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o ntr t p osp t o nr tos orr t

It has become apparent, since publication of our Letter on low nitrate:phosphate ratios in the global ocean (T. Tyrrell and C. S. Law, *Nature* **387,** 793–796; 1997; correction, **393,** 396; 1998), that the World Ocean Atlas 1994 (WOA94) database we used contains transcription errors for nutrient measurements. Discrepancies between the original data and the corresponding data sets in WOA94 have been confirmed for the eastern tropical Pacific (identified by A. Longhurst and S. Sutherland), the western North Pacific (M. Aoyama, K. Hirose and K. Ishikawa) and the Agulhas retroflection area south of South Africa (R. Schlitzer and A. Longhurst).

Removal of falsely identified low nitrate:phosphate points (LNP, $([NO_3^-] \div [PO_4^{3-}]) < 3.0$ and $[PO_4^{3-}] > 1.5$ μmol kg^{-1}) in these areas shows that: (1) LNP points do not occur in the open ocean away from the coast; and (2) the western and northern North Pacific does not represent a hitherto-unquantified significant site for denitrification, as we originally suggested.

However, by examining other independent and more rigidly controlled data sets and re-evaluating WOA94 data using stricter criteria, we have confirmed that LNP is a feature of the Baltic and Black Seas, the Peruvian upwelling system, the Cariaco trench, the Bering Straits, and Tomales Bay. Although this confirms our original premise that the Redfield ratio is not universally applicable, it is clear that LNP points are restricted to coastal and enclosed shelf sea regions. These observations accord with current understanding of the extent of denitrification.

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The errors in the World Ocean Atlas 1994 that were identified as a result of the publication of Tyrrell and Law's Letter (T. Tyrrell and C. S. Law, *Nature* **387,** 793–796; 1997) are, as part of our routine quality-control procedures, being corrected or flagged as suspect on this and related National Oceanographic Data Center databases.

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o mp t o t 17 3 o

It has been suggested that global warming has caused the El Niño/Southern Oscillation (ENSO) climatic events to become more frequent and intense. However, several ENSO events that occurred before 1880 had effects at least as intense and wide-ranging as those associated with the current event. This is the case particularly for the events in 1396 (ref. 1), 1685–88, 1789–93 and 1877–79. Here I discuss archival evidence, notably from South Asia and above all for the 1789–93 ENSO, for the strength of these historical effects.

In peninsular India, every major drought between 1526 and 1900 has been closely associated with the eastern Pacific El Niño. The 1789–93 ENSO event produced prolonged droughts, especially in South Asia, a region where the association between ENSO and the monsoon is well established[2]. The global impact of this event was recognized in 1816 by Alexander Beatson, governor of St Helena, who suggested that the 1791 droughts in India, St Helena and Montserrat were part of a single, connected phenomenon[3].

The earliest indications of the event in the tropics were meteorological observations, based on a 14-year data set started in the early 1770s by William Roxburgh at Samulcottah (Samalkot) in southern India[4]. He recognized the exceptional nature of the droughts beginning in 1789 and believed that their severity had only been approached by those in 1685–87 (ref. 5). Those years are now known to have been characterized by 'very severe' El Niño in the eastern Pacific in 1687–88 (ref. 6).

Roxburgh recorded the continuous failure of the South Asian monsoon between 1789 and 1792, the severest failure being in 1790 (Table 1). The first major rainfall reduction was in 1789 in southern India, more than a year before similar droughts occurred in Australia, Mexico, the Atlantic islands and southern Africa. By November 1792, 600,000 deaths were attributed to the resultant droughts in the northern Madras Presidency alone, where half the population died.

