A Novel Mutation in the X-Linked Inhibitor of Apoptosis Protein Causing a Multi-System Autoinflammatory Disorder

Ariane Standing, Despina Eleftheriou, Ebun Omoyinmi, Alice Chieng, Nigel Klein, Helen Lachmann, Phillip Hawkins, Kimberly Gilmour, Paul Brogan

Introduction
X-linked lymphoproliferative syndromes are primary immunodeficiencies affecting males, characterized by vulnerability to Epstein-Barr virus (EBV) infection, frequently resulting in haemophagocytic lymphohistiocytosis (HLH).[1] XLP type 1 (XLP-1) is caused by mutations in the gene SH2D1A (also named SAP), whereas mutations in the gene XIAP (X-linked inhibitor of apoptosis protein) also known as BIRC4 have recently been found to underlie XLP-2.[2] Whilst these rare diseases have hitherto been considered as primary immunodeficiencies with propensity to develop haemophagocytic lymphohistiocytosis (HLH), they can be associated with immune dysregulation and chronic inflammatory manifestations without full-blown HLH. We present a case of XLP-2 with features mimicking cryopyrin associated periodic fever syndrome (CAPS), to raise awareness of this differential diagnosis amongst rheumatologists.

Abstract
We present a case of X-linked lymphoproliferative syndrome type 2 (XLP-2) with autoinflammatory features mimicking cryopyrin associated periodic fever syndrome (CAPS) to raise awareness of this differential diagnosis amongst rheumatologists. Possible disease mechanisms involving proteasome activity are discussed.

Key words: X-linked inhibitor of apoptosis protein, X-linked lymphoproliferative syndrome type 2, autoinflammatory syndrome, proteasome
**Case report**

A 2-month-old Caucasian boy from a non-consanguineous kindred presented with fever, lethargy and a maculopapular rash. Examination revealed hepatosplenomegaly and bilateral cataracts. Investigations demonstrated: mild pancytopenia: haemoglobin 10.6g/L (reference range 13-16); white cell count 2.25x10⁹ (4-11 x10⁹); neutrophils 0.76 x10⁹, lymphocytes 1.25 x10⁹; platelets 83x10⁹ (150-450 x10⁹); screening for congenital infections was negative. A bone marrow aspirate revealed no evidence of malignancy or haemophagocytosis. Extensive investigations for metabolic disorders were negative/normal. Recurrent skin rashes and febrile episodes and bilateral anterior uveitis were prominent features in the first year of life. A liver biopsy at the age of 16-months showed a mixed chronic inflammatory cell infiltrate with no diagnostic features. At the age of 3-years he developed arthritis mainly involving hips and knees, treatment with intra-articular corticosteroid injections and weekly subcutaneous methotrexate was later discontinued due to hepatic steatosis. At 6-years-old he developed myositis, confirmed on magnetic resonance imaging (MRI) and muscle biopsy; followed by sensorineural hearing loss at the age of 9 years; and development of bilateral panuveitis. Further investigations included normal angiotensin converting enzyme (ACE), normal ferritin at 58 µg/L (15.1-70), normal chest radiographs, and a normal nitroblue tetrazolium test. He screened negative for NLRP3, MEFV, TNFRSF1A, MVK and NOD2 mutations thereby excluding the following inherited autoinflammatory diseases: Cryopyrin associated periodic syndrome (CAPS); familial Mediterranean fever (FMF); TNF receptor associated periodic syndrome (TRAPS); mevalonate kinase deficiency (MKD) also known as hyper-IgD and periodic fever syndrome (HIDS); and Blau syndrome. Antinuclear antibody screening was positive at a titre of 1 in 2560, though extractable nuclear antigen (ENA) was negative with negative autoantibodies against double-stranded DNA and normal complement. Serum amyloid A protein (SAA) was elevated at 23 mg/L (reference range 0-10). The combination of systemic inflammatory features, uveitis and sensorineural deafness suggested a possible clinical diagnosis of mutation negative CAPS, although the decreased absolute counts of white blood cells and platelets were atypical of CAPS. A therapeutic trial of subcutaneous anakinra was not tolerated because he developed a blistering skin rash, and he also failed to respond to sequential: mycophenolate mofetil; adalimumab; and hydroxychloroquine. Consequently he required daily corticosteroids to control his symptoms. At age 15 years he was referred to a national centre for further investigation and consideration of canakinumab therapy for a clinical diagnosis of atypical CAPS.

