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Research Letter

Absence of *RECQL4* Mutations in Poikiloderma With Neutropenia in Navajo and Non-Navajo Patients

To the Editor:

Poikiloderma with neutropenia (PN), previously referred to as Navajo poikiloderma (MIM #604173) is a rare, autosomal recessive disorder first described by Clericuzio et al. [1991] in the Navajo American Indian population [Erickson, 1999]. It is characterized by a distinctive poikilodermatous rash, noncyclical neutropenia, small stature, pachyonychia, and pulmonary disease (reactive airway disease and recurrent pulmonary infections). The molecular defect in this disorder has not been identified.

PN shares some overlapping clinical features with Rothmund-Thomson syndrome (RTS, MIM #268400), another autosomal recessive disorder characterized by poikiloderma, small stature, and nail abnormalities. In addition, RTS patients have skeletal manifestations, sparse hair, cataracts, and predisposition to malignancy, specifically osteosarcoma [Wang et al., 2001], not reported in PN. Both disorders are defined by poikilodermatous skin changes, but the pattern of the rash differs. In RTS, the rash typically starts in infancy on the cheeks as macular erythema (acute phase) and then spreads to involve the extremities, rarely affecting the trunk and abdomen. The rash of PN tends to start more peripherally as papular eczematous erythema which then spreads centrally to involve the trunk and face. The skin changes of both disorders ultimately evolve into a more chronic phase of poikiloderma. Whereas neutropenia is classically associated with PN but not RTS, an increasing number of cases of hematologic abnormalities are being reported in RTS, including isolated neutropenia [Welch et al., 1984], myelodysplastic syndrome [Rizzari et al., 1996], leukemia [Porter et al., 1999], and aplastic anemia [Knoell et al., 1999]. Mutations in the *RECQL4* gene at 8q24.3 encoding a DNA helicase have been detected in approximately two-thirds of RTS patients [Kitao et al., 1999; Lindor et al., 2000; Wang et al., 2002].

To examine whether PN could be due to homozygosity for a particular allele at the RTS locus, we performed sequence analysis of the *RECQL4* gene in three kindreds with the PN phenotype. One kindred included two affected Navajo siblings; the second kindred had a single affected child of Turkish and British descent; and the third kindred consisted of affected fraternal twins of Scottish descent. All subjects or their parents provided informed consent to participate in a research protocol approved by the Institutional Review Board for Human Subjects Research of Baylor College of Medicine, Houston, TX. The two Navajo subjects were sisters (ages 15 and 13 years at time of ascertainment) who had the classic rash of PN and neutropenia. Other findings included frequent infections in the first year of life, such as recurrent pneumonia with associated wheezing and recurrent otitis media. They had marked thickening and excessive curving of the fingernails and toenails. The Turkish/British subject was a 2-year-old female who carried an initial diagnosis of probable RTS. However her clinical findings were more consistent with PN. Her rash started at age 3 months on her lower extremities, then spread to involve upper extremities, and eventually more centrally to involve her trunk and face. It began as a mottled pink/red rash with an eczematous component and over time became more hyperpigmented and poikilodermatous. She had pachyonychia, especially of the toenails. She was found at age 20 months to have severe neutropenia (ANC 0.3×10^3/ul) that persisted and was noncyclical. Bone marrow examination was normal. Her growth (25th centile for weight and height) and development have been without delay. Chromosome analysis was normal (46, XX).

The third kindred consisted of 2-year-old male (sibling A) and female (sibling B) fraternal twins from Scotland who were born at 36 weeks gestation to nonconsanguineous parents. At the age of 2 months they developed an eczematous rash initially on the arms and legs and subsequently on the face. Gradually the eczema cleared and was replaced by poikiloderma (Fig. 1A and B). They also exhibited nail dystrophy starting at 3 weeks of age with subungual hyperkeratosis (Fig. 2). The nails were markedly thickened and difficult to cut. Both children had recurrent respiratory

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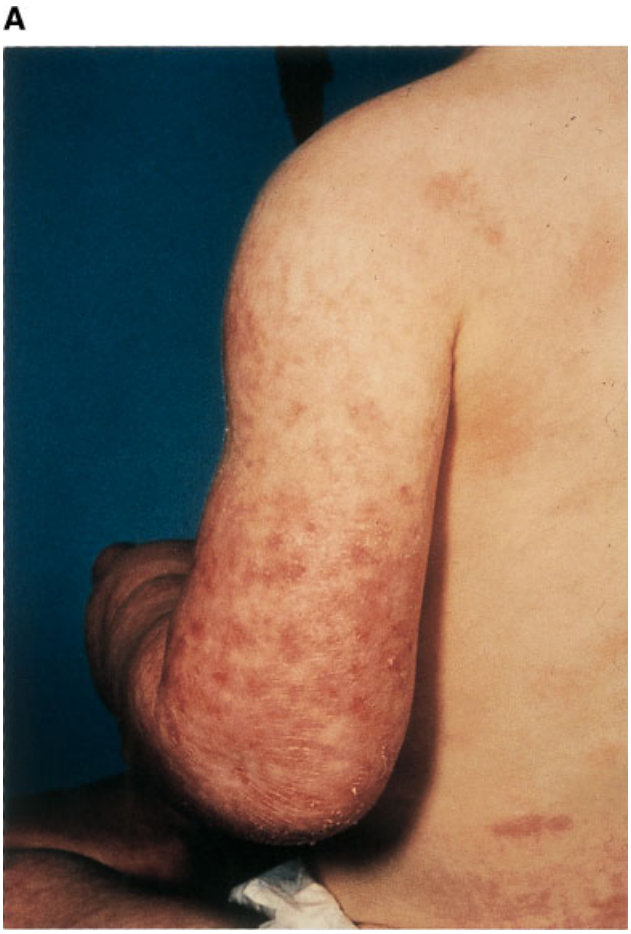

