MINIREVIEW

Genetic Basis of Hyperhomocysteinemia

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Homocysteine is a sulfur-containing, nonproteinogenic amino acid biosynthesized from methionine which has a key place in common between the folate cycle and the activated methyl cycle. Homocysteine export into the extracellular medium reflects an imbalance between homocysteine production and metabolism (1). Hyperhomocysteinemia has been associated with folate or cobalamine deficiencies, and also with pregnancy complications, neural tube defects, mental disorders, cognitive impairment in the elderly, psoriasis, and some tumors (2). Furthermore, moderately raised concentrations of total homocysteine have been associated with an increased risk of cardiovascular disease (3,4).

There are many genetic causes of elevated homocysteine levels. Enzymatic defects and variants have been associated with methylene tetrahydrofolate reductase, methionine synthase, and cystathionine β-synthase, to name only the most relevant. In the present minireview, the main genetic defects associated with increased levels of homocysteine are described.

METHYLENE TETRAHYDROFOLATE REDUCTASE MUTATIONS

The most common genetic defect associated with mild hyperhomocysteinemia is a point mutation, namely a C to T substitution at nucleotide 677 (677 C → T) in the open-reading frame of the gene for methylene tetrahydrofolate reductase. This point mutation causes a substitution of valine for alanine in the functional enzyme (5), giving rise to a thermostable variant of the enzyme with decreased total activity (6). This is an autosomal recessive mutation, and the frequency of the 677 C → T polymorphism varies among racial and ethnic groups, with 10–13% of T/T homozygous and 50% C/T heterozygous among Caucasian and Asian populations and a very low incidence among African-Americans (6,7).

The widely documented elevations in plasma total homocysteine levels associated with the homozygous T/T genotype could lead to a higher incidence of cardiovascular disease in the T/T population. However, little or no evidence has been found so far linking the T/T genotype with increased rates of cardiovascular disease (6,7), although some reports seem to link the T/T genotype with an increased incidence of certain forms of vascular disease in selected populations (2). In this context, it has been suggested that an elevated plasma homocysteine level may not necessarily be deleterious, but it could promote vascular blockage under conditions predisposing to vascular disease (2).

In cases of dietary folate-replete individuals with mild hyperhomocysteinemia due to this T/T genotype, it has been shown that there is a significant decrease in risk for colorectal cancer compared with either C/C or C/T genotypes (8,9). More recent data seem to suggest that this methylene tetrahydrofolate reductase polymorphism plays a role only in a late stage of colorectal tumorigenesis, protecting against malignant transformation in the subset of benign adenomas, which may progress to malig-
nancy (10). Clearly, more extensive studies are required to confirm these data.

A second common polymorphism of methylene tetrahydrofolate reductase is an A to C substitution at nucleotide 1298 (1298 A → C), which causes a substitution of glutamate for alanine in the enzyme (11). The allele frequency of the 1298 A → C polymorphism is similar to that of the 677 C → T polymorphism but it does not seem to be associated with elevated plasma homocysteine concentrations. The significance, if any, of this polymorphism requires further investigation.

METHIONINE SYNTHASE MUTATIONS

Evidence of polymorphism also has been reported for methionine synthase (12,13). One of the prevalent polymorphisms is the D919G mutation, which yields an aspartate to glycine substitution with little or no discernible effect on the risk of cardiovascular disease (6,14). However, some controversial data point to the need for further studies on the clinical relevance of this mutation. Thus, a recent paper by Harmon et al. (15) shows that the D919G polymorphism is a modest but significant determinant of circulating homocysteine concentrations, contributing to clinical conditions associated with mild hyperhomocysteinemia.

A cblG-variant form of methionine synthase deficiency has been described which produces functionally null mutations. The absence of methionine synthase protein in these variants is due to mutations causing premature translation termination, and consequently mRNA instability (16).

Finally, a mutation involving methionine synthase reductase but not methionine synthase deserves to be mentioned. This polymorphism is an I22M mutation which exhibits an allele frequency of 0.51 and produces an increased risk of neural tube defects when cobalamin status is low or when the 677 C → T mutation in the methylene tetrahydrofolate reductase is also present (17).

CYSTATHIONINE β-SYNTHASE MUTATIONS

The most common of the genetic causes of severe hyperhomocysteinemia and homocystinuria is a homozygous deficiency of cystathionine β-synthase, inherited as an autosomal recessive trait. At least 60 different mutations of the gene have been described, with I278T and G307S as the most common (18). The I278T polymorphism is more prevalent than previously thought, emphasizing the importance of measuring total homocysteine levels routinely in thrombophilia screening (19). The G307S allele appears to be a common allele among families of Celtic origin, and variable hyperhomocysteinemia phenotypes have been described in heterozygotes for this mutation (20).

Another described “benign” polymorphism consists of a 68-bp insertion at exon 8 (14), which is found in approximately 7.5% of individuals in the European populations sampled. This insertion has been shown to abolish the increasing effect of the thermolabile T/T methylene tetrahydrofolate reductase genotype, and might be of importance in cases of hyperhomocysteinemia (21). It should also be further studied. Very recently, it has been shown that a R266K point mutation is tightly linked to the 68-bp insertion (22).

CONCLUDING REMARKS

An increasing number of polymorphisms related to homocysteine metabolism is described. New ones await to be detected and described. In fact, almost half of the cases of hyperhomocysteinemia are not associated with micronutrient deficiencies, impaired renal function, and/or currently known genetic mutations. Further work is needed to study whether as yet unknown mutations, particularly those residing in the intronic sequences of the genes involved in homocysteine metabolism, or interactions of these genes with other factors may be the cause of currently unexplained cases of mild or severe hyperhomocysteinemia.

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REFERENCES


