Chapter 10

Molecular genetic evidence for an association between nasal polyposis and Peutz-Jeghers syndrome


Department of Pathology, Academic Medical Center, Amsterdam
Departments of Internal Medicine and Pathology, Erasmus Medical Center, Rotterdam
Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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Molecular Genetic Evidence of an Association between Nasal Polyposis and the Peutz-Jeghers Syndrome

TO THE EDITOR: The Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by hamartomatous polyposis of the gastrointestinal tract, melanin pigmentation of the skin and mucous membranes, and an increased risk for cancer (1, 2). It is caused by a germline mutation in the STK11/LKB1 gene on chromosome 19p13.3 (2). Hamartomas and carcinomas in patients with the Peutz-Jeghers syndrome show loss of heterozygosity at chromosome 19p13.3, indicating inactivation of the wild-type STK11/LKB1 gene (3).

Peutz described the first family with the Peutz-Jeghers syndrome as having "a highly remarkable combination of polyposis of the mucosa of the intestinal tract and of the nasopharynx, together with typical mucocutaneous pigmentations" (1). Although nasal polyposis in affected patients has been mentioned occasionally (4, 5), it is not a recognized extraintestinal manifestation of the disease. Consequently, we used a molecular genetic approach to investigate the association between nasal polyposis, the Peutz-Jeghers syndrome, and STK11/LKB1.

We studied 4 patients with the Peutz-Jeghers syndrome who came from 3 families with known germline mutations in STK11. Twelve nasal polyps from these 4 patients were available for study. We also analyzed 28 sporadic nasal polyps from 28 controls without evidence of the Peutz-Jeghers syndrome, the Kartagener syndrome, cystic fibrosis, or aspirin sensitivity. Polyp DNA was isolated from microdissected polyp epithelium, and wild-type DNA was isolated from stromal inflammatory cells. Loss of heterozygosity was assessed by comparing polyp DNA with normal DNA, as described elsewhere (3). The markers used were D19S886 and D19S565 (www.gdb.org), flanking the STK11/LKB1 gene on chromosome 19p13.3. Blood samples for haplotype analysis were collected from affected and nonaffected family members of a patient with the Peutz-Jeghers syndrome and nasal polyposis to determine which 19p13.3 allele segregates with the Peutz-Jeghers syndrome. The medical ethics committee of the University Hospital Rotterdam, Rotterdam, the Netherlands, approved the protocol, and all participants provided informed consent.

Figure. Loss of heterozygosity at 19p13.3 in nasal polyp DNA, and haplotype analysis confirming loss of the wild-type allele.

A. Loss of heterozygosity with marker D19S886 in nasal polyp DNA compared with normal DNA from patient III.1, analyzed with the ABI377 sequencer and Genescan software (PE Biosystems, Foster City, California). The peaks represent the two alleles (179 base pairs and 187 base pairs). In polyp DNA, the allele with 179 base pairs is lost; the small peak represents contamination with normal DNA from inflammatory or stromal cells. B. Marker D19S886 was used to analyze normal DNA from patient III.1, his spouse, and affected and nonaffected offspring. The allele with 179 base pairs from patient III.1 does not segregate with the Peutz-Jeghers syndrome; that is, the allele with 187 base pairs (*) contains the germline mutation responsible for the Peutz-Jeghers syndrome. Consequently, loss of heterozygosity in the nasal polyp of patient III.1 results in retention of only the mutant allele.
Nasal polyposis in Peutz-Jeghers Syndrome (I)

In two unrelated patients with the Peutz-Jeghers syndrome, four of eight nasal polyps showed loss of heterozygosity at 19p13.3. In contrast, loss of heterozygosity was not found in 23 sporadic nasal polyps \((P = 0.002)\). Haplotype analysis showed that loss of heterozygosity comprised deletion of the wild-type allele (Figure). Our findings indicate that nasal polyps related to the Peutz-Jeghers syndrome lack the functional STK11/LKB1 tumor-suppressor gene, suggesting a causal relationship between nasal polyp development and the Peutz-Jeghers syndrome. Loss of heterozygosity at 19p13.3 in nasal polyps of affected patients corresponds with reports of loss of heterozygosity in gastrointestinal hamartomatous polyps (3). Loss of heterozygosity at the STK11/LKB1 locus in nasal polyps related to the Peutz-Jeghers syndrome suggests that these lesions may be neoplastic in nature. This may also be reflected by the co-occurrence of nasal polyposis and nasopharyngeal squamous-cell carcinoma in a patient with the Peutz-Jeghers syndrome (4). We provide molecular genetic support for the initial observation of Dr. Peutz: Nasal polyposis can be an extraintestinal manifestation of the Peutz-Jeghers syndrome.

Jozbert J. Keller, MD
Academic Medical Center
University of Amsterdam
1105 AZ Amsterdam, the Netherlands

Marinus A.J. Waterman, PhD
G. Johan A. Offerhaus, MD, MPH, PhD
Academic Medical Center
University of Amsterdam
1105 AZ Amsterdam, the Netherlands

References