In view of the persistent hepatosplenomegaly and mild cytopenias, an underlying primary immunodeficiency was reconsidered: NK cell perforin expression was normal; CD107a granule release assay on NK and CD8+T cells was also normal, as was expression of signalling lymphocytic activation molecule (SLAM)-associated protein (SAP). X-linked inhibitor of apoptosis protein (XIAP) expression detected by flow cytometry was however abnormal on CD8 and NK cells, Figure 1a. Western blot on total peripheral mononuclear blood cell lysate showed an absence of XIAP protein compared to healthy control, Figure 1b. The epitope for the antibody used for detection by both flow cytometry and Western blot spanned the site of the truncation which made it possible to detect a degree of cellular expression by flow cytometry. Genetic testing of the XIAP gene confirmed a novel base change c1082C>G generating a nonsense mutation, Ser361X confirming a diagnosis of XLP-2 (Figure 2). Thus far we have not found this variant in 75 ethnically matched controls and it has not been reported to the National Centre for Biotechnology.

![Figure 1](https://www.aprjournal.org)
In addition we have not seen it in an additional 86 samples sequenced by us to date.

Of note the patient tested positive for IgG antibodies against EBV, compatible with prior exposure but without prior clinical evidence of severe HLH. Genetic testing of his brother revealed that he too had the mutation and is undergoing further investigation for immunological sequelae. At the time of writing the index case is being worked up for allogeneic haematopoietic stem cell transplantation.

Discussion

Mutations in XIAP were first identified as causing XLP2 in 2006,[2] however the pathogenic mechanism(s) of how this causes the disease remains undefined.[1] There are many clinical phenotypes within XLP, including fulminant infectious mononucleosis, lymphoproliferative disorders and dysgammaglobulinemia.[3] This is especially true of XLP2 where the phenotype can be even broader ranging from persistent hepatosplenomegaly with little or few clinical symptoms, through to patients with multi-systemic inflammatory disease including intestinal inflammation, prior to the development of full-blown HLH. Whilst we detected ANA in our patient, we suggest that rather than indicating autoimmunity per se this may be reflective of the crosstalk between the innate and adaptive immune systems and described in the context of other chronic autoinflammatory diseases.[4]

This is the first report of an autoinflammatory-like disease resulting from a mutation in this gene. The c1082C>G mutation in the XLP gene we describe in this case led to loss of the Ubiquitin Associated domain (UBA) and Really Interesting New Gene (RING) domain (an E3 Ubiquitin ligase) of the XIAP protein;[5] which may reduce the targeting of proteins for degradation via the proteasome. It is possible that the lost ubiquitin tagging by XIAP causes the build-up of unprocessed oxidised proteins, which is thought to be a possible mechanism of pathogenesis in other autoinflammatory diseases, such Nakajo Nishimura syndrome,[6] and Chronic Neutrophilic Dermatosis Lipodystrophy and Elevated Temperature (CANDLE) syndrome.[7] Feretti et al found Q423P polymorphism in the XIAP gene, associated with increased risk of idiopathic autoinflammatory disease.[8] This polymorphism caused greater XIAP expression in transfected monocytes, leading to decreased Caspase 9 activation and increased TNFα secretion, adding weight to the hypothesis that mutations (rather than polymorphisms) in the XIAP gene may also cause a distinct autoinflammatory disease.[8]

In summary we present the case of a boy with XLP2 presenting with autoinflammatory type symptoms mimicking CAPS. This is the first case to our knowledge of monogenic inflammatory disease resulting from a mutation in this gene. This inflammatory phenotype might be explained through reduced proteasome activity, resulting in excess pro-inflammatory cytokine production associated with this mutation. Paediatric rheumatologists should consider XLP2 in males being worked up for possible monogenic autoinflammatory diseases, even without features of full-blown HLH.

Key Message: XLP2 may present with autoinflammatory disease mimicking CAPS.

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References


