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Hypodontia - Genetic or Environmental? A Case Report of Monozygotic Twins

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ABSTRACT

In the present report, a case of 19 year-old monozygotic twin sisters with variable expression of hypodontia is presented. One of the twins had agenesis of mandibular lateral incisor. The occurrence of dissimilarity in the tooth agenesis in the monozygotic twins may suggest the influence of epigenetic factors in their etiology. DNA fingerprinting was used to confirm monozygosity.

Key words: Epigenetics, Hypodontia, Missing mandibular lateral incisors, Monozygotic twins.

INTRODUCTION

A twin is one of two offspring produced in the same pregnancy.Twins can either be *identical* (in scientific usage, "monozygotic"), meaning that they develop from one zygote that splits and forms two embryos, or *fraternal* ("dizygotic") because they develop from two separate eggs that are fertilized by two separate sperm.Identical or monozygotic (MZ) twins occur when a single egg is fertilized to form one zygote (hence, "monozygotic") which then divides into two separate embryos.

Human monozygotic (MZ) twins account for 4 in 1000 live births[1]. The likelihood of identical twins is uniformly distributed in all populations around the world[2]. This is in marked contrast to fraternal twinning, which ranges from about six per thousand births in Japan to 15 and more per thousand in some parts of India[3].

Twin research has been at the center of the nature versus nurture debate for years. They have been a valuable source of information about the genetic basis of complextraits for examining genetic and environmental influences on behavioral and medical characteristics. Twin studies are a fascinating method of research because of their ability to correctly isolate a characteristic and determine its impact. It is difficult to predict the exact influence of heredity due to various genetic patterns. However, twin studies are instrumental in offering evidence against the purely environmental model[4].

Classical twin studies involve comparing features of interest in large numbers of monozygotic (MZ) twin pairs with those in dizygotic (DZ) twin pairs. Assuming that the environmental influences are the same in both groups greater similarity between MZ twin pairs, who share the same genes, compared with DZ twin pairs, who only share half their genes on average, indicates that genetic factors are contributing to observed variation. Applications of this model to dental features have confirmed that there is a strong genetic contribution to variation in human dental morphology, and so researchers and clinicians have often tended to focus on the dental similarities between MZ twin

pairs rather than their differences. However, previously it was reported that MZ twin pairs can show quite different expressions of normal, small, peg-shaped and missing maxillary incisors, despite having the same genetic make-up. The term 'hypodontia' refers to the developmental absence of one or more teeth, either in primary or permanent dentition, excluding the third molars. The modes of inheritance for missing teeth in humans are still not clearly established. Pedigree studies of families showing missing teeth have indicated an autosomal dominant mode of inheritance, although autosomal recessive and X-linked modes of inheritance have also been suggested. Brook proposed a multifactorial model linking tooth size and tooth number, with superimposed thresholds, to account for the different patterns of expression of both missing and extra teeth observed in males and females. Even when the genes associated with missing and extra teeth are identified, we will still need to clarify the relationship between an individual's genetic make-up and their phenotype. Epigenetics, a term that, in its broad sense, refers to alterations in gene expression without changes in nucleotide sequencing, is critical in this regard but our understanding of these events remains far from complete[5]. Although molecular geneticists often focus nowadays on specific examples of epigenetic events, for example methylation and acetylation of DNA, we use the term in its broad sense in this paper.

Comparisons of MZ twin pairs who share the same genes but show differences in phenotypic expression provide one means of clarifying how epigenetic influences can affect phenotypic expression. Differences in tooth number between monozygotic co-twins, in particular, represent distinct and readily observable discordant features[5]. In this paper, we focus on variations in expression of hypodontia of mandibular lateral permanent teeth within MZ twin pairs.

Case report

A 19 year-old female patient, MZ1 was examined in the Public health dentistry department of Ragas Dental College as a part of another twin study, which assessed the oral health status of the twins. Diet chart was recorded. Extra oral clinical examination showed normal development and was noncontributory. On the intraoral clinical examination of MZ1 class I amalgam restoration were present in 15, 16, 17, 24, 26, 27,36,37,45,46,47, in addition she also presented with a unilateral missing permanent mandibular lateral incisor 42 with a drift in the midline. Her medical and family history was noncontributory to the oral findings. There was no reported history of extraction for orthodontic treatment or any orofacial trauma. The panoramic radiograph confirmed the absence of 42,48 (fig 1). No evidence of cysts, odontoma, supernumerary teeth or any other abnormalities was noted in the radiograph. Intra oral examination of the co-twin MZ2 showed normal development with full set of dentition except mandibular third molars. The panoramic radiograph (fig 2) confirmed the presence of all the teeth intact with unerrupted mandibular third molars 38 and 48. Zygosity of the twins was confirmed using DNA analysis.

Genetic Analysis method:Blood samples were collected from both the twins (Whatman®FTA Micro card). DNA profiling was done using Whatman®FTA kit. PCR analysis was done using Thermocycler and short tandem repeats (STR at 13 base pair sites) using highly polymorphic regions that have short repeated sequences of DNA. These STR loci are targeted with sequence-specific primers and amplified using PCR. The DNA fragments that result are then separated and detected using gel electrophoresis with silver staining.

