

Hereditary Leukemia Due to Rare *RUNX1c* Splice Variant (L472X) Presents with Eczematous Phenotype

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ABSTRACT

Deleterious mutations in the *RUNX1* gene cause hereditary leukemia due to a rare syndrome called Familial platelet Disorder with Associated Myeloid Malignancy (FPDMM). We describe the characteristics of a family with FPDMM due to a novel *RUNX1* mutation (L472X), located in the most 3-prime end of the gene reported to date. Our 36-year-old proband presented with incidentally detected thrombocytopenia and a family history suggestive of FPDMM. Contrary to previously described families, affected members of our kindred express an eczematous phenotype, reportedly most severe in members who develop leukemia. Pedigree analysis shows that the L472X mutation tracks with thrombocytopenia, acute leukemia, and eczema. The L472X mutation produces a stably expressed *RUNX1* protein product with a corresponding decrease in wild type *RUNX1* expression. Our data supports the inclusion of eczema in the FPDMM phenotype and suggests the possibility that the *RUNX1* L472X mutant causes the type of dominant negative affect that is associated with an elevated risk of leukemia in FPDMM families.

Keywords: Hereditary Leukemia; Eczema; FPDMM; L472X; *RUNX1c* Isoform

1. Introduction

Deleterious mutations in *RUNX1* (Runt-related transcription factor 1; MIM ID *151385) are associated with a rare Autosomal Dominant hereditary cancer syndrome (linked to 21q22.12) that is characterized by qualitative and quantitative platelet defects with a high-propensity for myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and lymphoid malignancies [1]. At least 20 different causative *RUNX1* gene mutations have been described in the more than 30 reported families with Familial platelet Disorder with Associated Myeloid Malignancy Syndrome (FPDMM; MIM 601399) [2,3]. Most of these reports, summarized in **Figure 1(a)**, describe heterozygous germline mutations that cluster in the amino-terminal (N-terminal) region of the gene within the DNA-binding runt homology domain [3-31].

We describe a North American family with FPDMM syndrome caused by an unusually located *RUNX1* frameshift mutation at the 3-prime end of exon 8 (L472X). This *RUNX1* L472X variant tracks with an atypical clinical history of early-onset eczema; reported in symptomatic members of our kindred across four consecutive

generations. Consistent with the phenotype seen in other families with FPDMM syndrome, the *RUNX1* L472X variant presents with a bleeding diathesis, variable degrees of thrombocytopenia, adult-onset myelodysplastic syndrome/acute myeloid leukemia, and juvenile-onset acute lymphoblastic leukemia. The eczematous phenotype, reportedly most severe in the affected family members who develop leukemia, is a unique clinical characteristic of our kindred.

2. Materials and Methods

2.1. Patient Selection

The proband and his mother were referred to physicians at the City of Hope for clinical consultation. Peripheral blood samples from each patient were sent to CLIA-approved laboratories for diagnostic *RUNX1* gene mutation analysis. Subsequently the proband, his mother, and family members were invited to participate in a COH Institutional Review Board (IRB)-approved Hereditary Cancer Research registry. The study participants provided personal and family health data for the construction of a five

