Variable phenotype in females with the same mutation could be explained by variations in expression due to differences in X inactivation among families, as suggested by Aradhya (2000). If so, an X-inactivation study could be helpful in predicting phenotypic outcome in a female heterozygote with the mutation. However, the proband in the family described here (HED-ID phenotype) and the female heterozygote in family XL344 (IP-like phenotype; Aradhya et al. 2001) yielded the same random X-inactivation pattern. We therefore suspect that an X-inactivation study would have limited predictive value.

To summarize, hypomorphic mutations in the *NEMO* gene can lead to the devastating HED-ID phenotype in female heterozygotes as well as males. The very broad phenotypic spectrum of female heterozygotes, ranging from normal to overt immunodeficiency, poses a challenge during counseling of families with HED-ID.

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Reply to Kosaki et al.

To the Editor:

The letter from Kosaki et al. (2001 [in this issue]) reports the first instance of immunodeficiency in a female heterozygous for a hypomorphic mutation of the X-linked *NEMO* gene. *NEMO* hypomorphic mutations result, in males, in the disorder hypohidrotic ectodermal dysplasia with immunodeficiency (HED-ID) (Zonana et al. 2000; Aradhya et al. 2001; Doffinger et al. 2001; Jain et al. 2001). In the 17 families previously reported, only males have had clinical immunodeficiency. As expected, owing to Lyonization, carrier females either were normal or had defects of their teeth, skin, or hair. A single female carrier, heterozygous for the same mutation reported in the family studied by Kosaki et al., had an elevated immunoglobulin A level (Zonana et al. 2000) but did not have immunodeficiency.

Null mutation of the *NEMO* gene generally results in prenatal lethality in hemizygous males and in incontinentia pigmenti in heterozygous females. Affected females are immunologically normal, presumably owing to preferential survival and proliferation of cells expressing the normal allele (skewed X inactivation). Female carriers with hypomorphic mutations have shown both random and skewed X inactivation, indicating that at least some of the mutations do not affect T- and B-cell survival or proliferation (Aradhya et al. 2001; Doffinger et al. 2001; Jain et al. 2001). Rarely, females can fully manifest X-linked recessive disorders, including other X-linked immunodeficiencies, such as Wiskott-Al-

drich syndrome (Puck and Willard 1998). However, in contrast to the patient reported by Kosaki et al., cases not due to cytogenetic abnormalities demonstrate skewed X inactivation, presumably of cells expressing the mutant allele. In these instances, the mutations do not impair cell proliferation or survival but still do cause cellular dysfunction.

It is difficult to reconcile Kosaki et al.'s finding of random X inactivation in the peripheral blood leukocytes with their patient's clinical manifestations. We would expect to find skewed X inactivation in which the X chromosome expressing the mutant allele is predominant. It is possible that a functionally important subset of B or T cells (Jain et al. 2001) would have displayed skewed X inactivation if Kosaki et al. had sorted the leukocytes into separate populations before analysis. Another remote possibility is that, unlike the patient's presumably heterozygous mother and sister, who had ectodermal findings but no immunodeficiency, the patient had a loss of her normal *NEMO* allele. The existence of a highly homologous *NEMO* pseudogene on the X chromosome makes it very difficult to distinguish hemizygosity from true heterozygosity.

Kosaki et al.'s findings are unique, but, as in other examples, fully manifesting females with X-linked recessive disorders—such as Duchenne muscular dystrophy and hemophilia B—usually represent rare events (Puck and Willard 1998). Families should still be counseled that generally, in HED-ID, only males manifest clinically significant immunodeficiency. Further cases of immunodeficient females with HED-ID must be described before such counseling should be altered.

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