# Genetic Adaptation and Selenium Uptake in Vertebrates

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Nutrients such as iron, zinc, selenium and iodine are needed only in trace amounts but are nevertheless essential to the vertebrate diet. Of these, selenium and iodine are unusual in that their dietary intake depends on their varying content in the soils and waters across the world. Selenium in particular is required due to its function in selenoproteins, which contain the amino acid selenocysteine (the twenty-first amino acid) as one of their constituent residues. This amino acid is encoded by a termination codon, and its incorporation into selenoproteins is mediated by numerous regulatory proteins. Vertebrate genomes have signatures compatible with adaptation to the different levels of selenium in the world. These signatures are shared among the genes using and regulating selenium and point to past and recent changes to the metabolism and homeostasis of selenium in vertebrate species. Dietary selenium has thus shaped the evolution of vertebrates throughout their history.

# Introduction

#### Macronutrients and micronutrients

Nutrients are chemical components in the diet of an organism required by it to survive and grow. Broadly, those nutrients required in large quantities are called macronutrients, whereas those required in small quantities are called micronutrients. While macronutrients provide the bulk of an organism's energy needs to function, micronutrients are used to build and repair tissues

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## Selenium in the diet

Of the essential micronutrients, selenium is unusual in that it has a very narrow margin between nutritionally optimal and potentially toxic (Wilber, 1980), making its uneven environmental distribution a challenge to the needs of the vertebrate diet. Diet is the most important source of selenium, and its intake depends on the selenium content of the soil on which food is gathered, hunted or grown (Johnson *et al.*, 2010; Ogle *et al.*, 1988). Soil selenium levels, in turn, depend largely on the underlying bedrock from which they are formed, which has created a patchwork of deficient, adequate and sometimes toxic areas across the world varying a hundredfold in their selenium levels. Selenium deficient areas of thousands of km<sup>2</sup> exist in parts of Northern Europe, East Asia, Oceania and North America, with the selenium content of Africa, South America and most parts of Asia remaining largely unexplored (Oldfield, 2002; Selinus and Alloway, 2005).

The varying levels of selenium in the soils entering the food chains of different vertebrates (both wild and farm animals) have been shown to cause diseases either from its deficiency or toxicity (Kim and Mahan, 2003; (Flueck, 2015; (Sager, 2006). In humans, mild selenium deficiency can cause immune dysfunction, reduced fertility, cognitive decline and increased risk of mortality (Rayman, 2012). In severely selenium-deficient parts of China, a disease of the heart muscle (Keshan disease), which has a high mortality rate in children, and a disabling disease of the bone and cartilage (Kashin–Beck disease) were endemic prior

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to the start of selenium supplementation programmes (Xia *et al.*, 2005). Indeed, selenium has a wide variance in dietary availability around the world, and up to 1 billion people worldwide may have a diet deficient in selenium (Nazemi *et al.*, 2012). Its distribution around the world is, however, highly localised. For example, China has both some of the highest and lowest soil selenium levels in the world (Oldfield, 2002).

Levels of selenium in waters worldwide also vary a hundredfold (Selinus *et al.*, 2005), but oceans, seas and other aquatic environments are generally an environmental sink for land selenium (Selinus *et al.*, 2005) with inorganic forms of selenium being rapidly and efficiently bioaccumulated in phytoplankton (100–1 000 000-fold enrichment from the water concentration (Stewart *et al.*, 2010)) and converted into organic forms of selenium that can enter the animal diet (Ogle *et al.*, 1988). Indeed, selenium bioaccumulation through the aquatic food chain has made fish foods a major source of selenium in the human diet. Thus, vertebrate species from different land and aquatic environments have evolved under different levels of selenium in their diets.

### The genetic basis of selenium use

The element selenium (with symbol Se) was first discovered in 1817, and owing to its similarity to tellurium (named after *Tellus*, the Roman god of the earth), it was named after the titanic god-dess of the moon, *Selena* (Berzelius, 1818). The role of selenium in biology was, however, neither discovered nor investigated until much later. Once selenium started being heavily used in various industries in the late nineteenth century, its toxic effect on humans came to the foreground (Dudley, 1938). In the 1930s, a systematic study of poisoning symptoms of farm animals showed their feed and the soil in which it is grown to have toxic levels of selenium (Painter, 1941). Yet, it wasn't until 1957 that selenium was seen as an element essential to life despite its toxicity when ingested in large amounts (Schwarz and Foltz, 1957).

