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


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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 pigmentation” (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.
Nasal polyposis in Peutz-Jeghers Syndrome (1)

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.

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References


