remained constant over geologic time.

Perturbations of the atmospheric O_2 balance can also be produced by forcings other than relative changes in the rates of oxidative weathering and reactive P supply to the oceans. A change in the intensity of ocean mixing, for example, would rapidly change the net rate of atmospheric O_2 production, by modifying the oceanic burial of organic carbon (*3*). However, it would not immediately affect the rate of O_2 uptake on the continents.

Thus, perturbations are likely to have affected the atmospheric O_2 balance during the Phanerozoic (*4*). Our modeling results suggest that the proposed feedback would have efficiently limited the impact of these perturbations on the atmospheric O_2 level. Whether the feedback acted alone or in concert with others remains to be determined (*5*).

According to Colman *et al.*, there is a lack of data from modern marine sediments supporting an inverse relation between the C:P ratio of buried organic matter and bottom water oxygenation. We proposed such a relation on the basis of a combination of data from modern marine and freshwater depositional environments, ancient shale sequences, wastewater treatment systems, and microbial studies (*6*). Additional evidence (Fig. 1) shows organic C:P ratios preserved in recent Black Sea sediments (*7*). The ratios are systematically higher for sites with permanently anoxic bottom waters. If the difference between oxic and anoxic end-members observed in the Black Sea were to be extrapolated to the entire ocean, our model would predict a strong stabilizing effect on atmospheric O_2 [figure 2C in (*1*)]. Although more studies are needed to isolate the effect of bottom water oxygenation from those of other environmental variables, the currently available evidence agrees with our hypothesis.

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REFERENCES

1. P. Van Cappellen and E. D. Ingall, *Science* **271**, 493 (1996).
2. T. W. Walker and J. K. Syers, *Geoderma* **15**, 1 (1976); P. N. Froelich, M. L. Bender, N. A. Luedtke, G. R. Heath, T. DeVries, *Am. J. Sci.* **282**, 474 (1982); P. N. Froelich, *Limnol. Oceanogr.* **33**, 649 (1988); R. A. Jahnke, in *Global Geochemical Cycles*, S. S. Butcher, R. J. Charlson, G. H. Orians, G. V. Wolfe, Eds. (Academic Press, San Diego, CA, 1992), pp. 301–315; S. N. Chillrud, F. L. Pedrozo, P. F. Temporetti, H. F. Planas, P. N. Froelich, *Limnol. Oceanogr.* **39**, 1130 (1994); R. A. Berner and J.-L. Rao, *Geochim. Cosmochim. Acta* **58**, 2333 (1994); K. B. Föllmi, *Earth-Sci. Rev.* **40**, 55 (1996).
3. D. E. Canfield, *Deep-Sea Res.* **36**, 121 (1989); P. Van Cappellen and E. D. Ingall, *Paleoceanography* **9**, 677 (1994).
4. R. A. Berner and D. E. Canfield, *Am. J. Sci.* **289**, 333 (1989).
5. L. R. Kump and F. T. Mackenzie, *Science* **271**, 459 (1996).
6. I. S. Kulaev, in *Environmental Regulation of Microbial Metabolism*, I. S. Kulaev, Ed. (Academic Press, San Diego, CA, 1985); E. D. Ingall, P. A. Schroeder, R. A. Berner, *Geochim. Cosmochim. Acta* **54**, 2617 (1990); D. F. Toerien, A. Gerber, L. H. Lötter, T. E. Cloete, *Adv. Microb. Ecol.* **11**, 173 (1990); R. Gächter and J. S. Meyer, *Hydrobiologia* **253**, 103 (1993); E. D. Ingall, R. M. Bustin, P. Van Cappellen, *Geochim. Cosmochim. Acta* **57**, 303 (1993); E. D. Ingall and R. A. Jahnke, *ibid.* **58**, 2571 (1994); *Mar. Geol.*, in press.
7. E. Ingall, T. Lyons, V. Tersol, *Eos* **75**, 383 (abstr.) (1994).
8. T. W. Lyons, in *Black Sea Oceanography*, E. Izdar and J. W. Murray, Eds. (Kluwer, Dordretch, Netherlands, 1991), pp. 401–441.

