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Review

Polymorphisms in genes involved in folate metabolism and orofacial clefts

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ABSTRACT

Background: Orofacial clefts (OFCs) are one of the most common birth defects in humans. Maternal use of folate antagonists including dihydrofolate reductase inhibitors has been associated with a higher risk of OFCs thus suggesting that folate-related metabolism and associated genes may be involved in pathogenesis of OFC. The association between folate intake and risk of OFCs however is inconsistent.
Objective: To review the published evidence that polymorphisms in genes that affect folate metabolism are associated with an increased risk of OFCs.
Methods: We reviewed articles published up until October 2010, on polymorphisms of genes related to folate and homocysteine metabolism and their associations with OFCs. Articles were identified via Medline searches.
Conclusions: No consistent evidence emerged of a strong association between risk of OFCs and any known gene related to folate metabolism. Further, recent genome-wide association studies have not identified associations between OFCs and folate-related genes. Further studies are warranted to determine whether gene–environment interactions, including gene–nutrient interactions and epigenetic modifications of genes affect the risk of OFCs.

Contents

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1. Introduction

Orofacial clefts (OFCs) are one of the most common birth defects in humans. They may occur as an integral part of the complex malformation syndrome or as an isolated anomaly. Non-syndromic orofacial clefts are heterogeneous with a great variation in aetiology, and are believed to arise from a combination of genetic and environmental factors. The most common non-syndromic orofacial cleft presents as non-syndromic cleft lip/palate (NSCL/P), and its frequency is the highest in Asian and Native American populations of Asian genetic origins, intermediate in Caucasian populations and the lowest in African and African-American populations.

Studies of NSCL/P in twins have consistently found a higher concordance amongst monozygotic compared to dizygotic twins. The actual concordance rates vary widely for NSCL/P (17.6%) and cleft palate only (CPO) (40%) in monozygotic twins,[1] which supports the role of in utero environment in modifying the risk of this craniofacial disorder.

Although there is substantial evidence that genetic factors contribute to orofacial clefts, the complex mode of inheritance involving both genetic and environmental influences is less understood. The incomplete penetrance of genes in orofacial cleft embodies limitation in linkage analysis, because it cannot be assumed that unaffected family members do not carry the susceptibility allele. Other complex aspects of inheritance in orofacial clefts are genetic heterogeneity and variable expression. Finally, there is a strong evidence for the inheritance which should not be interpreted by conventional genetic models. Genetics of NSCL/P is currently an area of intense research and has shown progress. For example, large family registries and increasing genomic information are facilitating identification of loci and genes related to the syndromic and nonsyndromic orofacial clefts. This information will help future research and eventually will improve diagnosis, prognosis, and management.

2. Genes encoding folate, homocysteine and methionine metabolism

OFC can occur as a result of defects in many genes. Various hypotheses have been published regarding the pathogenic mechanism of decrease in folate in periconceptional period manifesting as birth defects. Epidemiologic studies have provided evidence that consumption of 4 mg of folic acid/day reduces risk of many birth defects.[2] Presence of higher homocysteine level in the blood of mothers bearing a child with OFC and the findings of some studies of an association between maternal use of folic acid-containing supplements and a reduced risk of birth defects indicate that the genes involved in folic acid and methionine metabolism could plausibly be associated with the pathogenesis of orofacial clefts. Folate supplementation (0.4 mg/day) has been recommended by the US Public Health Service for all women of child bearing age to reduce the risk of birth defects[3] yet the role of folate in orafacial clefts is uncertain.

3. Folate, homocysteine and methionine metabolism

Folate (pteroiloglutamic acid) is one of the most vital substrates for cell metabolism. Folates are cofactors and co-substrates for synthesis of methionine and S-adenosylmethionine (SAM) for essential methylation reactions including DNA methylation and provide one-carbon moieties for the synthesis of guanine, adenine and thymine bases of DNA and also function as regulatory molecules (Fig. 1). In general the intracellular concentrations of the different folates are in general much lower than their Michaelis constant values for the enzymes, hence the rate or steady state of the reaction can change over a huge range of cellular folate concentrations.[4]

Tetrahydrofolate (THF) and its derivatives are the biologically active forms of folic acid, they are specialised cosubstrates for a variety of enzymes involved in one-carbon metabolism. Mainly methylated derivates of folate – N10-formyltetrahydrofolate and N5,N10-ethylenetetrahydrofolate (5,10-MTHF) – are donors of one-carbon groups for nucleotide synthesis. N5-methyltetrahydrofolate (5-MTHF) is another important biologically active derivative of folic acid produced from 5,10-MTHF by methylenetetrahydrofolate (MTHFR). 5-MTHF works in concert with vitamin B12 (methylcobalamin) in the conversion of homocysteine (Hcy) a sulphur-containing amino acid to methionine (Met), which provides methyl groups for numerous other biochemical reactions in the body. This reaction is catalysed by methionine synthase (EC. 2.1.1.13, MS). Methionine synthase activity is very important in maintaining sufficient levels of methionine and for preventing accumulation of homocysteine. Activity of methionine synthase depends on the presence of a second protein, methionine synthase reductase (EC 2.1.1.135), the enzyme that maintains the methionine synthase-bound cobalamin in its fully reduced active state. When the cobalamin gets oxidised, methionine synthase reductase catalyses its reductive methylation, using S-adenosylmethionine as a methyl donor to regenerate methylcobalamin.[5] Methionine is an essential amino acid metabolised into S-adenosylmethionine (SAM), by the enzyme methionine adenosyltransferase (MAT). SAM is the main biological methyl donor in many transmethylation reactions, upon losing the methyl group, SAM is converted to S-adenosylhomocysteine (SAH).[6] During normal physiological conditions, SAH is hydrolysed to homocysteine (Hcy) and