Co-mutation based genetic networks to infer temporal mutation dynamics in ancient human mitochondrial genomes

Keywords: co-mutation networks, mtDNA, evolution, human diet, genes

Extended Abstract

Motivation. The mitochondrial genome has acquired genetic adaptations to different environments which can shed light on temporal and biogeographical evolutionary processes [1]. The central role that mitochondrial genes play in metabolism allows us to use ancient mtDNA variation to infer how the availability of nutrients has influenced human migration and subsequent evolution [2,3]. The mitochondria are the site of essential metabolic processes necessary to generate energy from proteins, carbohydrates, and fats [4,5]. The availability of food, and its nutritional content, has been strongly linked with human population diversity [6] and mitochondrial gene expression patterns [7]. The protein-carbohydrate makeup of a human's diet influences the function of mitochondrial complex I both qualitatively and quantitatively [5]. Recent studies have even shown that mtDNA variation can also have diet-dependent effects on longevity [8].

Approach and Methodology. We constructed and analyzed co-mutation-based genetic networks for ancient mtDNA covering six geological ages of human evolution. We constructed gene trees using a maximum likelihood (ML) algorithm for each age to comprehend the co-mutation networks. Lastly, we determined the Dn to Ds ratios within humans per protein coding mitochondrial gene for each age (ωpolymorphism) and the divergence Dn to Ds ratios through alignment to the panTro6 chimpanzee reference mitochondria (ωdivergence) and used these to perform McDonald-Kreitman tests that we interpreted with the neutrality index (NI = ωpolymorphism / ωdivergence).

Results. We identified a set of highly connected genes for each age and found that NADH dehydrogenase complex genes co-mutate with cytochrome B and cytochrome oxidase complex genes throughout each age, suggesting a functional, modular role for these genes in defining the nutritional habits throughout recent human evolution. The phylogenetic networks found that phylogenetic concordance and discordance in these populations correlates with reduced/enhanced genetic interaction networks, respectively. This suggests the importance of specific genes as found through the co-mutation networks.

Conclusions and Outlook. In summary, our results demonstrate that co-mutation networks effectively capture the temporal dynamics of mitochondrial genome variation across human evolutionary periods. These findings establish co-mutation networks as a powerful framework that, when integrated with phylogenetic approaches, provides nuanced insights into the interplay of functional, epistatic and evolutionary forces shaping mitochondrial genome dynamics.

References

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Table 1: **Structural properties of co-mutation networks.** Variable sites are number of nodes participating in network construction at $P_{ij} < 0.05$, N_{LCC} is the number of nodes in the largest connected component, E_{LCC} is the number of connections, $\langle k \rangle$ is the average degree and $\langle cc \rangle$ depicts the average clustering coefficient of the largest connected component

Age	**Variable sites**	**N_{LCC}**	**E_{LCC}**	**<k>**	**<cc>**	**Modularity**
Mesolithic	219	185	1087	11	0.74	0.67
Neolithic	530	511	3400	13	0.67	0.71
Copper	491	461	3005	13	0.76	0.82
Bronze	722	712	4003	11	0.26	0.59
Iron	375	335	1723	10	0.80	0.83
Middle	580	560	6338	22	0.84	0.79

Figure 1: The tree-based gene networks and the genetic interaction networks are compared here.