Distinct mutations in STXBP2 are associated with variable clinical presentations in patients with familial hemophagocytic lymphohistiocytosis type 5 (FHL5).

Abstract:
Familial hemophagocytic lymphohistiocytosis (FHL) is a genetically determined hyperinflammatory syndrome caused by uncontrolled immune response mediated by T-lymphocytes, natural killer (NK) cells, and macrophages. STXBP2 mutations have recently been associated with FHL5. To better characterize the genetic and clinical spectrum of FHL5, we analyzed a cohort of 185 patients with suspected FHL for mutations in STXBP2. We detected biallelic mutations in 37 patients from 28 families of various ethnic origins. Missense mutations and mutations affecting 1 of the exon 15 splice sites were the predominant changes detectable in this cohort. Patients with exon 15 splice-site mutations (n = 13) developed clinical manifestations significantly later than patients with other mutations (median age, 4.1 year vs 2 months) and showed less severe impairment of degranulation and cytotoxic function of NK cells and CTLs. Patients with FHL5 showed several atypical features, including sensorineural hearing deficit, abnormal bleeding, and, most frequently, severe diarrhea that was only present in early-onset disease. In conclusion, we report the
largest cohort of patients with FHL5 so far, describe an extended disease spectrum, and demonstrate for the first time a clear genotype-phenotype correlation.