Mutations in the gene cause severe congenital neutropenia as well as Shwachman-Diamond-like syndrome

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Résumé en anglais	Congenital neutropenias (CNs) are rare heterogeneous genetic disorders, with about 25% of patients without known genetic defects. Using whole-exome sequencing, we identified a heterozygous mutation in the gene, encoding the signal recognition particle (SRP) 54 GTPase protein, in 3 sporadic cases and 1 autosomal dominant family. We subsequently sequenced the gene in 66 probands from the French CN registry. In total, we identified 23 mutated cases (16 sporadic, 7 familial) with 7 distinct germ line mutations including a recurrent in-frame deletion (Thr117del) in 14 cases. In nearly all patients, neutropenia was chronic and profound with promyelocytic maturation arrest, occurring within the first months of life, and required long-term granulocyte colony-stimulating factor therapy with a poor response. Neutropenia was sometimes associated with a severe neurodevelopmental delay (n = 5) and/or an exocrine pancreatic insufficiency requiring enzyme supplementation (n = 3). The SRP54 protein is a key component of the ribonucleoprotein complex that mediates the co-translational targeting of secretory and membrane proteins to the endoplasmic reticulum (ER). We showed that SRP54 was specifically upregulated during the in vitro granulocytic differentiation, and that mutations or knockdown led to a drastically reduced proliferation of granulocytic cells associated with an enhanced P53-dependent apoptosis. Bone marrow examination of -mutated patients revealed a major dysgranulopoiesis and features of cellular ER stress and autophagy that were confirmed using -mutated primary cells and knockdown cells. In conclusion, we characterized a pathological pathway, which represents the second most common cause of CN with maturation arrest in the French CN registry.
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