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Methylenetetrahydrofolate-dehydrogenase 1958G→A polymorphism is a genetic determinant of NTD risk for Italian mothers

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Neural Tube Defects (NTDs) have a well-established genetic basis, although specific genetic predisposing factors had not been identified until now. Genetic variants of enzymes involved with folate pathway might be expected to have impact on NTD risk. Given its key role in folate metabolism, the methylenetetra-hydrofolate dehydrogenase (*MTHFD1*) could represent an attractive candidate in NTD etiology. *MTHFD1* is a trifunctional protein and mediates the interconversion of 5,10-MTHF; 5,10-methenylTHF; and 10-formylTHF. 10-formyl THF and 5,10-methenylTHF are the donor cofactors for *de novo* purine and pyrimidine biosynthesis and, thus, the biosynthesis of DNA. Recently, a polymorphism, G1958A, in the *MTHFD1* gene was suggested as maternal genetic risk factor for NTD in the Irish population. In this study, we examined the impact of the *MTHFD1* G1958A polymorphism on NTD risk in the Italian population by a case-control study and family-based studies. The study population consisted of 95 unrelated Italian NTD children, 42 mothers and 40 fathers who were recruited from the Spina Bifida Center of the Gaslini Hospital, Genoa. A total of 145 healthy individuals were recruited from a blood donors accessible bank and used as control group. The presence of the *MTHFD1* 1958G→A, *MTHFR* (methylenetetrahydrofolate reductase) 1298A→C and *RFC-1* (reduced folate carrier 1) 80A→G polymorphisms was investigated by PCR-RFLP methods. We found no increased risk for *MTHFD1* mutant genotypes of the children and fathers. On the contrary, significant risk estimates resulted for the homozygous 1958AA genotype of the mothers (OR = 3.05; P = 0.046). This maternal effect was confirmed by transmission disequilibrium test (TDT) that showed no preferential transmission of 1958A allele to the affected children from informative parents. Since our previous study has shown that the *MTHFR* A1298C and *RFC-1* A80G polymorphisms are genetic determinant of NTD risk for Italian mothers, potential gene-gene interactions were examined. We found a significant interaction between the *MTHFD1* G1958A polimorphism and both *MTHFR* A1298C (4.46-fold increased risk) and *RFC-1* A80G (9.14-fold increased risk) mutant alleles in the mothers. We conclude that a common genetic variant of *MTHFD1* gene, the G1958A, is a maternal genetic risk factor for NTD. These findings highlight the importance of further considering maternal genotype when evaluating NTD susceptibility loci.