From Polar Bears to People: The Role of Ethnic Genetic Variation in Thermoregulation and Heat-Related Health Risk

Alexandra Baumann[1,*][a], Jakob Thiel[2,*][b], Nina Haffer[3,4][c], Shailendra Gupta[1][d] and Markus Wolfien [2,5][e]

[1]*Department of Systems Biology and Bioinformatics, University of Rostock, Rostock, Germany*

[2]*Institute for Medical Informatics and Biometry, Faculty of Medicine and University Hospital Carl Gustav Carus, TUD Dresden University of Technology, Dresden, Germany*

[3]*Berlin Institute of Health at Charité - Universitatsmedizin Berlin, Germany*

[4]*Charité - University Medicine Berlin, Germany*

[5]*Center for Scalable Data Analytics and Artificial Intelligence (ScaDS.AI), Dresden/Leipzig, Dresden, Germany*

fi

Keywords: Heat Illness, Heat Susceptibility, Climate Change, Ethnicity, Genetic Association.

Abstract: As climate change increases the frequency and severity of acute heat events, it is crucial to determine factors for appropriate healthcare strategies and predictive models. Previously, it was stated that socioeconomic factors primarily play a role in heat-related illness risk. Analogous to the polar bear's unique adaptations to the cold, humans exhibit distinct genetic traits shaped by their migration to diverse climates. This position paper hypothesizes that genetic differences among human ethnic groups, in addition to socioeconomic and other factors, also contribute to variations in thermoregulation and influence susceptibility to heat-related diseases. To understand genetic adaptations across human ethnicities (initially European and African), we propose a genetic association analysis of single nucleotide polymorphisms (SNPs) in genes associated with thermoregulation. An assessment of changes in thermoregulation gene regulation networks will be possible by conducting a functional pathway analysis. Expected outcomes include identifying differences in SNP distributions of thermoregulation-associated genes across ethnicities. Challenges such as the underrepresentation of African populations in genomic databases must also be addressed. This research aims to provide a foundational understanding of genetic contributions to heat adaptation, guiding the development of personalized, equitable healthcare responses to climate-induced heat stress.

1 BACKGROUND

1.1 The Polar Bear's Struggle with Climate Change

Climate change is driving widespread environmental shifts, notably the melting of the ice caps and an overall increase of global temperatures. The polar bear, native to arctic regions, faces challenges as its habitat warms beyond its evolutionary adaptations. Unlike other bear species, the polar bear differentiates by diverse characteristics, such as adaptation to colder temperatures by dual-layered fur or slip-proof feet (Welch et al., 2014). Imagine a polar bear visiting black bears or grizzly bears in warmer regions, where it lacks adaptations for heat. While black bear's ears are large for heat dissipation, the ears of the polar bear are smaller and the they have a thick layer of subcutaneous fat (Rinker et al., 2019). The polar bear is also bigger than the other bear species in warmer regions. This can be explained by a rule proposed by the scientist Carl Bergmann, who discovered that these size variations relate to the surface area-to-body mass ratio (Bergmann, 1848). Smaller body size is typical in populations near the equator, while larger body size is more common in colder regions.

[a] https://orcid.org/0009-0003-8946-8741
[b] https://orcid.org/0009-0007-1951-1678
[c] https://orcid.org/0000-0002-9541-2811
[d] https://orcid.org/0000-0002-3470-3260
[e] https://orcid.org/0000-0002-1887-4772
[*] Shared first authorship.