In 1974, selenocysteine (with symbol Sec) was discovered as the selenium-containing amino acid (Rother, 2015) through which selenium is incorporated into proteins (Stadtman, 1974). These selenium-containing proteins, known as selenoproteins, are essential to life (Kasaikina et al., 2012). However, neither the mechanism of its production nor of its incorporation into selenoproteins was known until later. In 1983 (Hawkes and Tappel, 1983), it was shown that rat liver can accomplish the de novo synthesis of selenocysteine from selenite and that this amino acid can be incorporated into glutathione peroxidase via a transfer ribonucleic acid (tRNA) (see Glossary) that brings selenocysteine for protein synthesis (selenocysteyl-tRNA). Moreover, the study suggested that selenocysteine could be coded for by a codon (see Glossary) with a dual role in the genetic code - which was validated in 1986 (Chambers et al., 1986) when for the first time a selenoprotein messenger ribonucleic acid (mRNA) (see Glossary) was sequenced. In this study, it was discovered that the amino acid selenocysteine in the active site was encoded by an in-frame UGA codon – a finding the authors considered highly intriguing - since UGA was originally thought to serve only as a termination codon See also: Selenocysteine. They further made a note that some factor other than the UGA codon itself must be responsible for its different usage. This was demonstrated in 1993 with the discovery of the SElenoCysteine Insertion Sequence (SECIS) element, an ribonucleic acid (RNA) structure of about 60 nucleotides (see Glossary) responsible for directing the translation of the UGA codon into selenocysteine (Berry et al., 1993). Soon it became evident that an elaborate machinery of cofactors was required for the recoding of the UGA codon to incorporate selenocysteine, and by the end of the 1990s, most of these factors were discovered. In 1999, computational methods were developed to identify selenoproteins independently by two separate groups (Lescure et al., 1999; Kryukov et al., 1999). In both cases the key idea was that a SECIS element is absolutely required to translate selenoproteins. Thus, they designed algorithms to look for SECIS elements in mRNA sequences. Following these newly developed methods, the race to find novel selenoproteins in complete genomes continued at full throttle and in less than a decade, all the 25 human selenoprotein known to us today were correctly identified (Kryukov et al., 2003; Gromer et al., 2005).

#### Annotation of selenoprotein genes

While the approaches required to correctly identify selenoproteins have been known for many years, most genomic databases still wrongly annotate selenium-containing genes. This is mainly because most databases use the UGA codon, a termination codon, to identify the end of the open reading frame (ORF) (see Glossary) of each gene and ignore the possibility of the codon being in-frame and co-translationally incorporating selenocysteine. To address this problem, dedicated databases to selenoprotein genes now exist (Castellano et al., 2008; Bekaert et al., 2010; Romagné et al., 2014) that annotate thousands of selenoprotein genes in dozens of species. SelenoDB 2.0 (Romagné et al., 2014) in particular includes multiple transcripts for human selenoprotein genes and single-nucleotide polymorphism (SNP) (see Glossary) for many human populations worldwide. With the availability of these correctly annotated selenoprotein genes, a number of genetic studies previously unfeasible have now been undertaken.

#### Selenocysteine and cysteine

Selenocysteine is a structural analogue of the cysteine amino acid with the sulfur ion in cysteine replaced by that of selenium. Cysteine is encoded by the UGC and UGT codons, a mutation away from the selenocysteine UGA codon. We define a protein to be cysteine containing, if it is homologous to a selenoprotein and has a cysteine residue in place of selenocysteine. In 1996 (Stadtman, 1996), it was shown that a direct substitution of selenocysteine to cysteine in a selenoprotein reduces the catalytic activity of the enzyme to 5% or less of the selenocysteine-containing enzyme. This lower activity of cysteine, compared with selenocysteine, had been considered the main reason for the evolution and existence of selenoproteins even though a selenoprotein requires elaborate and resource hungry machinery. However, in 2003 (Gromer et al., 2003), it was demonstrated that a cysteine-containing enzyme can approach the catalytic efficiency of the corresponding selenoenzyme. This was a surprising result showing that a few compensatory mutations were sufficient to yield high selenium-independent activity, and the authors suggested that selenocysteine might not be essential for a particular enzyme reaction but rather expands the metabolic capacities in terms of activity towards a wider variety of substrates and over a broad range of pH.