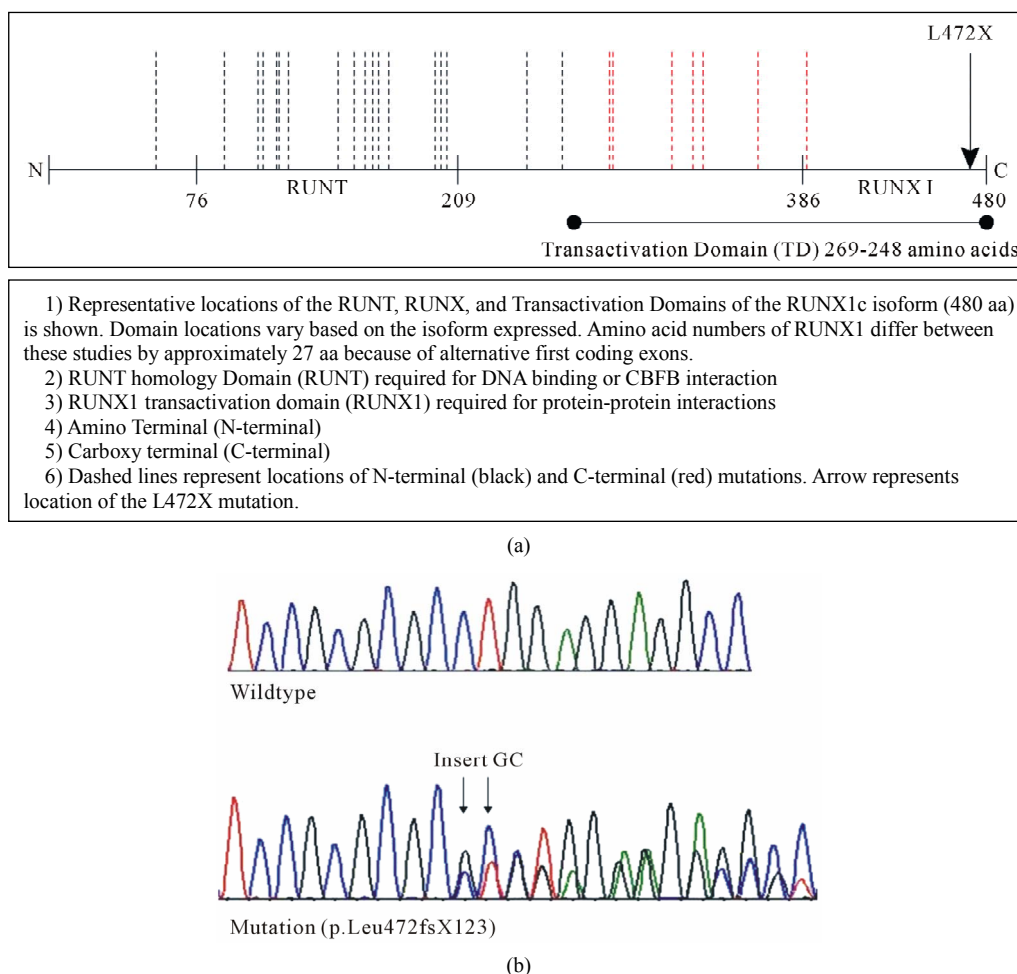


Figure 1. (a) *RUNX1* mutations associated with familial platelet disorder with associated myeloid malignancy phenotype; (b) *RUNX1* L472X mutation. DNA sequence analysis: Sequencing chromatograms showing a GC insertion in Exon 8 of the *RUNX1* gene.

generation pedigree. All studies were approved by the City of Hope IRB, consistent with the Declaration of Helsinki, and informed consent was obtained from all subjects.

2.2. Mutation Analysis

Genomic DNA from peripheral blood lymphocytes (and paraffin embedded non-malignant spleen tissue from one deceased member of the kindred; **Figure 2** case IV-20) was extracted by standard procedures. Polymerase chain reaction amplification and bidirectional sequencing of exons one through eight (and flanking regions) of the *RUNX1* gene was performed using DNA from the proband and his mother. Site-specific mutation analysis was performed for all other at-risk family members tested.

2.3. Western Blot Analysis

Western Blot Analysis was performed using total protein

isolated from peripheral blood and bone marrow mononuclear cells from the proband, his mother, and two healthy controls. Equal amounts of protein (25 μg) were loaded onto a 4% - 20% SDS-PAGE gel, transferred onto a nitrocellulose membrane, and probed with rabbit polyclonal *RUNX1* antibody (Cell Signaling). The membrane was stripped, washed, and reprobed with mouse monoclonal anti-Actin antibodies (Sigma-Aldrich). Antibody detection was done using enhanced chemiluminescence (Super Femto kit, Pierce Biotechnology). The levels of Actin served as loading controls.

