

In her editorial, Lee<sup>5</sup> proposes indications for the diagnostic referral of short children to pediatric endocrinologists: a height below the 3rd percentile, stature that is not commensurate with the parents' heights, or a growth rate below the 25th percentile. The first has significant resource implications, requiring 120,000 consultations annually in the United States. More than 95 percent of short children will be found not to have disease; rather, they will be found to have stature that is appropriate for their genetic potential, constitutional delay, or both.<sup>6</sup> As Lee states, to detect a pathologic process, primary physicians must monitor growth rates and consider the parents' heights for all children. In most cases, investigations and referral are not necessary.<sup>7</sup>

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**DR. LEE REPLIES:** Height that falls below the 3rd percentile is a well-established definition of short stature and has been a standard criterion in pediatrics for determining the need for further evaluation.<sup>1,2</sup> Although the majority of children with a height below the 3rd percentile (more than 2 SD below the mean) have no organic disease, community screening studies have identified a pathologic process in 12 to 18 percent of these children.<sup>3,4</sup> Revision of the criteria for referral of children with short stature — such as the change from the 3rd to the 0.4th percentile, proposed by some clinicians in the United Kingdom — would have resulted in an inability to identify two of the eight cases of silent disease detected in the Wessex Growth Study<sup>5</sup> and would miss a percentage of children with growth hormone deficiency and other organic causes of short stature whose heights fall between these two percentiles. Thus, the use of more stringent criteria will decrease the number of unnecessary referrals but may result in the exclusion of children with disease from needed evaluation and therapy.

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## Genetics of Neurodegenerative Disorders

**TO THE EDITOR:** We disagree with Nussbaum and Ellis's statement that gene variations other than the APOE  $\epsilon$ 4 allele are elusive in the nonfamilial form of Alzheimer's disease (April 3 issue).<sup>1</sup> The candidate-gene approach has already identified genes with a potential role in the etiology of the disease.<sup>2</sup> In addition, over the past 15 years, a number of inflammatory mediators have been observed in the brain affected by Alzheimer's disease. In this disease, inflammation clearly occurs in pathologically vulnerable regions of the brain and may influence other

neuropathologic hallmarks of the disease, although it is unclear whether altered immune responses constitute an event secondary to ongoing neurodegeneration or whether they participate in its ignition.<sup>3</sup> However, several polymorphisms in genes encoding immune molecules have been associated with an increased or decreased risk of Alzheimer's disease,<sup>4,5</sup> suggesting a genetic link between immunoinflammatory processes and Alzheimer's disease. Genetic variants associated with a decreased risk of Alzheimer's disease also seem to increase the chance of

reaching the extreme limit of the human life span.<sup>6</sup> Therefore, the role of immunoinflammatory responses in Alzheimer's disease and longevity deserves further study.

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**THE AUTHORS REPLY:** Our review article was meant to provide a brief update for clinicians on the progress made in applying genomic science to the understanding of two neurodegenerative disorders. There are alleles at many loci other than APOE for which an

association with Alzheimer's disease has been proposed.<sup>1</sup> However, many of these studies have yet to be replicated, and among those that have been replicated, controversy persists.<sup>1</sup> For example, an association between Alzheimer's disease and alleles at the  $\alpha_2$ -macroglobulin locus has been proposed<sup>2,3</sup> but has not been replicated for at least one of the alleles.<sup>4,5</sup> For the purposes of our review article, we decided to draw a distinction between these putative associations and the association with APOE  $\epsilon 4$ , which has been confirmed in a sufficient number of studies for some to suggest that an APOE genotype test might be useful for clinical applications. We look forward to the association studies that Caruso et al. list and will await their replication by other investigators.

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## Throat Clearing in Asthma

**TO THE EDITOR:** Mantzouranis et al. (April 10 issue)<sup>1</sup> call attention to a feature of the patchy epithelial inflammatory disease we name according to the area of prime involvement as asthma, allergic rhinitis, or eczema. In adults, the manifestation noted by these authors is termed "postnasal drip." The assumption is that the secretions seen are formed in the nasal cavity and "drip" down to the trachea, where they induce cough. This complex of symptoms and that described by Mantzouranis et al. as throat clearing are more likely to reflect the same type of inflammation seen in the small airways and nasal mucosa in asthma and allergic rhinitis. In the study by Mantzouranis et al., not all the children with this isolated symptom had abnormal values for the forced expir-

atory volume in one second (FEV<sub>1</sub>), yet all responded to therapy — a finding that supports the idea that the inflammation may be localized to the trachea in those without functional impairment. I think we should recognize this clinical manifestation more widely in adults as well as in children. More useful names would be allergic pharyngitis, tracheitis, or pharyngotracheitis.

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