To the editor:

**Kindlin-3: a new gene involved in the pathogenesis of LAD-III**

Integrins constitute the major and largest cell adhesion receptor family. These heterodimers undergo dramatic allosteric conformational changes in response to various activation signals acting on their beta integrin subunit tails.1 In hematopoietic cells, these events are critical for platelet aggregation, firm leukocyte adhesiveness to vascular endothelium, and immune synapse formation. Talin1 is the primary cytoskeletal regulator of integrin activation.2 Recent evidence suggests that Kindlins,3 3 structurally related adaptors, cooperate with talin in activating integrins in different cell types.4 In contrast to Kindlin1 and 2, Kindlin-3 (FERMT3) expression is restricted to the hematopoietic system and is particularly high in megakaryocytes and spleen.4 Unlike loss of talin1, which is embryonically lethal, deletion of individual Kindlin family members is not, but dramatically affects integrin activation in different hematopoietic cells. Deletion of Kindlin-3 in mice results in severe defects in platelet β3 and β1 integrin activation and osteopetrosis whereas integrin function in non hematopoietic cells remained conserved.4

Upstream of talins and Kindlins, integrin activation is tightly controlled by the Ras-related guanosine triphosphatase (GTPase), Rap1.6 Deletion of the Rap-1 guanine exchange factor (GEF), CalDAG-GEFI (CDGI, Ras guanine nucleotide releasing protein-2 [RASGRP2]) results in major defects in platelet integrin activation7 strikingly similar to the defects associated with Kindlin-3 deletion.4 CDGI and Rap-1 also control inside out integrin activation in leukocytes.8,9 We have identified impaired expression of CDGI in human hematopoietic cells, a result of a homozygous splice junction mutation in exon 16, which led to a rare autosomal recessive leukocyte adhesion deficiency syndrome, LAD-III, a combined defect in β3, β2 and β1 integrin activation in platelets, neutrophils and lymphocytes.10 These LAD-III cases also suffered from severe osteopetrosis (Kilic, submitted). All of these LAD-III patients were of Turkish origin, children of heterozygote carriers of the same exon 16 CDGI mutation (10) and not shown). Two patients died at age 3 to 6 years and a third infant underwent bone marrow transplantation.

In light of the striking similarity between CDGI and Kindlin-3 knockout platelet dysfunction,4,7 we sequenced Kindlin-3 in our 3 CDGI defective LAD-III cases. Genetic sequencing of Kindlin-3 revealed a homozygous stop codon in R513 (CGA > TGA) of Kindlin-3 in all 3 patients (Figure 1 and Document S1, available on the Blood website; see the Supplemental Materials link at the top of the online article). The patients’ parents were all confirmed to be heterozygous carriers of this mutation, which was absent in all 68 control chromosomes tested from Turkish donors (Figure 1 and data not shown). This mutation alters the F3 PTB–containing integrin binding subdomain of Kindlin-3. Notably, Kindlin-3 is expressed in the same locus of CDGI (11q13) and the 2 genes are 503 029 bp apart, whereas other Kindlins are expressed on other chromosomes. None of the patients suffered from nonhematopoietic abnormalities associated with other Kindlin deficiencies.

Taken together, the LAD-III phenotype reported by us could manifest a combined defect in both upstream and downstream integrin regulatory effectors, namely, CalDAG-GEFI and Kindlin-3, respectively. Our findings predict a potential role for Kindlin-3 in regulating integrin activation in both platelets and leukocytes. Although extremely rare, the presence of identical mutations in 2 functional genes within the same locus in 3 Turkish families may suggest a common ancestor allele carrying both of these mutations. To our knowledge this is a first report of multiple mutations in 2 separate genes which function within a similar signaling axis in a key biologic process. Additional LAD-III cases can serve as ideal model systems to address the cooperative roles of CDGI Rap-1 signaling, talin1, and Kindlin-3 in integrin activation on different hematopoietic cell types.

Approval was obtained from the Rambam Medical Center institutional review board for these studies. Informed consent was obtained in accordance with the Declaration of Helsinki.

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