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Polyalanine Expansion in Synpolydactyly Might Result from Unequal Crossing-Over of *HOXD13*

Yasuteru Muragaki *et al.* (*1*) state that synpolydactaly, an autosomal dominant condition resulting in variable webbing and duplication of the digits, results from a polyalanine repeat expansion in the protein HOXD13. They found that the normal human HOXD13 contains 15 alanine residues near the amino terminus of the protein and, in three families segregating synpolydactaly, the disorder was associated with unusual *HOXD13* alleles that predict an expansion of the polyalanine tracts to 22, 23, and 25 residues, respectively. It is likely that the expanded polyalanine tract alters or changes the function of the mutant HOXD13, thereby leading to the disorder. However, Muragaki did not comment on the mutational mechanism that may lead to these abnormal alleles.

Recently, it has been stated that expanded polyglutamine tracts are responsible for a number of hereditary neurodegenerative diseases (*2*). These disorders are a result of the unstable expansion of the glutamine codon CAG, which is believed to result in an altered function of the mutant proteins. Because of these similarities, one could in-

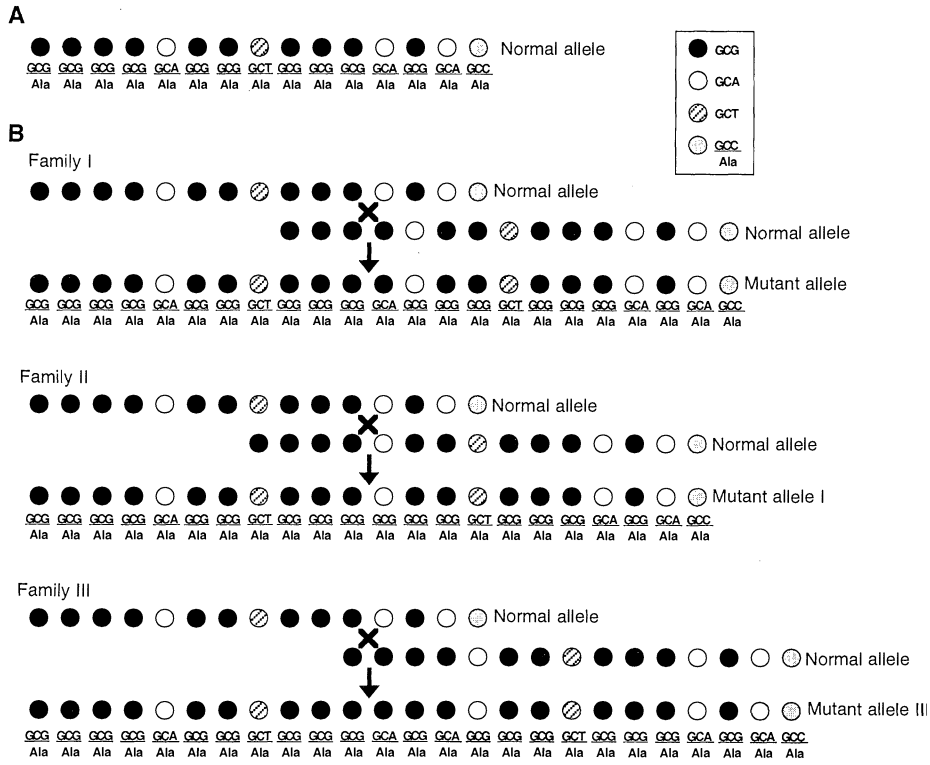

Fig. 1. (**A**) DNA sequence of the polyalanine tract of the normal human *HOXD13* gene. Each distinct alanine codon is represented by a unique circle. (**B**) Derivation of each of the three mutant *HOXD13* alleles found in synpolydactaly by unequal crossing-over of two normal alleles. Possible point of exchange is indicated by an X, and the resulting reading frame is shown below each mutant allele. Mutant alleles are numbered according to families I, II, and III of the report by Muragaki *et al.* (*1*).

