

Delayed Helix Formation of Mutant Collagen

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Table 1. Possible year (B.C.) of SO_4^{2-} signal in the GISP2 ice core for 18 volcanic eruptions between 1 and 7000 B.C. based on calibrated age of the eruption from Southon and Brown (*1*).

Eruption	Year (B.C.) of SO_4^{2-} signal
Bardarbunga (Veidivotn), Iceland	1454, 1457, 1459
Aniakchak, Alaska	1623, 1669
Santorini (Minoan eruption), Greece	1623*, 1669
Long Island, New Guinea	2617
Hekla (H-4), Iceland	2310
Black Peak, Alaska	2958, 3201
Akutan, Alaska	3977
Towada, Japan	4267
Kikai, Ryuku	5277, 5279
Avachinsky, Kamchatka	5277, 5279
Masaya, Nicaragua	No appropriate signal
Mazama, Oregon	5675, 5676
Hekla (H-5), Iceland	5781
Hangar, Kamchatka	5781
Kizimin, Kamchatka	5954, 5995
Tao-Rusyr, Kurile Island	6271, 6338
Karymsky, Kamchatka	6476
Vesuvius, Italy	6955

*Our suggestion that the signal for the Santorini eruption could be 1623 B.C. was based on the similar age suggested by dendrochronological evidence. See note 32 of our report (*1*).

sphere with high amounts of sulfur-bearing gases because of the potential for efficient degassing and the eruption of large volumes of magma (*3*). Atmospheric loading estimates derived from the petrologic method may be unreliable, thus the Aniakchak eruption may not be the most likely source for the highest sulfate peak recorded in the 17th century B.C. (*4*).

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2. Problems associated with the correlation of high-resolution calendrical chronologies of volcanism with radiocarbon-dated events were discussed in D. M. Pyle, *Archaeometry* **31**, 88 (1989) and M. G. L. Baillie, *J. Theor. Archaeol.* **2**, 12 (1990).
3. M. R. Rampino, S. Self, R. B. Stothers, *Ann. Rev. Earth Planet. Sci.* **16**, 73 (1988); M. R. Rampino and S. Self, *Nature* **359**, 50 (1992).
4. The recent work by T. M. Gerlach *et al.* [*J. Volcanol. Geotherm. Res.* **62**, 317 (1994)] has again shown that the petrologic method may severely underestimate the amount of sulfur degassed during an eruption. J. S. Vogel *et al.* [*Nature* **344**, 534 (1990)] used that method to compare the sulfur output from the many large eruptions dated to around 3400 ^{14}C year B.P.

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J. Bella *et al.* (*1*) demonstrate that the conformation of triple helices formed by collagen-like $(Pro\text{-}Hyp\text{-}Gly)_{10}$ peptides is altered when a Gly → Ala substitution is introduced in the center of each peptide, which results in a small local untwisting of the triple helix and reduced thermal stability. Bella *et al.* conclude that similar conformational changes may occur in Gly → X mutated collagens responsible for various heritable connective tissue disorders. It has been repeatedly shown that these mutant collagen molecules exhibit decreased thermal stability, decreased collagen secretion, and increased proteolytic sensitivity (*2*) and —as Bella *et al.* quote—it has been *suggested* that this kind of mutation represents a defect in the folding of the triple helix (*3*).

We have demonstrated the hitherto postulated delay in the proper, zipper-like folding of collagen I in fibroblasts derived from patients with osteogenesis imperfecta (*4*), a heritable, generalized connective tissue disorder characterized by brittleness of bones and weakness of other tissues rich in collagen I (*5*). In five cell strains harboring a single Gly → Cys substitution at positions 94, 223, 526, 691, and 988 in the helical domain of the α1(I) chain, formation of full-length protease-resistant triple-helical molecules containing mutant α1(I) chains was delayed by 5 to 60 min. The delay was correlated inversely with the thermal stability of abnormal molecules. In another cell strain that harbors the mutation Gly → Cys in the COOH-terminal telopeptide just outside the helical region, folding time and melting temperature were normal. The mutations representing identical steric obstacles in the backbone of the triple helix caused different kinetic hindrance depending on their position on the molecule. Similar delays were observed with other mutations in collagens I and III (*6*). The observed differences in the folding delay in the Gly → Cys mutations might be, as suggested, a result of local variations in torsional flexibility which, in turn result from the appearance of particular residues in the X and Y positions (*1*). This sequence dependence of the triple-helical conformation will be clarified as crystal structures of other peptides containing non–Pro-Hyp-Gly triplets are determined by the approach chosen by Bella *et al.* (*1*).

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