The long droughts were interspersed with short periods of highly destructive rainfall. In three days at Madras in late October 1791, 25.5 inches of rain fell, "more than… has been known within the memory of man"[7]. Unseasonal severe droughts were experienced in Java, and in New South Wales, Australia, in the same year. On 5 November 1791, the governor of this colony, Arthur Phillip, reported that the normally perennial 'Tank Stream' river flowing into Sydney Harbour had been dry for "some months". It did not flow again until 1794. Phillip marks the start of the droughts in July 1790; no rain had fallen by August 1791 (ref. 8).

In Mexico, the level of Lake Pátzcuaro fell steadily between 1791 and 1793, giving rise to disputes over the ownership of the land that emerged[9]. By mid-August 1791, the desiccating effects on the islands of the Antilles were the severest since 1700, and no rain had fallen on the islands of St Vincent and Montserrat[10]. The drought continued on Montserrat until November 1792.

Droughts on St Helena were later than those in the Caribbean, lasting from late 1791 to mid-1794. The River Nile fell to very low levels from 1790 to 1797, as a result of reduced rainfall in the Ethiopian highlands. Evidence from the rest of Africa is scanty, but prolonged droughts in Natal and Zululand between 1789 and 1799 resulted in the *Mahlatule* famine, the severest known to have affected Southern Africa before 1862 (ref. 11).

This evidence that the 1789–93 ENSO had a strong global impact indicates that it was

Table 1 **Monthly rainfall at Samulcottah, Andhra Pradesh, India: May–November 1788–92 (in inches and twelfths of an inch)[15]**

	17	17	17 0	17 1	17
May	15.	1			3.6
June	7.	6	1.	.1	5
July	.3	6.10	.	5.6	6.
August	1 .	1.1	3.		1.
September	.	1.	.	3.	7.5
October	5.	10.1	1.5	3.3	13.11
November	6	1.3	1.	6.	
Total	77.5	3.10	17.	6.11	37.10

one of the most severe on record. An early precursor of the event may have been an unusually cold winter in western Europe in 1787–88, followed by a late and wet spring and summer drought, resulting in the crop failures preceding the French Revolution[12]. This may have resulted from a weak phase in the North Atlantic Oscillation, which would fit an established correlation between inter-annual variability in the North Atlantic Oscillation and Indian summer monsoon rainfall[13]. Indeed, the Indian monsoon is an active feature of tropical circulation and monsoon failure is efficient in foreshadowing ENSO[14].

As with the 1685–88 ENSO, the early stages of the 1789–93 event were observable in southern India more than a year before the El Niño effect was recorded in the Pacific basin. However, a few ENSO events, including the present event of 1997–98, coincide with a failure of the Southeast Asian monsoon rather than that of South Asia. In the case of the 1789–93 ENSO event, the monsoon failed in both regions.

So the developmental sequence of the 1789–93 ENSO is important as a basis for comparison with other, very severe, ENSO events.

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onn n 6 n n to om n nt n ss

A high proportion of all cases of congenital deafness is caused by mutations in a gene coding for a gap-junction protein, connexin 26. The deafness associated with this gene, *Cx26,* is the autosomal recessive form, DFNB1 (refs 1–3); its involvement in autosomal dominant forms of deafness has remained controversial[4]. Here we show that a mutation in *Cx26* underlies the dominant form of deafness, DFNA3.

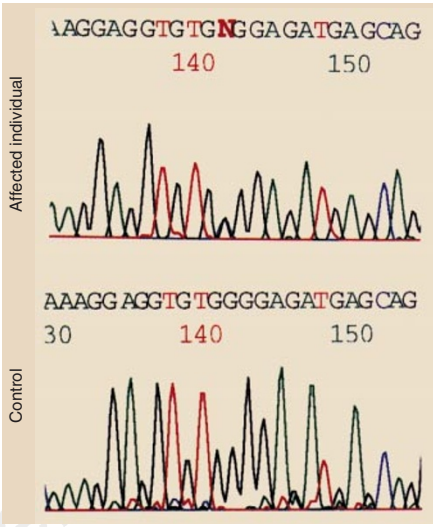
About 70% of prelingual hereditary deafness is non-syndromic (or isolated) sensorineural deafness[5]. Autosomal recessive forms (DFNB) make up about 85% of these cases, autosomal dominant forms (DFNA) 12–15%, and X-linked forms (DFN) 1–3%. The postlingual forms have been less well studied, but seem to be mainly sensorineural defects with a dominant mode of transmission in a high proportion of cases. The non-syndromic forms of deafness are extremely heterogeneous, with up to 100 genes being involved.

