Retrospective diagnosis of X-linked hyper-IgM syndrome in a family with multiple deaths of affected males

All males in two generations of a Hungarian family died of interstitial pneumonia. History and records suggested X-linked hyper-IgM syndrome (X-HIGM). DNA sequencing of a female carrier revealed a c. 654C→A transversion of the CD40L gene that predicts premature termination of *CD40L* synthesis. This report points to the importance of early carrier detection and genetic counseling in families with X-linked primary immunodeficiency diseases. We propose that the c.654C→A sequence variant may associate with severe X-HIGM phenotype.

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A 35-year old healthy but psychologically desperate woman came to medical attention because of her burdened family history (Figure; Patient III.3). She was unaware of any consanguinity in the family, but all her three brothers and two maternal uncles died of interstitial pneumonia. In addition, eight maternal great-uncles died of infectious diseases during the first decade of the past century. Her mother and maternal aunt were healthy, and had had no lymphoma or other hematological malignancies. One of the proband's brothers (Patient III.4) was hospitalized 6-7 times a year with recurrent, severe bacterial infections of the gastrointestinal and respiratory tracts until his death at age 10. Laboratory evaluations between 1971 and 1977 demonstrated severe hypo-gammaglobulinemia with normal or elevated IgM levels (IgG, 0.85-2.95 g/L; IgA, 0.10-0.87 g/L; IgM, 1.37-3.72 g/L). These data together with the family history suggested X-HIG.[1-2]

We performed mutational analysis of the CD40L of the proband and her mother. The proband's aunt (II.4) who died at 70 years of age, and had no children, was not available for genetic testing. Genomic DNA was isolated from whole blood samples. Exons 1 to 5 of the CD40L, and the flanking intron regions were amplified by PCR.[3] The PCR products were sequenced with the BigDye Terminator Cycle sequencing kit (Applied Biosystems). DNA mutation numbering was based on the cDNA sequence (GeneBank Accession No. L07414.1), and the first nucleotide is the *A* of the ATG translational initiation codon. Genetic analysis revealed wild type sequences of the proband, and heterozygosity for a c.654C>A sequence variant resulting in premature termination of CD40L synthesis (p.C218X) in her mother (Figure 1). These data confirmed that the deadly disease in this family was X-HIGM due to CD40L deficiency. Using these data proper genetic counseling was performed.

Retrospective diagnosis of primary immunodeficiency diseases (PIDs) may be a professional and psychological

