hence, it must somehow be coupled to the rate of oxidative weathering. Nonetheless, the reactions and crustal constituents involved in oxidative weathering differ from those releasing P. Furthermore, P mobilized from primary minerals is extensively recycled on land, before being supplied, under variable chemical forms, to the oceans (2). Thus, the relationship between the reactive (bio-available) flux to the oceans and the rate of O2 uptake by weathering depends on variables such as the lithology of drainage basins, continental topography, and climate. It is therefore unlikely that this relationship has remained constant over geologic time.

Perturbations of the atmospheric O2 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 O2 production, by modifying the oceanic burial of organic carbon (3). However, it would not immediately affect the rate of O2 uptake on the continents.

Thus, perturbations are likely to have affected the atmospheric O2 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 O2 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 relationship 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 stronger stabilizing effect on atmospheric O2 [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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Poyalanine Expansion in Synpolydactyly Might Result from Unequal Crossing-Over of HOXD13

Yasutaro Muragaki et al. (1) state that synpolydactyly, 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 synpolydactyly, 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 instability and expansion (4). Therefore, some similarities exist between synpolydactyly 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 synpolydactyly. 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


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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.

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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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 synpolydactyly 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).
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