

## TWO NOVEL MITOCHONDRIAL DNA CONTROL REGION MUTATIONS IN CHILDREN WITH CYCLIC VOMITING SYNDROME

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**BACKGROUND AND AIM.** Cyclic vomiting syndrome (CVS) is a functional gastrointestinal disorder affecting mostly children and characterized by recurrent attacks of unremitting nausea and vomiting, often associated with lethargy and features of autonomic arousal. The pathogenesis is unknown, but recent studies suggest a matrilineal pattern of inheritance and that some predisposing genetic factor is located on the maternally-inherited mitochondrial DNA (mtDNA). The mtDNA D-loop, the regulatory region, is a "hot spot" for mutations that might alter the rate of DNA replication by modifying the binding affinity of important trans-acting factors.

**MATERIALS AND METHODS.** Nine Italian children with CVS (7 males and 2 females, median age 10.7 years) – diagnosed according to the Rome III criteria after thorough investigation aimed at excluding known causes of recurrent vomiting – and their first-degree relatives were recruited. Clinical and demographic characteristics of patients and relatives were noted. Over 1200 bp of mtDNA, including the D-loop region, were amplified by nested PCR using primers L15990-H617. Four overlapped nested PCRs were performed using primers L15990-H16434, L16431-H162, L039-H407, and L361-H617. PCR products were analyzed by automatic sequencing.

**RESULTS.** Taking the mtDNA D-loop from the Anderson sequence as reference, we found two novel mutations in two children with CVS and a positive family history of migraine in the matrilineage. A homoplasmic C>T mutation at np 571 of the D-loop region was detected in a 3 year old boy with mild lactic acidemia, as well as in his brother and mother who suffered from kinetosis. A homoplasmic G>A mutation at np 396 of the D-loop region was detected in a 14 year old boy as well as in his mother. Several previously described mtDNA polymorphisms were also found in both families. Neither patient had distinctive clinical or biochemical features. The first patient did not seem to have CVS "plus", since there was no evidence of psychomotor retardation or neuromuscular disorder and no alterations of aminoacid or organic acid metabolism were found. Following prophylactic therapy with cyproheptadine, the first patient had a partial response, whereas the second patient went into remission for one year and did not relapse off therapy.

**Conclusions.** Our findings provide further support for a possible pathogenetic role of mtDNA mutations in CVS and further evidence of a matrilineal mode of inheritance in this disorder.