3. Results

3.1. Phenotype

Our 36-year-old proband is a healthy, non-dysmorphic, male with mild eczema and asymptomatic thrombocytopenia (range 94 to 120,000), initially detected during a routine physical exam. A bone marrow evaluation showed

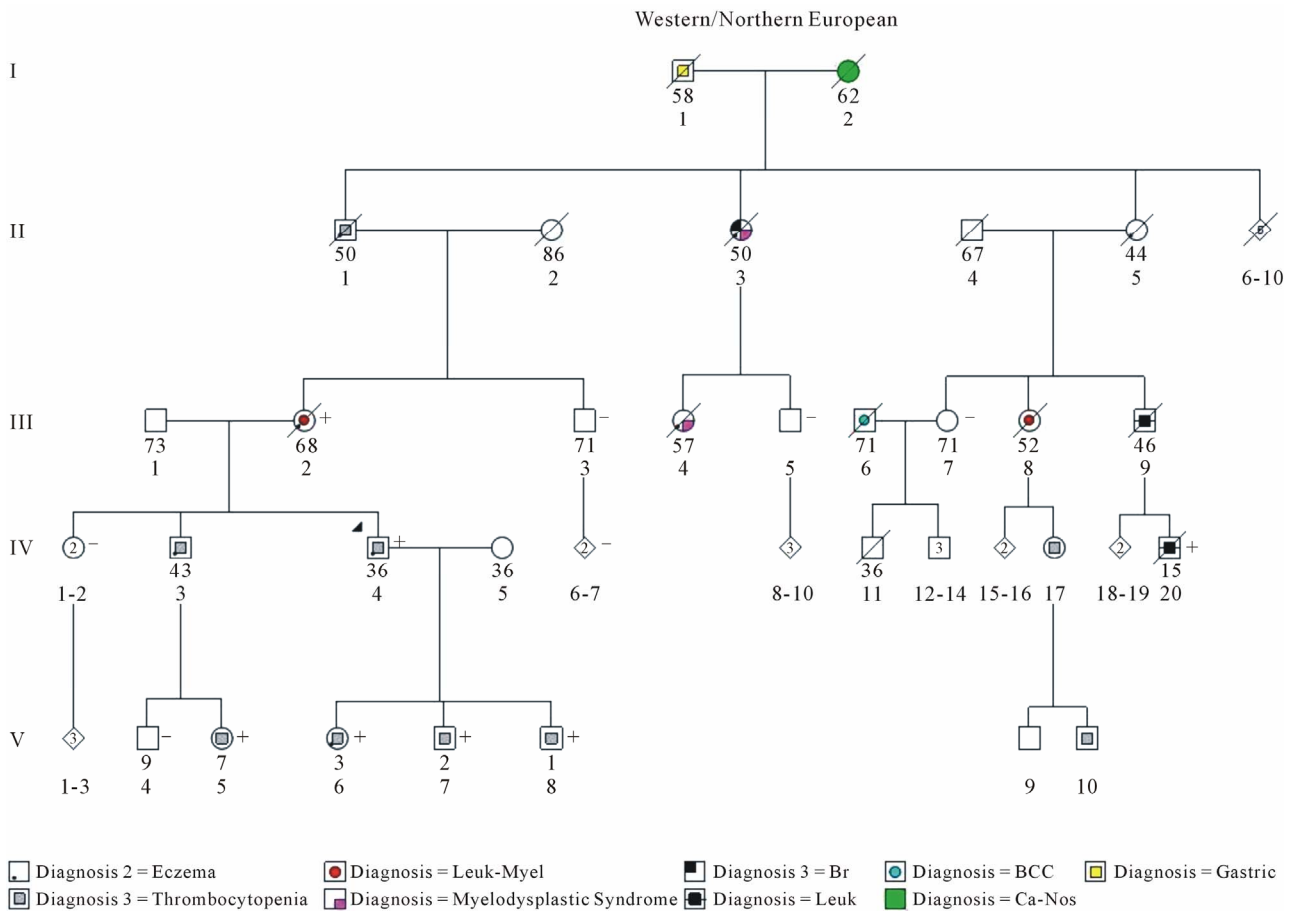


Figure 2. COH fpdmm kindred. A five generation (I-V) pedigree of a City of Hope (COH) family with Familial Platelet Disorder with Associated Myeloid Malignancy (FPDMM) is shown. The index patient (proband) is indicated by an arrow. The family members with confirmed *RUNX1* L472X gene mutations are identified by the plus sign (+); negative cases are identified with a (-) sign. The square symbols represent males; the circles represent females; the \diamond represents gender which is not specified or unknown. Symbols that contain numbers represent more than one family member. The current age/age at death (years) for each family member is noted directly below the symbol. Family members affected by cancer [myelodysplastic syndrome, acute myeloid leukemia (Leuk-Myel), acute lymphoblastic leukemia (Leuk), basal cell carcinoma (BCC), breast (Br), gastric, and cancer not otherwise specified (Ca-NOS)] or other disease-related characteristics [thrombocytopenia and eczema] are identified by symbols. Pathological and/or medical record documentation is available for all family members with leukemia, myelodysplastic syndrome, and thrombocytopenia. Dashed symbols represent deceased individuals. Five generations are represented with Roman numerals (I, II, III, IV, and V). Identification numbers representing family members within each generation are located immediately under each person's current age/age at death. The proband's mother is case III-2.

normal trilineage hematopoiesis without evidence of leukemia or myelodysplasia. He was referred for a cancer genetics risk evaluation after his mother was diagnosed with myelodysplastic syndrome. Our proband's mother was a 68-year old who had a ~3-year-history of progressive anemia. Sequential bone marrow evaluations confirmed myelodysplastic syndrome with the subsequent development of acute myeloid leukemia. Despite chemotherapy, she eventually died from progressive, refractory disease. Our proband provided an extensive family history of hematological disorders and leukemia involving four generations of family members along his mater-

