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References

1. World Resources Institute, World Bank, *World Resources 1996-97* (Oxford Univ. Press, New York, 1996).
2. D. Hinrichsen, *Our Common Seas: Coasts in Crisis* (Earthscan, London, and Nairobi, Kenya, 1990).
3. ———, personal communication.
4. ———, *Issues Sci. Technol.* **12** (no. 4), 39 (1996).
5. W. Tobler, U. Deichmann, J. Gottsegen, K. Maloy, "The global demography project" (Technical Report 95-6, National Center for Geographic Information and Analysis, University of California, Santa Barbara, CA, 1995).
6. CIESIN, "Gridded population of the world," www.ciesin.org/
7. National Imagery and Mapping Agency, "World Vector Shoreline," www.164.214.2.59/

Response: We thank Cohen *et al.* for their analysis, which should become the standard statement on coastal populations.

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Genetics of Parkinson's Disease

The identification by Mihael H. Polymeropoulos *et al.* of an Ala53Thr alteration in the α-synuclein gene in persons with autosomal dominant Parkinson's disease (PD) provides support for the genetic basis of PD (Reports, 27 June, p. 2045). Because the identical alteration was found among four "unrelated" families [one Italian (Contursi) and three Greek kindreds], Polymeropoulos *et al.* suggest that this genetic alteration is causative. This mutation nevertheless appears to be rare in familial PD, as others have not detected linkage to 4q21-q23 in sizable series of PD pedigrees, except for one (family K), where it remains unclear whether or not family K is linked to 4q21-23 (*1*). Assuming that the linkage of the Contursi kindred to 4q21-q23 is valid, we are concerned that this molecular alteration may not be the disease-causing mutation, but represents a neutral variant in linkage disequilibrium with a neighboring PD disease gene.

Factors including selection, admixture, finite population size, migration and mutation, co-ancestry, genetic hitchhiking, and growing population can affect linkage disequilibrium (*2*). Contursi, in the Salerno province, lies close to the port of Naples on the west coast of Italy. Close contact between Greece and Italy has occurred through the port of Naples for centuries. Thus, it is possible that these four kindreds are distantly related (co-ancestry) and that the Ala53Thr alteration represents an α-synuclein polymorphism in allelic association with a neighboring PD disease gene. Other neurological disorders, such as idiopathic torsion dystonia and Machado-Joseph disease, demonstrate linkage disequilibrium between microsatellite markers and the disease gene among different national populations (*3*).

The mutated residue is not evolutionally conserved, in contrast with adjacent residues, which are conserved between species. The "mutant" human sequence has a threonine at residue 53 like the wild-type rodent sequence. Thus, the sequences are identical in this domain of the protein. We know of no precedent for a pathogenic mutation to result in conversion of the human amino acid sequence "back" to the rodent amino acid sequence.

Notably, α-synuclein is found in Lewy bodies, the pathological hallmark of PD (*4*). However, as many other proteins (for example, neurofilament, and ubiquitin) are present in Lewy bodies (*4*), the presence of α-synuclein, although intriguing, does not prove that α-synuclein is a candidate PD disease gene. The report by Polymeropoulos

et al. is a major step forward in PD research. Even if α-synuclein is not the PD gene, the Ala53Thr alteration provides further localization of the PD disease gene that may lie within one megabase of α-synuclein.

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References and Notes

1. W. K. Scott *et al.*, *Science* **277**, 387 (1997); T. Gasser *et al.*, *ibid.*, p. 388.
2. M. Xiong and S.-W. Guo, *Am. J. Hum. Genet.* **60**, 1513 (1997).
3. N. Risch *et al.*, *Nature Genet.* **9**, 152 (1995); G. Stevenin *et al.*, *Am. J. Hum. Genet.* **57**, 1247 (1995).
4. M. G. Spillantini *et al.*, *Nature* **388**, 839 (1997); J. E. Goldman, S.-H. Yen, F.-C. Chiu, N. S. Peress, *Science* **221**, 1082 (1983); M. L. Schmidt *et al.*, *Am. J. Pathol.* **139**, 53 (1991); S. Kuzuhara *et al.*, *Acta Neuropathol.* **75**, 345 (1988); G. Lennox *et al.*, *J. Neurol. Neurosurg. Psychiatry* **52**, 67 (1989).
5. T.L. is a Florence Irving Scholar and is supported by NIH grant 1K08NS01966-01A1, the Parkinson's Disease Foundation, and the Lowenstein Foundation.

Response: Lynch *et al.* write that the mutation in the α-synuclein gene that we described in some families with PD may "not be the disease-causing mutation," but a variant in linkage disequilibrium with the disease allele. We have no evidence that linkage disequilibrium is present in any of the four families carrying the mutation. The bias toward Mediterranean basin populations simply reflects the origin of our sample, and not necessarily a representation of all samples. We know of no distant relationships between the families carrying the mutation, but it is possible that a founder effect is present.

There is a precedent for the presence of a human mutation as the normal allele in the rodent: the ApoE4 allele, which has been demonstrated to confer susceptibility to Alzheimer's disease; the identical amino acid change is present in the rodent (*1*). The mutation that we previously described in the α-synuclein gene constitutes genetic evidence for, and not proof of, the role of this molecule in the pathogenesis of PD. Recent data from our own studies and those published by Spillantini *et al.* (*2*) suggest that synuclein is an abundant component of the Lewy body in brains of patients with idiopathic PD. This finding provides biological evidence that the α-synuclein molecule is indeed a molecular player in PD. It seems therefore possible that the mutation in the α-synuclein gene is one of the molecular mechanisms leading to the aggregation of this molecule in the Lewy body and thus provides us with an important clue about the generation of PD pathology.

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References

1. A. D. Roses and A. M. Saunders, *Curr. Opin. Biotechnol.* **5**, 663 (1994).
2. M. G. Spillantini *et al.*, *Nature* **388**, 839 (1997).

Letters to the Editor

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