DISCUSSION

To date, molecular studies in humans have focused on locating the genes associated with missing teeth rather than extra teeth. Over 100 genes are associated with dental development, so any of them could be a candidate for hypodontia. Finnish researchers looked for evidence of linkage between hypodontia and several candidate genes thought to have important roles in odontogenesis and were able to exclude EGF, EGFR and FGF-3, and probably FGF-4, as possible sites for gene mutation in the families they studied. They also excluded the homeobox genes, MSX1 and MSX2 as causative loci for hypodontia but others have suggested that there may be a connection. Recently,

genome-wide searches have found an association between the PAX9 gene and oligodontia. Although the precise location of the genes involved in simple hypodontia remains unknown, ongoing genome-wide searches are likely to enable loci to be assigned in the near future[5].

A study was performed by Lapteretalin a sample of 96 twin pairs to establish prevalence of hypodontia in the twin sample and to assess the degree of its heritability. Hypodontia was found in 22 out of the total of 192 twins analyzed (11.5%). Among 96 pairs of twins hypodontia was observed in 17 pairs (7 MZ and 10 DZ pairs). They concluded that prevalence of hypodontia in twins observed in this study was significantly higher than in the general population. A high degree of heritability pointed to high genetic determination[6]. Keenefound that agenesis of teeth, other than third molars, was two to three times more frequent in a sample of 262 American twins than in the general population[7].

The similarities in the agenesis of permanent teeth have suggested the possibility of a genetic influence. Markovicreported that most of the MZ twin pairs he examined were completely concordant for missing teeth[8].

MZ twins constitute an excellent example of how genetically identical individuals can exhibit differences and therefore provide a unique model to study the contribution role of epigenetic modifications in the establishment of the phenotype. The variable expression of hypodontia in monozygotic twins has previously been reported and the hereditary nature of hypodontia is revealed in familial and twin studies. Gravely and Johnson found discordant expression in MZ co-twins in their studies of missing teeth and Kotsomitis*et al*. also noted that most of the MZ twin pairs they examined with missing teeth displayed variable expression. Boruchov and Green showed that 55 percent of monozygotic twins are discordant for hypodontia. Townsend *et al* displayed discordance for agenesis of permanent maxillary lateral incisors in five pairs of monozygotic twins, and suggested a possible link with disperate birth weights of the twins.Seddon*et al*. concluded, after reviewing eight previous cases and one of their own, that mesiodens were likely to be concordant in MZ twins with respect to number but they noted that minor variations in shape and orientation were common[9]. Martin *et al*. have described a wide range of genetic and environmental influences to explain why MZ twin pairs might not be identical phenotypically. They have listed differential placental implantation and nutrition, as well as differential transplacental teratogens and infections as possible environmental effects. Post-zygotic genetic effects could include differential imprinting, post-zygotic non-disjunction and differential trinucleotide repeat expansion. Molenaar*et al*. have referred to 'a third source of developmental differences, in addition to genetic and environmental factors, that they propose accounts for phenotypic differences in development. They argue that this third source consists of nonlinear epigenetic processes that can create variability at all phenotypic levels, both somatic and behavioural[5].

What does make MZ twins differ? By using whole-genome and locus-specific approaches, Mario *et al* found that approximately one-third of MZ twins harbored epigenetic differences in DNA methylation and histone modification. These differential markers between twins are distributed throughout their genomes, affecting repeat DNA sequences and single-copy genes, and have an important impact on gene expression. They also established that these epigenetic markers were more distinct in MZ twins who were older, had different lifestyles, and had spent less of their lives together, underlining the significant role of environmental factors in translating a common genotype into a different phenotype. Their findings also support the role of epigenetic differences in the discordant frequency onset of diseases in MZ twins.

Differences in epigenetic patterns in genetically identical individuals could be explained by the influence of both external and internal factors. Smoking habits, physical activity, or diet, among others, are external factors that have been proposed to have a long-term influence on epigenetic modifications. Similar pattern is also observed in the present study between the twin sisters where a significant difference in oral health status was observed. However, it is possible that small defects in transmitting epigenetic information

through successive cell divisions, or maintaining it in differentiated cells, accumulate in a process that could be considered as an "epigenetic drift" associated with the aging process. Accumulation of epigenetic defects would probably occur at a faster rate than that corresponding to genetic mutations because their consequences in survival are probably less dramatic and cells have not developed a comparable amount of mechanisms to correct them.

Other evidence indicates that relatively small differences in epigenetic patterns can have a large impact in phenotype, for instance in cloned animals, with MZ twins representing natural human clones. Another powerful example is provided by the *agouti* mouse. In this model, diet affects the methylation status of an inserted intracisternalA particle element that changes the animal's coat color: an environmental factor interacting with a single geno-type, mediated by an epigenetic change, to produce a different phenotype. In humans, the investigation of how assisted reproductive technology that uses media with undisclosed concentrations of methyl-donors associates with epigenetic errors such as imprinting defects and cancer has been proposed. Our comparison of MZ twins suggests that external and, or internal factors can have an impact in the phenotype by altering the pattern of epigenetic modifications and thus modulating the genetic information. Future studies should now address the specific mechanisms responsible for the observed epigenetic drift of MZ twins[10].

CONCLUSION

There is considerable evidence suggesting that genes play a significant role in the etiology of many dental anomalies. In the present case report of a pair of monozygous twins, the occurrence of variable expression of hypodontia, suggest the influence of epigenetic factors in their etiology.

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