Letter to the Editor

Risk of Down syndrome conferred by *MTHFR* C677T polymorphism: Ethnic variations

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Sir,

Down syndrome (DS) well known for trisomy of the 21st chromosome (MIM 190685) is a complex genetic disorder with prevalence of 1/800 live births. Chromosomal non-disjunction during meiosis, mostly in mothers with DS child, was hypothesized to be the cause for trisomy 21.[1] Studies on human cell line have shown that DNA hypomethylation can induce chromosomal instability.[2]

One of the most crucial enzyme in methionine cycle is Methylenetetrahydrofolate reductase (*MTHFR*; E.C.1.5.1.20 [MIM 236250]) that reduces 5,10-methylenetetrahydrofolate (5,10-methylene THF) into 5-methyltetrahydrofolate (5-methyl-THF). *MTHFR* regulates DNA replication by supplying 5-methyl-THF, a primary form of circulatory folate, which is a substrate for methionine formation and required for *de novo* nucleotide biosynthesis. Reduced activity of *MTHFR* along with low plasma folate level was hypothesized to be a risk factor for meiotic non-disjunction and risk of having DS child.[3]

Association of *MTHFR* C677T (rs#1801133) polymorphism with risk of DS have been much discussed;[3,4] the mutant T allele, associated with reduction in enzymatic activity, was found to be a risk factor for DS.

Our family-based association analysis (75 DS families from West Bengal, 22.82°N, 88.2°E) revealed preferential transmission of wild type C677 allele to DS children (Haplotype-based Haplotype relative risk analysis, χ^2 =3.83, p=0.05; Transmission disequilibrium test, χ^2 =5.76, *P*=0.016); paternal transmission of C allele from heterozygous CT father was significant (χ^2 =5.56, *P*=0.018), while no significant difference in maternal transmission was observed (χ^2 =3.33, *P*=0.068). No difference in allelic frequencies was observed (χ^2 =0.065, *P*=0.968) between DS mother (n=68; C=0.846, T=0.154) and control mother (n=59; C=0.839, T=0.161).

An earlier report from Varanasi (25.33°N, 83°E),[4] a north-eastern state of India, had shown strong association of 677T with Indian DS patients and 677T allele was considered as a risk factor for DS contributed by either parent. However data obtained in our study, based on eastern Indian population, do not support the conclusions made by earlier investigators; allelic frequencies were not much different in parents of DS patients as compared to controls. Any preferential transmission of T allele was also not observed.

As Indian population is heterogeneous with large number of ethnic groups, differences in allele frequencies among ethnic groups from different geographical locations are not surprising. However, the present study warrants consideration of 677T polymorphism as a risk factor for DS in Indian mothers. Role of 677T in connection with the “hypomethylation theory” should be explored further, in different ethnic groups.

References

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