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INF 501: Tollis Response

When I envision the field of informatics, genomic studies is one of the first fields I picture because of its large datasets and high impact in healthcare. This week Dr. Marc Tollis provided two papers that introduced the class to comparative genomics and followed with a comprehensive talk that engagingly walked through issues in comparative genomics through the lens of cancer evolution. Our discussion then helped to clarify complex topics in genomics such as DNA replication, gene alignment, and how identification of homologous genes in DNA sequencing works. In this paper I will focus on first summarizing Dr. Tollis' work and contextualizing each major topic within a larger scope of science. I will then draw similarities and differences between Dr. Tollis' research and my own research interests, both past and present.

1 Dr. Tollis' Research

This week's topic focused two papers from Dr. Tollis: one a synthesis of mammalian cancer suppression, the other on the diversification of *Anolis* lizard lineages. These papers set the stage for a broad talk that guided us into the world of comparative genomics. The mammalian cancer suppression synthesis laid a solid foundation of the issues in comparative genomics and insights gained to ultimately better understand human cancer prevention and treatment. The second paper on anoles lizard evolution showed how rapid background evolution in anoles and snakes was juxtaposed by highly preserved protein coding sequences resulting in unique morphometric diversity. Dr. Tollis then began his talk introducing Peto's Paradox which was used to motivate other questions in evolutionary genomics and cancer studies. Peto's Paradox provided an ideal foundation to base Dr. Tollis' research on. The paradox lays out the expectation that either large bodied species or long lived species should theoretically have high cancer rates. Instead we observe lower than expected cancer rates, thus providing a paradox. The talk concluded with 'frontiers in comparative oncology' and Dr. Tollis' personal research goals.

1.1 Mammalian Cancer Suppression Evolution

Cancer suppression genetic studies are an ever-growing topic due to their potential to inform human cancer prevention. Dr. Tollis' paper (Tollis et al., 2017) highlights cancer suppression mechanisms across multiple mammalian species in a synthesis that allowed the reader to

understand how these studies can possibly impact human cancer prevention. The paper opens with the 'unique' African naked mole rat which is unique because of its seven-fold longer lifespan than the mouse even though both species are of similar body size. This introduces how body size does not simply explain expected lifespans. Additionally, lifespans for all multicellular organisms are assumed to be shortened by the occurrence of cancer. Further, genomics studies sought to explore why there is such a disparity in life spans discovering the divergence of telomerase activity from other mammal telomerase activity in the naked mole rat. The divergence in telomerase activity in the naked mole rat is one of the many mechanisms that enhances cancer suppression. More work is required to solidify this idea.

Alternative proposed forms of cancer suppression, including mutations in the TP53 tumor suppressor gene and both DNA damage repair genes and response pathway genes were contextualized in moles, bats, bowhead whales, and elephants, to name a few. The range in size of species that developed cancer suppression activity was then described using Peto's Paradox which states that an animal's body size should be proportional to its likelihood of cancer occurrence, a relationship that does not hold for the aforementioned species and hence the paradox. However, an important caveat to the paradox is that it holds true at the organismal level, but not at the species level possibly due to fewer cells and lower levels of growth hormone for smaller individuals.

These examples highlight how diverse cancer suppression can be for different species with different life histories and how findings may one day be applied to aid human patients. Diversity in cancer suppression is an exciting field of study because it could lead scientists to develop and test multiple novel methods in human cancer prevention. Additionally, by studying multiple species' cancer suppression tactics, we better understand the mechanics of the genome and document more regions of the mammalian metagenome.

1.2 *Anolis* Comparative Genomics

The paper on mammalian comparative genomics and cancer laid out a useful background from which to read the anoles lizard paper (Tollis et al., 2018). The study focused on three species that occupy different neotropical microhabitats. This selection in species allowed for the study of both ecological and phylogenetic diversification histories. The methods for the paper at first were difficult to follow for but after Dr. Tollis' presentation and our discussion the methods were more intuitive. The study proceeded by sequencing each species' genome and identifying

regions that shared similarities in protein coding which then allowed for genome alignment. Following alignment, each genome was compared by summing base pair substitutions per million years which revealed more rapid evolution of the 400 anole lizard species than other vertebrate evolution rates. The hypotheses for this rapid evolution were attributed to either punctuated equilibria models or ecological opportunity. Even though the anoles species experience accelerated evolution, the acceleration was observed in non-functional regions of the genomes while protein coding regions were highly conserved. There were exceptions, however, where observed differences occurred for behavior, sensory perception, reproduction, and limb development genes. The take-aways from this study focus on improving the understanding of vertebrate evolution and advancing reptile genomics which has received relatively little attention compared to mammalian studies. Instead of applicability to healthcare, this paper can contribute to understanding how diversity in taxonomic evolution emerged and may be helpful informing conservation efforts. This will require deeper research in to more diverse species as gene sequencing only recently became affordable and has primarily focused on a narrow range of mammalian genomes.