So far, at least 15 DFNB and 14 DFNA loci have been mapped to human chromosomes[6,7]. However, mutations in the *Cx26* gene, responsible for DFNB1 (ref. l), have been shown to underlie half of the cases of prelingual autosomal recessive forms of non-syndromic deafness[2,3]. Moreover, one specific mutation (30delG, also named 35delG; ref. 3) accounts for about two-thirds of the detected mutations[2].

By linkage analysis of a French family (family LY1) affected by pre-lingual deafness, we previously mapped the gene responsible for a dominant form of deafness, DFNA3, to chromosome band 13ql2, the same region as the gene responsible for DFNB1 (ref 8). The affected individuals exhibited progressive hearing loss predominantly affecting the high frequencies. This led us to propose that the same defective gene could underlie both DFNB1 and DFNA3. So far, a single *Cx26* mutation, resulting in a methionine-to- threonine substitution at codon 34, has been reported in a small family affected by an autosomal dominant form of deafness[1].

However, it has recently been shown that this substitution is also present in normal hearing individuals, and therefore corresponds to an asymptomatic polymorphism[4]: we have observed this polymorphism in 4 out of 190 unrelated individuals with normal hearing.

We searched for *Cx26* mutations in family LY1 and in another family (LY2) from the same geographic area showing a significant log likelihood ratio score (3.6), by using polymorphic markers flanking the *DFNA3* locus, namely *D13S175*, *D13S143* and *D13S115* (data not shown). Family LY1 is composed of 10 deaf individuals and 17 normal hearing individuals[8]; family LY2 is composed of 10 deaf individuals and 19 normal hearing individuals. In all the 20 affected individuals, we detected a heterozygous G-to-C transversion (Fig. 1) which creates a tryptophan-to-cysteine substitution at codon 44 (W44C). None of the 36 non-affected individuals of these two families carried the mutation. The mutation was not detected in 190 unrelated control individuals.



r 1 q n n ss o t 6 o n on n n t n s o n t to tr ns rs on t o on pos to n . mp tons r rr o t s n s to pr m rs t t o mp to n o t n tr o n s q n o 6 r .). q n n o o str n t mp t s s p r orm t or s nt o n ot s on n pp os st ms 373) s q n r. so mp to n pro ts rom t n s r s on n s q n .

Connexins are gap-junction proteins; six connexin subunits assemble into a half-channel named connexon and two connexons align to make a complete intercellular channel. The topology of connexins is highly conserved, consisting of four transmembrane domains linked by one cytoplasmic and two extracellular loops, with cytoplasmic termini.

The extracellular domains of connexins have been much studied because they represent the site of interaction between connexons from adjacent cells. The tryptophan at position 44 is located in the first extracellular loop. This residue is present in 12 out of the 13 rodent connexins characterized so far; the last one harbours a tyrosine at this position, which has similar biochemical characteristics[9]. In addition, both extracellular loops contain a conserved pattern of three cysteines. These cysteines are involved in interloop disulphide bonds, and their presence has been demonstrated, by site-specific mutagenesis[10], to be critical for channel function[11].

The presence of an additional cysteine in connexin 26 is likely to interfere with the formation of normal disulphide bonds. Therefore, the W44C mutation is expected to have a dominant-negative effect due to incorporation of mutant connexins into intercellular channels, thereby disrupting channel activity. This hypothesis is further supported by the observation that patients heterozygous for *Cx26* mutations that lead to premature