nal lineage (Figure 2). Interestingly, our proband's 7-year-old niece was clinically diagnosed by a pediatric hematologist with an *MYH9*-related disorder known as Sebastian syndrome (OMIM 605249), due to her history of thrombocytopenia, easy bruisability, and a confirmed aspirin-like platelet defect. No causative *MYH9* mutation could be identified by DNA sequence analysis of genomic DNA from this child; testing was performed by a commercially available diagnostic laboratory. Our proband's maternal grandfather died after a ~6-month-long illness characterized by easy bruisability, mucosal membrane bleeding, and progressive splenomegaly.

3.2. Genotype

A heterozygous c.1413_1414insGC (p. L472X) germline mutation was identified in exon 8 of the *RUNX1* gene in our proband, his mother, and five additional family members; a total of 7 mutation carriers out of 14 family members studied (**Figure 1(b)**). Each of the *RUNX1* L472X mutation carriers in this family were reported to have mild to severe eczema, which directly correlated to their degree of thrombocytopenia and/or clinical bleeding difficulties. There were no reports of eczema in family members without clinical or genotype evidence of FPDMM syndrome. The probability that our proband's daughter (**Figure 2**; case V-6) and his cousin (case IV-20) share the *RUNX1* L472X germline mutation by chance alone is 1.6% (1/64), according to Mendelian probability estimates.

3.3. Protein Expression

Because the L472X mutation causes a frameshift near the stop codon of the gene, it is predicted to bypass the normal termination codon and produce a run-on RNA product. If stable, this run-on RNA product could be translated into a substantially extended protein product (p.Leu472fsX123), which would be detectable by Western Blot analysis.

Peripheral blood cells from the proband (case IV-4) and his mother (case III-2) demonstrated low levels of expression of a >55 kD *RUNX1* variant protein as well as the expected 55kD wild type *RUNX1* protein, which was expressed at reduced levels (**Figure 3**). The 55 kD *RUNX1* variant protein was also detected in samples from the proband's bone marrow (data not shown) and was not detected in healthy control samples (normal 1 and 2). These results indicate that the heterozygous *RUNX1* L472X germline mutation produces a stably expressed *RUNX1* protein product, but that expression of wild type *RUNX1* is reduced.