It remained unclear whether the distinct role of selenocysteine compared with cysteine in selenoproteins illustrated the distinct contribution of selenium to protein function. In 2009, Castellano, Andrés, and others set out to address this question from an evolutionary perspective by the simultaneous identification of the patterns of divergence in almost half a billion years of vertebrate evolution and diversity within the human lineage for the full complement of enzymatic selenocysteine residues in these proteomes. Their results indicated strong evolutionary constraint on selenocysteine and cysteine sites across selenoproteomes (set of selenoproteins in a genome), consistent with a unique role of selenocysteine in protein function, low exchangeability with cysteine and an unknown degree of functional divergence with cysteine-containing homologues. They concluded that the distinct biochemical properties of selenocysteine, rather than the geographical distribution of selenium, global oxygen levels (due to the sensitivity of selenocysteine to oxidation - but see (Snider et al., 2013) for an alternative view) or selenocysteine metabolic cost, appeared to play a major role in the preservation of vertebrate selenoproteomes. The need for selenium in protein function despite its scarcity raises the possibility that selenoprotein genes and genes that regulate selenium - through regulatory or amino acid changes (other than selenocysteine) - have adapted to the wide variation of selenium levels across the world. In this regard, the evolutionary patterns of genes that use or regulate selenium have recently been investigated at two different time scales, namely, (1) a longer time scale focusing on the divergence of selenoprotein genes and genes that regulate selenium in vertebrate species and (2) a shorter time scale focusing on the genetic diversity of selenoprotein genes and their regulatory regions in a worldwide sample of human populations (White *et al.*, 2015).

#### Selenoproteins in vertebrates

The first vertebrates appeared on Earth about 530 million years ago, and since then vertebrate species have adapted to most of the Earth's vast range of environments. These environments differ widely in the availability of selenium, and vertebrates depend on it today to different extents. Vertebrate species have evolved to have a varying number of selenoprotein genes, ranging from 24 in mouse to 38 in zebrafish, with the ancestor of all vertebrates carrying 28 selenoproteins (Mariotti et al., 2012). Thus, despite the overall low exchangeability of selenocysteine and cysteine residues (Castellano et al., 2009), vertebrates have lost selenocysteine and gained cysteine in proteins a few times. In addition, fishes have had multiple selenoprotein gene duplications (see Figure 1). Apart from the selenoproteome size, the number of selenocysteine residues in selenoprotein P (SelP), which transports selenium from the liver to all other tissues, varies in a wide range among different species (from 7 in guinea pigs to 18 in frogs) (see Figure 2). Since fishes have a larger selenoproteome as well as more selenocysteine residues transported by SelP than mammals, it has been suggested that fishes have developed greater dependence on environmental selenium, whereas mammals have reduced their reliance on it (Lobanov et al., 2008). This would be in agreement with the sea and other aquatic environments being an environmental sink for land selenium (Selinus et al., 2005).

While this hypothesis needs to be tested, a more general question worth asking is whether the different availability of selenium



Figure 1 Cartoon view of the loss (by gene deletion, in grey; by selenocysteine to cysteine mutation, in green) and gain (by gene duplication; in red) of selenoprotein genes throughout vertebrate history. The range in the number of selenoprotein genes today is given in parenthesis for each vertebrate clade. Based on Castellano, Andrés, *et al.* (2009); Mariotti *et al.* (2012).