1.3 Presentation

Dr. Tollis was able to take concepts from his papers primarily Peto's Paradox and introduce motivations for why comparative genomics is an important field. These motivations included how genomics contribute to conservation work, the need to better understand the tree of life, and cancer research. In conservation, it is important to understand whether endangered or threatened species are pressured by human actions, such as the development of solar arrays and their impact on desert tortoises. If human development impacts sensitive species that represent unique genomes, the impact may be detrimental to the animal population and in turn the development may have to be altered. Genomics can also bolster phylogenetic studies that until the past few decades focused on classifying species relations solely on phenotypic similarities and dissimilarities. This becomes important to better understanding evolutionary pathways and mysteries, such as why the Tuatara lineage has remained relatively unchanged since the Triassic. The final motivation was that genomics can be used to understand cancer suppression in various species. Peto's Paradox framed how long lived and large bodied species have paradoxically low rates of cancer when they should instead have high cancer rates. Similarly, birds not only have low cancer rates and small bodies but also violate Cope's Rule which states species lineages

develop larger bodies over time. Interestingly, the aves class has reduced in body size over time. This is hypothesized to be due to the evolution of flight allowing for avoidance of predation but retaining larger ancestral cancer suppression methods. Understanding how drastically different species' life histories can independently develop cancer suppression is one method to potentially apply useful genes, proteins, or weaknesses in cancer. We can then apply findings to human medicine treatment. Dr. Tollis easily transitioned between these topics and concluded by emphasizing his desire to continue science community engagement, specifically here on the Colorado Plateau. His future work aims at furthering cancer suppression pathway evolution and taxonomic diversification.

2 Relationship to Personal Research

I found it surprising how easily I could relate to Dr. Tollis' work, particularly his research on anoles lizard evolutionary diversity. In addition, one of Dr. Tollis' leverages for genomics hinged on conservation of species. This aligns well with work that I am pursuing in identifying species that share both evolutionary diversity and globally endangered classification (EDGE). But, I also related to the work because, prior to my time at NAU, I focused on studying evolutionary ecology, a field that shares many theoretical and applied principles with comparative genomics. Even though I have no direct relationship to comparative genomics, the underlying motivations are shockingly similar to my own research interests.

The anoles work most closely resembles the work I am currently involved in at NAU. Dr. Tollis' study selected a suite of species that occupied unique spatial niches with unique evolutionary pathways relating to their niche space. For example, differences in limb morphometry were found to evolve rapidly since roughly the Cenozoic Era allowing for lizard species to occupy unique microhabitats. The occupation of different habitats was in part due to differences in genomic evolution for tropical anoles resulting from species ability to explore unique spatial niches, of which over 400 species exist due to rapid evolutionary diversification. This is similar to my current work which focuses on classifying species in niche distribution models, or simply mapping potential ecological spaces where species may occur in the past, present, and future. Modelling species distribution in the past ties in with understanding how anoles limb evolution allowed for species to occupy unique spatial habitats. We do not

incorporate evolutionary factors very often, as they are highly complex and difficult to spatially contextualize. Instead, we opt to use historical, modern, and projected climate and topographic data to map species extent.

At the end of Dr. Tollis' presentation he mentioned future motivations for himself that are focused on going into museum collections to find unique species of the Colorado Plateau that may supply rare DNA sequence samples. This research aims to supplement the community with information on biodiversity, particularly for species that are vulnerable or endangered. My work with species distribution modelling also includes the mapping of Redlist species which are species with a range of conservation concern levels (i.e. endangered or vulnerable). Specifically it is a goal to refine this list of species using a metric that further classifies species by their evolutionary 'uniqueness' (EDGE species) or how much information would be lost in their taxa if they became extinct (Gumbs et al., 2018). My research and Dr. Tollis' research aim to better understand biodiversity; however, we seek to do so from different scales.

Finally, a more tangential relationship, in my undergraduate career I studied evolutionary ecology which focused on ecological concepts but included work with genomics and molecular biology. It has been quite some time since I was involved with evolutionary ecology but there are many similarities between the work with miRNA that I was involved in and Dr. Tollis' DNA sequencing. I found comparative biology extremely interesting; studying how species uniquely develop specific phenotypes and behaviors and how these are based in evolutionary development. In summary, the underlying scientific principles (e.g. the interrelatedness between habitat suitability and evolutionary pressures) and a desire to understand biodiversity metrics link my work with Dr. Tollis' quite well.

3 Conclusions

This week, Dr. Marc Tollis exposed the class to the diverse and powerful field of comparative genomics. Studies within this field range from uncovering various pathways of cancer suppression to understanding how extremely diverse taxa, like *Anolis*, have rapidly evolved over relatively short time spans. His presentation contextualized the readings within Peto's Paradox, a paradox that lays out the complex relationship of higher expected cancer rates not correlating with body size. This motivated future studies in genomics to help the public better understand the history of cancer across multiple mammalian species. The work paralleled my

own research interests understanding how biodiversity plays a role in nature at the genomic or continental scale. Dr. Tollis was able to communicate many complex topics allowing for the discussion to expand into how his work fits within a larger scientific lens.

References

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