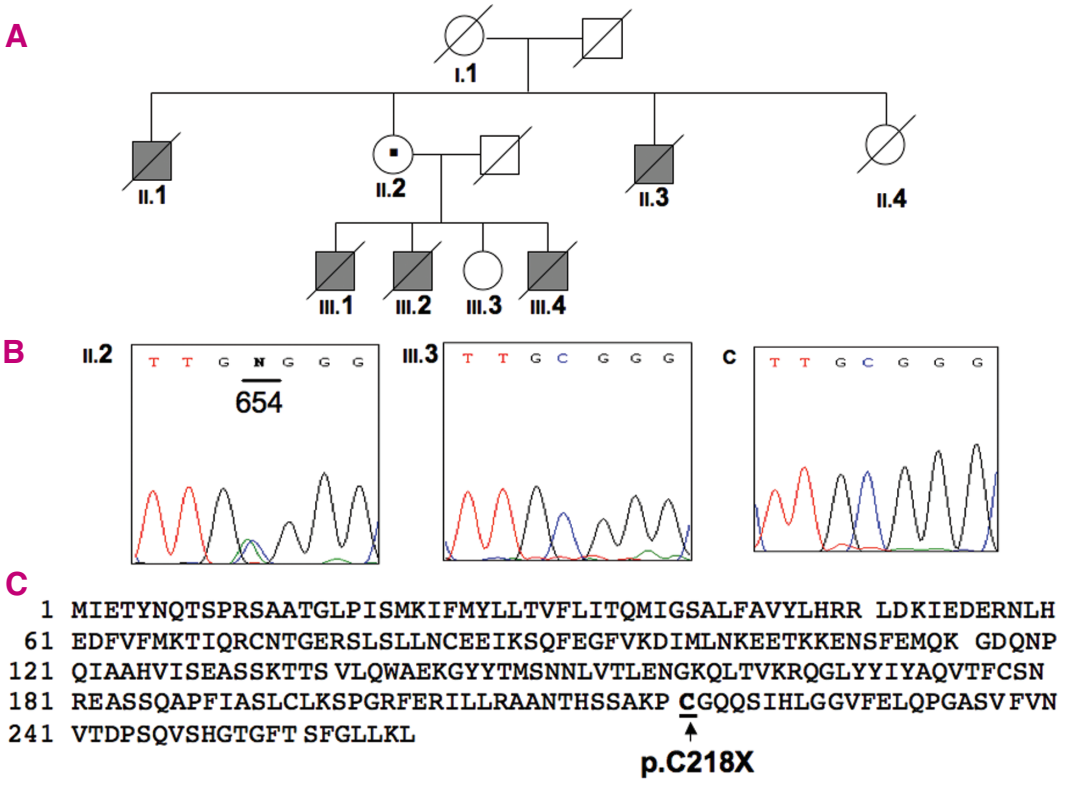

Figure 1. Phenotype and genotype information. a, Clinical phenotypes of the patients and their relatives. Filled squares, male patients with recurrent, severe infections; bars indicate they died. Patients II.1, II.3, III.1, and III.2 died of interstitial pneumonia at ages of 6, 12, 7, and 13 months, respectively. Patient III.4 presented with clinical and immunological phenotypes of X-HIGM, and died at 10 years of age. b, Sequence analysis of the CD40L revealed wild type sequences in the proband, and heterozygosity for a c.654C→A nucleotide substitution in her mother in exon 5; C, control. Mutation position is underlined. c, Amino acid sequence of the CD40L protein; in hemizygous patients the c.654C→A sequence variant is predicted to result in stop codon.

challenge in X-linked inherited disorders like X-HIGM,[1,2] X-linked lymphoproliferative disease,[3] X-linked agammaglobulinemia,[4] the Wiskott-Aldrich syndrome,[5] Interleukin-2 receptor gene deficiency,[6] or chronic granulomatous disease (gp91-phox deficiency).[7] Our report describes a unique life situation which may occur in families with X-linked PID, and points to the importance of early mutational analysis to define carriers, and to provide genetic counseling and prenatal diagnosis. The p.C218X mutation has been reported in 5 patients from three groups (8-10). Our report and published data suggest that the recurrent c.654C>A sequence variant results in severe clinical phenotype of X-HIGM.

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Key words: hyper-IgM syndrome, CD40 ligand, mutational analysis.

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ERRATA CORRIGE

In the article by Göran Carlsson, Andrew A.G. Aprikyan, Kim Göransdotter Ericson, Steve Stein, Vahagn Makaryan, David C. Dale, Magnus Nordenskjöld, Bengt Fadeel, Jan Palmblad, Jan-Inge Hentera. *Neutrophil elastase and granulocyte colony-stimulating factor receptor mutation analyses and leukemia evolution in severe congenital neutropenia patients belonging to the original Kostmann family in northern Sweden* published on Haematologica 2006;91:589-595 the name of dr. Jan-Inge Henter was incorrectly written. Correct name should read Jan-Inge Henter instead of Jan-Inge Hentera. Our apologizes to the author.

In the article by Isidorins A, Tani M, Bonifazi F, Zinzani P, Curti A, Motta MR, Rizzi S, Giudice V, Farese O, Rovito M, Alinari L, Conte R, Baccarani M, Lemoli RM. *Phase II study of a single pegfilgrastim injection as an adjunct to chemotherapy to mobilize stem cells into the peripheral blood of pretreated lymphoma patients* published on Haematologica 2005;90:225-31 the name of dr. Alessandro Isidori was incorrectly written. Correct name should read Alessandro Isidori instead of Alessandro Isidorins. Our apologizes to the author.