in various Earth environments constitutes an important selective pressure on the use and regulation of selenium throughout vertebrate evolution. In an attempt to answer this question, compared the evolutionary forces acting on selenoproteins and genes involved in the regulation of selenium and selenocysteine to those acting on the cysteine-containing paralogous genes along the vertebrate phylogeny. The evolutionary forces on proteins were compared using the dN/dS ratio (see Glossary). If differences in dietary selenium pose different selective pressures among vertebrate lineages, the selenium-related genes are expected to have evolved under varying strengths of natural selection in vertebrates. At the same time, genes that do not depend on selenium (cysteine-containing genes) are expected to be uninfluenced by its abundance throughout the world and, hence, to evolve under a more or less uniform strength of selection across vertebrate species. They found that the strength of natural selection has substantially changed across all vertebrates for genes that use or regulate selenium and selenocysteine, while it does not vary in the cysteine-containing genes. This suggests that selenium availability, which differs widely among Earth environments, has indeed played a role in shaping the evolution of multiple vertebrate genes - suggesting polygenic adaptation - in multiple vertebrate lineages. They further compared the variation in the strength of natural selection among the different vertebrate clades. The results indicated that for the corresponding genes that use (selenoproteins) or regulate selenium and selenocysteine across vertebrates, the strength of selection varied most within the fish clade.

#### More selenoproteins in fishes

In addition, fishes have the greatest number of selenoprotein genes. While some of these additional genes in fishes were due to the loss of the corresponding genes in other vertebrates, several of them resulted from gene duplication (see Figure 1). Some of these duplicated genes are found only in specific fish lineages and were most likely the result of duplication events long after fishes separated from other vertebrate species and each other. However, seven genes trace back their origin to the ancestral fish lineage and were most likely the result of an ancient whole genome duplication event. Such an unusually high retention of duplicated genes (7 of 28 genes present in the ancestral vertebrate) suggests that fishes might have found new ways to use selenium in protein function. Indeed, the rate of evolution between gene copies is quite uneven. That one copy of the duplicated gene accumulated amino acid changes faster than the other is suggestive of neo-functionalization. This again would be in agreement with the world waters being an environmental sink for land selenium (Selinus et al., 2005). Thus, fishes may have generally evolved with variable but ample selenium. Bioaccumulation through the aquatic food chain may have contributed to this (Stewart et al., 2010).

# Selenium transport in fishes and other vertebrates

Other than the largest selenoproteome size, fishes also have the largest number of selenium atoms (in the form of selenocysteine) transported in the plasma via SelP (except for frogs) (Lobanov *et al.*, 2008). Interestingly, the ability to transport selenium in this protein is under strong evolutionary constraint in fishes, whereas it has evolved neutrally in mammals and other non-fish lineages. As a result, mammals and many other non-fish lineages transport today about half of the selenium atoms that fishes do in SelP (see **Figure 2**). This may be related to the size of their selenoproteomes (Lobanov *et al.*, 2008).



Figure 2 Cartoon view of the loss (by selenocysteine to cysteine mutation, in green) and gain (by cysteine to selenocysteine mutation; in red) of selenium atoms in selenoprotein P (SelP) throughout vertebrate history. The number of selenium atoms transported today by SelP is given in parenthesis for each vertebrate clade. Some laurasiatheria are whales, dolphins, pigs, horses, cows, bats, cats, bears, hedgehogs and related species.



Figure 3 Worldwide map of the human populations surveyed in White *et al.* (2015) to assess the patterns of polymorphism in 25 selenoprotein genes, 6 cysteine-containing genes and 19 genes that are involved in the metabolism and homeostasis of selenium.

#### Selenoproteins in humans

As humans migrated out of Africa around 60000 years ago (Fu et al., 2013), they came to live in a wide range of different environments. In order to thrive in these diverse environments, human populations have not only employed cultural and technological advances but have often also experienced adaptation at the genetic level. One important factor to which humans have adapted is variation in the composition of the diet in different parts of the world. Such recent genetic adaptations in human populations in response to variation in the human diet have been demonstrated in recent scientific literature. Adaptation to prolong the expression of lactase into adulthood has occurred independently in African and European dairy-herding populations (Tishkoff et al., 2007; Olds and Sibley, 2003; Itan et al., 2009). Similarly, it has been suggested that some populations have locally adapted in response to the levels of iodine in their environment (López Herráez et al., 2009).