Baumann, A., Thiel, J., Haffer, N., Gupta, S. and Wolfien, M.
From Polar Bears to People: The Role of Ethnic Genetic Variation in Thermoregulation and Heat-Related Health Risk.
DOI: 10.5220/0013256100003911

In *Proceedings of the 18th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2025) - Volume 1*, pages 655-660
ISBN: 978-989-758-731-3; ISSN: 2184-4305

1.2 Human Heat Adaptations Around the Globe

This natural variation among bears serves as a vivid analogy: just as bear species adapt to specific climates, human population may also exhibit diverse adaptations in resilience to heat - an increasingly important consideration in our warming world. Climate adaptations affect not only physical characteristics but also health factors, such as birth weight and fetal growth, in populations across diverse climates (Lambert et al., 2008). As humans migrated across different climates, it was necessary to slowly adapt to the environment over multiple generations, which led to phenotypic variation across ethnicities. Research on thermoregulation in different ethnicities suggests both genotypic and phenotypic adaptations to heat (Taylor, 2006; Lim, 2020). Since 2006, genetic variation has been proposed as an adaptive mechanism for heat tolerance, with regulatory processes controlling individual heat responses (Taylor, 2006). Observable adaptations include skeletal morphology and traits like nose shape, hair type, and lip structure, with one of the most prominent being skin and eye color (Lambert et al., 2008). Often, multiple genetic variants collectively influence a single phenotype, highlighting the polygenic nature of these adaptations (Cortés et al., 2020). The study by Huang et al. identified 299 single nucleotide polymorphisms (SNPs) differing across populations, primarily in genes influencing skin and eye color, suggesting a genetic adaptation to environmental factors such as increased heat and UV exposure (Huang et al., 2015). For instance, melanin in the skin provides UV protection for people living in regions closer to the equator, while depigmentation enhances vitamin D3 synthesis in populations living farther north (Lambert et al., 2008). These adaptations also impact metabolic traits. Metabolic rates vary across populations, and epigenetic factors may contribute to thermoregulatory differences (Cramer et al., 2022). Cold tolerance appears to be higher among individuals from colder regions, while those from tropical regions may exhibit a reduced response to heat. Natural selection likely favored thermoregulatory mutations, such as those supporting heat production in northern populations (Lambert et al., 2008). Differences in metabolic rate, subcutaneous fat levels, thyroid activity, and mitochondrial DNA (mtDNA), may all contribute to increased metabolic heat production in colder climates (Lambert et al., 2008). Furthermore, molecular differences can influence protein functions and even drug responses across populations with implications for treatments related to heat-induced health conditions (Duello et al., 2021). Studying these diverse adaptations may help inform healthcare practices that address climate-related health risks more effectively.

1.3 Impact of Ethnicity and Socioeconomics on Heat-Related Illness

Apart from region-specific heat adaptations, climate change is increasing the frequency and intensity of acute heat events (WHO, 2023). Heat impacts health in various ways, causing both direct and indirect effects. Directly, exposure to high temperatures can result in heat-related illnesses, such as heat stroke, dehydration, or heat collapse (Xu et al., 2023). Indirectly, heat can increase the risk of severe events like heart attacks and is associated with higher mortality rates among vulnerable populations, including cancer patients (Hüsing et al., 2024). The rise in acute heat events also places a considerable strain on healthcare systems (WHO, 2023). One response to this challenge is the development of predictive models to forecast hospital resource needs, combining climate and medical data (Thiel et al., 2024). Adding patient-specific characteristics as risk factors, such as age and gender, can improve the accuracy of these models (Cheng et al., 2019).) Studies by Berberian et al. (2022) and Jackson et al. (2022) indicate that people with darker skin may be at higher risk of heat-related illnesses (Berberian et al., 2022; Jackson et al., 2022). Both studies highlight that socioeconomic factors often underlie this increased risk. However, genetic factors influencing thermoregulation may also contribute to these differences, as discussed above. This suggests that ethnic background could be an essential factor in developing predictive models for heat illnesses, providing a more comprehensive approach in protecting diverse populations.

This position paper presents the hypothesis that it would be valuable to investigate whether genetic differences between individuals of different ethnicities can be associated with thermoregulation and, consequently, the risk of heat-related illnesses. By investigating these genetic factors, the study aims to identify potential contributors to heat-related illness susceptibility, ultimately supporting the development of precise prevention measures and predictive models.

