one or more genes with the products of other genes and their interaction with non-genetic environmental and behavioural factors. In these diseases, it is likely that complex allelic variants of multiple different genes act synergistically with environmental factors to increase or decrease the likelihood of developing a disease.

Work to identify the genetic determinants of dental caries has a long history. Animal studies in the middle of the last century suggested that selective breeding could result in caries-resistant and caries-susceptible lines. Studies comparing caries incidence in identical (monozygotic) and non-identical (dizygotic) twins have provided further evidence of a genetic component to caries. However, as Shuler concluded in a 2001 review, the relative magnitude of genetic effects compared to environmental effects remains uncertain.

As for periodontal disease, while there have been successes in identification of mutations responsible for rare syndromic forms, e.g. Papillon-Léfevre syndrome, Kinane and colleagues recently reported that we are still some way from determining the genetic basis of either aggressive or chronic periodontitis (Kinane et al. 2005).

The role of genetics in oro-facial clefting has been subject to considerable research. While it is clear that clefts can occur as part of genetically influenced syndromes, the majority of cleft lip and palate defects occur in a non-syndromic form. Work is continuing to elucidate candidate genes that contribute to non-syndromic cleft lip and palate (Marazita and Mooney, 2004).

Considering oral cancer, genetic defects have been linked to inherited cancer syndromes (Prime et al. 2002). However, while some studies have suggested that there is an inherited component to sporadic oral cancer, there are difficulties in separating the effects of shared genes from a common environment in family studies. Slavkin has described three phases in the evolution of the genetics of oral oncology: firstly the identification of genes associated with, or linked to oral cancers; secondly, establishing how these genes influence protein function in cells and tissues and thirdly, how these aberrant proteins predispose to oral cancer initiation and progress. This will lead to an understanding at a molecular level of human variation and the individual characteristics of oral cancers (Slavkin, 2001). From a population perspective, in the longer term, a greater understanding of genetic factors in oral cancer may contribute to risk identification, chemoprevention, improved diagnostics and treatment regimes.

So what is the potential of genetic advances to improve health at a population level?

Scientific advances and the implications of the Human Genome Project.

Traditional gene mapping techniques have been complex and resource intensive. At the present time, clinical genetics is limited by and large to single gene defects, and genetic counselling and services focus on these conditions. However, the publication of the human genome sequence, in combination with the tremendous scientific and technological advances of recent years mean that unravelling the basis of common, complex conditions at a biological and cellular level is becoming easier. DNA-chip-based assays (microarrays), that contain as many as 500,000 single nucleotide polymorphism assays on a single slide are now available. While still relatively expensive, over the next decade these assays will allow complex gene-gene and gene-environment interactions to be better understood. These advances have potential to impact on disease from a population perspective. In the medical literature, there is however, currently a debate on the real potential of genetic testing in disease prevention. It has been argued that as genetic risks are by and large not modifiable, the word prevention leads to ethical debates and difficult areas such as the eugenic implications of prevention through pre-natal diagnosis and termination – "genotypic prevention" (Khoury, 1997). In the media, the implications of advances in genetic research have generated much debate, with concerns ranging from "designer babies" to the implications of a particular test on ability to obtain life insurance.

However, in the context of common, multifactorial disease, the argument is made that knowledge of genetic susceptibility should be used to aid modification of environmental factors, "phenotypic prevention" (Khoury, 1997). Although testing for common genetic polymorphisms is not currently available for clinical practice, several companies in the United States and the United Kingdom have prematurely offered genetic testing for susceptibility to various conditions, including periodontitis (Interleukin Genetics Inc.), cardiovascular disease, cancer and infectious diseases. (Gollust et al., 2002, Khoury et al. 2005). Concerns over such tests have lead the Human Genetics Commission in the U.K. to report on the surveillance of genetic tests delivered direct to the public (Human Genetics Commission, 2003).

Past dental research has devoted much effort to identifying high risk groups in order to target dental interventions. To date these have focused largely on

environmental and behavioural determinants of risk. Most, if not all human disease, results from the interaction between genetic susceptibility and environmental factors. The ability to better characterise susceptibility to disease, based on genotype, has the potential for health improvement, but will depend on whether a genetic test can lead to a dental, behavioural or environmental intervention that prevents disease and disability.

As the field of genetic epidemiology advances, it will have implications for the prevention of dental and oral disease. In the short term, research efforts are likely to focus on the major contributors to morbidity and mortality such as cancers and cardiovascular disease and we can anticipate tests for multiple genetic variants (so called "genetic profiles") for testing disease susceptibility or resistance. However, as technology advances, the potential for new genetic knowledge to impact on oral health needs to be explored.

In concluding this brief overview we return to clinical anecdote. The mother who is convinced that "soft teeth" run in her family, will be familiar to many readers of this Journal. To be able to quantify and explore this concept is just one of the many possibilities that lie ahead.

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