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Two cases of misinterpretation of molecular results in incontinentia pigmenti, and a PCR-based method to discriminate NEMO/IKKgamma dene deletion.

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Source: Hum Mutat. 2003 Jan;21(1):8-11

Date: Jan-2003

Language: English

Publication Type: Article

Keywords: DNA Mutational Analysis - methods
Diagnostic Errors
Female
Gene Deletion
Humans
I-kappa B Kinase
Incontinentia Pigmenti - diagnosis
Molecular Diagnostic Techniques - methods
Molecular Sequence Data
Pedigree
Polymerase Chain Reaction - methods
Protein-Serine-Threonine Kinases - genetics
Pseudogenes

Abstract: Familial incontinentia pigmenti (IP) is a rare X-linked dominant disorder that affects ectodermal tissues. Over 90% of IP carrier females have a recurrent genomic deletion of exons 4-10 of the NEMO (IKBKG-IKKgamma) gene, which encodes a regulatory component of the IkB kinase complex, required to activate the NF-kB pathway. In IP, mutations in NEMOlead to the complete loss of NF-kB activation creating a susceptibility to cellular apoptosis in response to TNF-alpha. This condition is lethal for males during embryogenesis while females, who are mosaic as a result of X-inactivation, can survive. Recently, a second nonfunctional copy of the gene, DeltaNEMO, was identified, opposite in direction to NEMO in a 35.5-kb duplicated sequence tract. PCR-based detection of the NEMO deletion is diagnostic for IP disease. However, we present instances in which ex 4-10 DeltaNEMO pseudogene deletion occurs in unaffected parents of two females with clinically characteristic IP. These were missed by the currently standard PCR-based method, but can be easily discriminated by a new PCR-based test reported here that permits unambiguous molecular diagnosis and proper familial genetic counseling for IP.

PubMed ID: 12497627 View in PubMed