Because adequate selenium intake is so important to human health and fertility, and the levels of selenium in the diet vary widely around the world, it could be hypothesised that differences in dietary selenium intake sustained over many generations may have shaped the evolution of selenium-associated genes in humans. To understand the evolution of the use of this micronutrient in humans, White and colleagues (2015) surveyed the patterns of polymorphism in all 25 selenoprotein genes, 6 cysteine-containing genes and 19 genes that are involved in their regulation in 855 unrelated individuals from 50 human populations from around the world (see Figure 3). First, they looked for local adaptation in selenium-related genes by measuring population differentiation with the  $F_{\rm ST}$  statistic (see Glossary) according to the formula of Weir and Cockerham (1984) to see if any parts of the world stand out from the others in terms of unusually large differences in the frequency of genetic variants among populations. They found that selenoproteins and regulatory genes show a signal of local adaptation in central South Asia and East Asia. Most of the populations from East Asia come from China, a part of the world known to have large selenium-deficient regions (Oldfield, 2002; Xia et al., 2005). Low-selenium soil has also been reported in Pakistan where most of the central South Asian populations were sampled (Cavalli-Sforza, 2005; Khan et al., 2006, 2008; Ahmad et al., 2009). It therefore seems likely that these signals of positive selection reflect adaptation to selenium levels in the environment. In contrast, with cysteine-containing genes, they did not find any signal of local adaptation in any part of the world, suggesting that these genes are independent of selenium and in humans do not have compensatory role in low selenium conditions. They (White et al., 2015) further looked more closely at the signal of adaptation in China, since it has been known to have large selenium-deficient regions. They grouped the populations from China by whether they live in regions that are selenium-deficient or in selenium-adequate regions. The selenium-deficient regions include areas where severe selenium deficiency diseases, such as



Figure 4 Populations from China grouped by whether they live in regions that are selenium deficient or adequate. The selenium-deficient regions include areas where severe selenium deficiency diseases, such as Keshan disease and Kashin–Beck disease, were endemic in the past. Populations living in the selenium-deficient regions have allele frequency changes that differentiate them most from other populations.

Keshan disease and Kashin–Beck disease, were endemic in the past (before selenium supplementation). This grouping revealed that the signal of local adaptation within China is restricted to the selenium-deficient regions of the country (see **Figure 4**). This supports the idea that it is selenium deficiency that is driving the adaptive signal. Interestingly, this adaptation results from the concerted evolution of multiple genes – suggesting polygenic adaptation – underlying the use and regulation of selenium and not of individual genes. The results suggest that the micronutrient selenium appears to have been important during recent human evolution and, as humans spread around the world, adaptation in the genes that incorporate selenium or regulate its use may have helped humans to inhabit environments that are deficient in selenium. This may result in human populations today having different risks of selenium-related diseases.

# Conclusions

Since the first discovery of selenocysteine and selenoproteins in the 1970s, our understanding of them has come a long way. Many novel selenoproteins have been identified and annotated. However, not a lot has been known about the underlying forces that shaped the evolution of the use of selenium in the proteins of various lineages. While there have been a few hypothesis regarding how the environment could have affected the evolution of selenium use in proteins, evolutionary tests on selenoprotein sequences are needed to confirm (or reject) them. In this regard, evolutionary approaches have shown that selenocysteine and cysteine are generally not exchangeable in vertebrate proteins (Castellano *et al.*, 2009), attesting to the unique role of selenium in protein function. Thus, selenium in vertebrates is functionally indispensable despite its unevenness (from deficient to toxic) around the world. It is then not surprising that recent evolutionary studies suggest that vertebrates adapted to selenium availability in ways other than abandoning its use. The strength of selection on genes that use or regulate selenium has changed substantially across vertebrates, whereas it has not in genes that have lost their dependence on selenium. This suggests that selenium deficiency, abundance and toxicity across the world have shaped vertebrate evolution. In particular, fishes have genetic signatures of adaptations to abundant selenium, whereas humans (and possibly other mammals) have genetic signatures compatible with adaptation to selenium deficiency. In both cases, the adaptive signatures are shared among genes that use or regulate selenium, suggesting that it is the overall use, metabolism and homeostasis of selenium that adapts to its long-term variation. A better understanding of the mechanisms and the alleles underlying the local adaption of humans and other vertebrates to selenium is needed.

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