Fig. 1. The rash of poikiloderma with neutropenia (PN) often begins on the extremities as papular erythema and gradually over time develops a poikilodermatous appearance. Chronic rash on (**A**) left upper extremity of sibling A and (**B**) right lower extremity of sibling B (both from kindred 3).

infections with prominent wheezing and recurrent otitis media. At age 20 months, they were both found to have isolated severe neutropenia ranging from 0.1×10^3 to 0.9×10^3/ul. They had low levels of IgM (28.5 mg/dl)

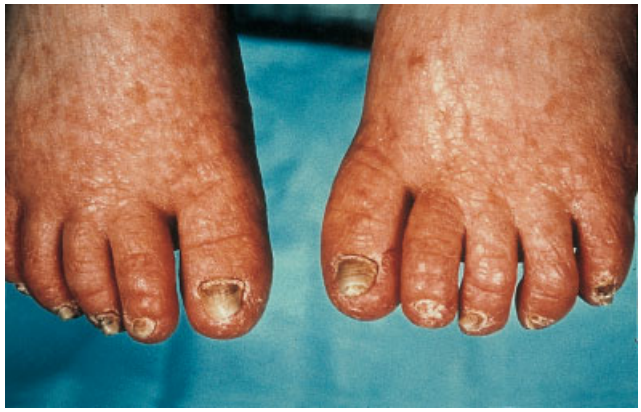

Fig. 2. Pachyonychia, or thickening of the nails, is a common feature of PN. Toenails of sibling A (kindred 3) demonstrating subungual hyperkeratosis.

with other immunoglobulin levels normal. One of the twins (sibling A) had loose stools since infancy and colon biopsy showed mild colitis. His symptoms spontaneously resolved by the age of 2 years. Bone marrow studies were not performed on the twins. Skeletal surveys were negative.

Peripheral blood was obtained from subjects and family members, and DNA was extracted. PCR analysis and sequencing of all 21 exons and all 13 short introns of *RECQL4* were performed. Sequences were analyzed for mutations by visual inspection and alignment of chromatograms using Sequencher™, version 4.0 (Gene Codes Corporation, Ann Arbor, MI).

Our molecular results showed that none of the five PN subjects carried deleterious mutations in *RECQL4*. We did not detect any of the 21 different truncating mutations previously reported in RTS patients [Kitao et al., 1999; Lindor et al., 2000; Wang et al., 2002]. We performed analysis of several common single nucleotide polymorphisms within the *RECQL4* gene (submitted to dbSNP, http://www.ncbi.nlm.nih.gov/SNP/index.html). In all three kindreds, the probands were found to be homozygous for these SNPs. However, they did not share a common haplotype. In the Scottish kindred, DNA was available from an unaffected sibling. This sibling shared the same haplotypes as the affected twins, suggesting that *RECQL4* may be unlinked to the disorder. However, *RECQL4* cannot be definitively excluded because of the possibility of incomplete penetrance.

van Hove et al. [2000] described in abstract format another set of three affected siblings of Turkish descent with some features of PN and showed that they were unlinked for polymorphic markers near the *RECQL4* locus. Taken together, these data suggest that (1) PN is not due to deleterious mutations in *RECQL4* and that (2) PN is not limited to members of the Navajo population. Although all 14 of Clericuzio's patients were Navajo, she originally termed the disorder "immune deficient poikiloderma." Our non-Navajo patients are phenotypically similar to the Navajo patients, although they do not have a clearly defined immune-deficiency other than neutropenia and the previously described low IgM

values in two patients, leading us to propose using the more specific name "Poikiloderma with Neutropenia" instead of Navajo poikiloderma to describe this syndrome.

While RTS and PN share some clinical features, they also remain distinctly different with respect to other features such as cancer, alopecia, and skeletal anomalies. Cancer has not been associated with PN, while osteosarcoma is clearly increased in RTS. The risk of developing osteosarcoma in RTS is associated with the presence of truncating mutations in the *RECQL4* gene [Wang et al., 2002]. However there is a subset (approximately one-third) of RTS patients without detectable mutations in *RECQL4* and who are at lower risk for cancer. This group may represent mutations in a different gene from *RECQL4*. Whether this subset of RTS patients shares a common molecular defect with patients with PN remains to be determined. Further studies on the molecular basis of PN are warranted, and genotype/phenotype analysis may lead to understanding of the hematologic defects in these patients. PN may serve as a rare but unique paradigm disorder for the study of inherited neutropenia.

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