Table 1 Point mutations in the Runt domain associated with blood or bone disease

Mutation	Disease	Type	DNA binding	Hetero-dimerization	Ref.
Arg80→Cys	AML	Monoallelic	-	+	3
Lys83→Asn	AML	Monoallelic	-	+	3
Arg177→Gln	AML	Monoallelic	-	+	3
Arg139→Gln	FPD	Monoallelic	NT	NT	2
Arg174→Gln	FPD	Monoallelic	NT	NT	2
Met124→Arg	CCD	Monoallelic	-	NT	5
Ser140→Asn[a]	CCD	Monoallelic	-	-	5
Phe146→Ser[a]	CCD	Monoallelic	-	-	7
Lys167→Asn[b]	CCD	Monoallelic	-	NT	
Arg174→Gln[b]	CCD	Monoallelic	NT	NT	

AML, acute myelogenous leukemia; FPD, familial platelet disorder; CCD, cleidocranial dysplasia; NT, not tested; -, loss-of-function; +, similar to wild-type. Numbering according to AML1. DNA binding tested by electrophoretic mobility shift with recombinant protein; heterodimerization tested by electrophoretic mobility shift and/or affinity chromatography with recombinant protein. [a]Ser140→Gly and Phe146→Asp are deficient for both DNA binding and heterodimerization and were not isolated as being disease-related; the Asn and Ser mutations at these positions, respectively, have only been tested for DNA binding and are presumed to be heterodimerization-deficient. [b]H. Kanegene, personal communication.

mosomal abnormalities in addition to *AML1* mutations[2]. One possibility is that *AML1* acts as a tumor suppressor. Haploinsufficency of a tumor suppressor could predispose patients to a variety of secondary mutations[2]. Alternatively, secondary defects may be linked to the TGF-β/BMP signaling cascade, which regulates cell proliferation and cell-fate determination. The Smad proteins interact with all three α-subunit gene products and have a synergistic role in activating transcription (ref. 14; Y-W. Zhang and Y. Ito, personal communication).

The idea that heterozygous loss-of-function can result in a tumor-prone phenotype alters our concept of what it means for a protein to act as a tumor suppressor[15]. $p27^{Kip}$, an inhibitor of cyclin-dependent kinases and suppressor of cell proliferation, is a second candidate tumor suppressor for which haploinsufficiency has been causally associated with tumor progression[16]. To evaluate the role of tumor-suppressor haploinsufficiency in the development of heritable leukemias, it is important to determine whether or not the unaffected allele is fully functional. Secondary mutations, genetic and epigenetic mechanisms could all inhibit normal function of the wild-type gene product. Confirmation of *AML1* haploinsufficiency in tumor cells may indicate new approaches to pharmacological intervention. A detailed characterization of the biochemistry of the normal and mutant gene products will be necessary for the development of therapeutic agents that take advantage of any biochemical differences between mutant and wild-type *AML1* and are capable of rescuing the activity of the wild-type gene. Differences in *AML1* heterodimerization efficacy could be an excellent example of this approach[9–10]. However, development of effective leukemia therapeutics will also require the creation of bona fide mouse models of *AML1* haploinsufficiency to study the genetic and biochemical mechanisms of tumorigenesis.

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Ancient HTLV-1

The ancestors of the Andean indigenous people are believed to have originated in Asia and migrated to South America about 20,000 years ago. This explains their genetic similarities with the Japanese, including their similarity in human T-cell lymphotrophic virus type I (HTLV-1) haplotypes. To determine whether the ancient Andeans (Paleo-mongoloids) migrated with this HTLV-1 haplotype, Cartier *et al.* (page 1428, this issue) analyzed DNA isolated from bone marrow of mummies excavated from the Atacama desert in north Chile. People buried in cemeteries of this region were naturally mummified by the dry and salty conditions of the desert, and thousands of mummified bodies have been discovered. Two of 104 mummies tested actually had ancient HTLV-1 DNA, and these viral DNA sequences were almost identical to those of modern-day Chilean and Japanese HTLV-1-seropositive individuals. The authors suggest that the HTLV-1 provirus of these mummies might be the aboriginal HTLV-1 prevailing among Mongoloid populations in Asia and the Andes over 1,500 years ago. The picture shows one of the mummies from this region, a woman estimated to be 1,300–1,700 years old, at the Instituto de Investigaciones Arqueologicas y Museo in San Pedro de Atacama, Chile.

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