correctly infer that the polyalanine expansion in synpolydactaly might result from a dynamic trinucleotide repeat expansion mutation (*3*). Examination of the data in the report (*1*) suggests otherwise. Unlike disorders with trinucleotide repeat expansion, the expanded *HOXD13* tract encoding polyalanine is quite stable when transmitted from one generation to another. The variable expressivity of synpolydactaly appears to be the result of dosage differences of the mutant allele rather than repeat length variation. Furthermore, examination of the *HOXD13* sequence encoding the polyalanine tract reveals it to be a cryptic repeat of alanine codons GCG, GCA, GCT, and GCC (Fig. 1A). Such cryptic interruptions are believed to stabilize the repeats at dynamic mutation loci and it has been proposed that tracts of approximately 25 to 35 perfect trinucleotide repeats are required for instability and expansion (*4*). Therefore, some similarities exist between polysyndactaly and dynamic mutations at the protein level, but the mechanisms of mutation appear to be different.

Unequal crossing-over is a plausible mechanism for the mutations described for polysyndactaly. Inspection of the three mutant alleles described by Muragaki *et al.* and comparing them with the normal allele reveals that each mutant allele can be derived from recombination between two mispaired normal alleles (Fig. 1B). In each instance, unequal pairing with variable degrees of overlap could generate each of the mutant alleles by crossing over within a short tract of trinucleotide repeat. The cryptic nature of sequence encoding the polyalanine tract easily demonstrates this if each distinct alanine codon is coded (Fig. 1B). Because recombination is occurring within the trinucleotide repeat, the reading frame is maintained, which results in expansion of the polyalanine tract. The reciprocal event of the unequal crossing-over would predict alleles with truncated polyalanine tracts of fewer than eight residues. Such mutant alleles might lead to other digital anomalies; Muragaki *et al.* point out that the introduction and lengthening of the polyalanine tract of *HOXD13* over evolutionary time may have lead to the distinctive limb differences from teleost fish through mammals.

Many proteins have been described with homopolymer runs of single amino acids (*5*). Because the coding sequences in most are not simple trinucleotide repeats, but are cryptic, as is the *HOXD13* gene, they have been discounted as candidate loci for trinucleotide repeat expansion (*6*). However, such loci may be prone toward unequal crossing-over with maintenance of the reading frame, as in this example. Therefore, although the mechanism of the mutations may not be similar, the lengthening of tracts of single amino acids leading to altered or change-of-function proteins may be a common mechanism of human genetic disease.

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REFERENCES

1. Y. Muragaki, S. Mundlos, J. Upton, B. R. Olsen, *Science* **272**, 548 (1996).
2. C. T. Ashley Jr. and S. T. Warren, *Annu. Rev. Genet.* **29**, 703 (1995).
3. J. C. K. Barber, *J. Med. Genet.* **33**, 718 (1996).
4. E. E. Eichler *et al.*, *Nature Genet.* **8**, 88 (1994); C. B. Kunst and S. T. Warren, *Cell* **77**, 853 (1994).
5. H. Green, *Cell* **74**, 955 (1993); H.-P. Gerber *et al.*, *Science* **263**, 808 (1994).
6. S. H. Li, M. G. McInnis, R. L. Margolis, S. E. Antonarakis, C. A. Ross, *Genomics* **16**, 572 (1993); G. J. Riggins *et al.*, *Nature Genet.* **2**, 186 (1992).

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Response: We fully agree that unequal crossing-over is a plausible mechanism for the mutations we described in our report on polysyndactyly (*1*).

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REFERENCES

1. Y. Muragaki, S. Mundlos, J. Upton, B. R. Olsen, *Science* **272**, 548 (1996).

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NOTICE TO MEMBERS

The following proposed amendment[1] to the AAAS constitution will be considered by the Council during its annual meeting on February 16, 1997 in Seattle, Washington. The Board of Directors is proposing this change in order to improve the effectiveness of the Board.

Article VIII. Section 2. The Board shall consist of ~~thirteen members:~~ the Chairman of the Board, the President, the President-Elect, the Treasurer, the eight Directors elected for four-year terms, **up to two Directors appointed by the eleven Elective Officers for three-year staggered terms**, and the Executive Officer, ex officio, without vote. **Appointed Directors shall provide special expertise needed by the Board and may not serve more than six years on the Board in that capacity.** The Executive Officer shall serve as secretary.

[1]**Bold** is an addition, and ~~strike-through~~ is a deletion.