4. Discussion

Genotype characteristics of *RUNX1* germline mutations are known to have clinically significant functional consequences that may predict leukemia risk in germline carriers. Families carrying mutations that retain greater degrees of biological activity of the wild type *RUNX1* protein (e.g. deletions and frameshift mutations that act via haploinsufficiency) have an ~20% risk of MDS/AML as compared to a ~60% risk in families that carry mutations with little residual functional activity (e.g. dominant negative or biallelic nonsense mutations) [15]. Our data suggests that the *RUNX1* L472X mutant may inhibit the transcription or translation of wild type *RUNX1* protein,

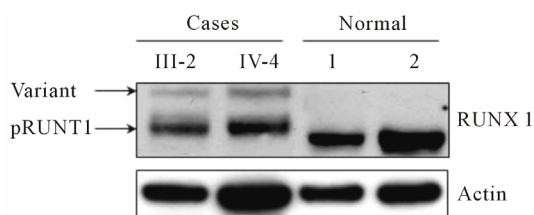


Figure 3. *RUNX1* L472X expression. Protein Expression: Western Blot analysis of total protein from the proband (case IV-4) and his mother (case III-2) showed low expression of the normal 55 kD *RUNX1* protein and identified the presence of an abnormal *RUNX1* band (variant).

possibly leading to the type of dominant negative effect that has been associated with a higher risk of leukemia in some FPDMM families. Although speculated to have the functional capacity to cause leukemia in humans, the tumorigenesis potential of the *RUNX1c* isoform has not been well established.

Expression of functional *RUNX1* protein is tightly regulated at the level of transcription, mRNA processing (splicing), and translation. At least three splice variants of the *RUNX1* gene have been identified to date: *RUNX1a* (250 amino acids, aa), *RUNX1b* (453 aa), and *RUNX1c* (480 aa) [NCBI NP_001745; UniProt Q01196] [32]. The *RUNX1c* variant represents the longest and least abundant isoform of the *RUNX1* protein; it is transcribed from the distal P1 promoter, encoding for its own distinct N terminal region [33,34]. The *RUNX1b* variant is transcribed from the proximal P2 promoter and is 27 amino acids shorter than *RUNX1c*. The *RUNX1a* variant is also transcribed from the P2 promoter; but, it differs in the 3-prime coding and UTR regions (compared to variants 1b and 1c) and it lacks the *RUNX1* transactivation domain. The distal exon 8 location of the L472X mutation suggests that alternative splicing of the *RUNX1* protein occurs in (at least) the mutation carrying members of our kindred who, presumably, express the *RUNX1c* variant.

In addition to demonstrating that the novel L472X *RUNX1* mutation associates with FPDMM clinical characteristics, our report expands the FPDMM phenotype by adding eczematous skin rashes to the clinical findings associated with this disease. To our knowledge, this is the first report to confirm an association between eczema and FPDMM.

Leukemia-associated skin rashes are typically due to infection, leukemic infiltration, or paraneoplastic phenomenon. A prior history of eczema has been associated with a ~30% decreased risk of childhood acute lymphoblastic leukemia, an increased risk of viral (esp. human T-cell lymphotropic virus) and non-virus associated forms of lymphoma, but no clear alterations in risk for acute myeloid leukemia [35-38]. The only clear link

between eczema and a hereditary cancer syndrome is Wiskott-Aldrich syndrome (WAS). WAS is an X-linked disease that often presents with a classic triad of severe-treatment resistant eczema (that persists into adulthood), thrombocytopenia (with small platelets), immunodeficiency, and a high-risk of lymphoma (occasionally presenting with bone marrow dysplasia in young people) [39]. Eczema is not a reported characteristic of other chromosome 21-linked disorders with propensity for leukemia and/or impaired erythroid and megakaryocyte hematopoiesis (e.g. Down syndrome and X-linked (macro) thrombocytopenia) [40-42]. Functional investigations of our L472X variant protein may provide novel insights into the biological consequences of distal C-terminal *RUNX1* mutations and the genetic pathways that control skin manifestations of immune dysfunction, autoimmunity, and megakaryocytopoiesis [39].

In conclusion, our data supports the inclusion of eczema in the FPDMM phenotype and suggests the possibility that the *RUNX1* L472X mutant causes the type of dominant negative affect that is associated with an elevated risk of leukemia in FPDMM families.

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