2 PROPOSED APPROACH ON ANALYZING THE IMPACT OF ETHNICITY ON THERMOREGULATION

The impact of ethnic genetic variation on heat-related diseases has to be inspected to test the hypothesis. Existing literature on thermoregulation-associated genes and gene regulation networks provides a foundation for this investigation, offering insights into pathways and mechanisms in heat resilience and adaptation. Heat regulation plays a crucial role in cellular housekeeping and homeostasis as well as in stress response (Charlebois et al., 2018). Further processes and biological components that might be of interest are thermo-receptors, thermo-sensitive neurons, or lipolysis (Valero et al., 2014). Diverse databases offer a systematic framework to identify genes related to biological processes such as Gene Ontology (GO) (Aleksander et al., 2023; Ashburner et al., 2000), or even associations between diseases and variants like Disgenet (Pinero et al., 2017). Relevant GO terms, amongst others, include ”heat acclimation” (GO:0010286), ”response to heat” (GO:0009408), ”cellular response to heat” (GO:0034605), ”heat generation” (GO:0009409), ”temperature homeostasis” (GO:0001659), ”circadian temperature homeostasis” (GO:0003052), or ”sweat gland development” (GO:0061114). For example, the GO term ”heat acclimation” is linked to 366 genes and gene products across all organisms in the database, of which six are human genes. Similarly, ”temperature homeostasis” is associated with 264 genes across all organisms, including 34 human genes. As a starting point, a genetic association analysis could be conducted utilizing common SNP databases such as dbSNP (Sherry et al., 1999) or gnomAD (Karczewski et al., 2020) to identify SNPs in thermoregulation-related genes, with allele frequencies analyzed according to ethnicity. Initially, the primary comparison groups will be Europeans (non-Finnish) and Africans (/African Americans), as these ethnicities are already represented in common SNP databases, enabling a robust baseline analysis of allele frequency differences. To predict the potential effect of each variant on gene function, including regulatory roles, the Ensembl Variant Effect Predictor (VEP) tool will be applied (McLaren et al., 2016). The main focus will be on SNPs in protein-coding regions. A preliminary analysis focusing on 40 genes associated with the GO terms ”heat acclimation” and ”temperature homeostasis” revealed 288 variants from the gnomAD v4.1.0 database with allele frequency differences greater than 0.5 % between the two before-mentioned populations. First filtering steps excluded variants in intronic (not splice-relevant) and UTR regions or variants with an allele frequency below 0.5 % in the population with the maximum allele frequency. Ten variants with highest difference between the two population allele frequencies in Europeans (non-Finnish) and Africans (/African Americans) are depicted in (Table 1).

There are some noticeable differences between variant allele frequencies across the two populations in genes associated to thermoregulation. Both populations are represented with either higher or lower allele frequencies for the variants. Synonymous as well as missense variants or splice-associated ones can be found in this first view. The variants have to inspected for their relevance in gene functions. In this first consideration, only exonic and splice region variants were investigated. However, as SNPs in intronic and intergenic regions can influence transcription regulation or affect regulatory RNAs (such as micro RNAs), those SNPs will be examined as well. This analysis will help to simulate and assess changes in gene regulation networks involved in thermoregulation. Additionally, functional pathway analysis tools, such as KEGG (Kanehisa and Goto, 2000) or Reactome (Fabregat et al., 2017), could be applied to map these SNPs within thermoregulation pathways, deepening our understanding of how variations in these pathways may contribute to heat resilience or susceptibility. While the initial focus will be on European and African ethnicity, future analyses could be expanded to include other ethnic groups (such as East Asian or Indigenous populations) to achieve a more comprehensive view on thermoregulatory adaptations across diverse environments. Incorporating environmental data, such as historic climate conditions associated with each population, could further contextualize observed genetic variations as adaptive responses to different climates.

3 EXPECTED INFLUENCES AND CHALLENGES

We expect to find differences in SNP distributions between the two ethnicities under study, specifically within genes associated with thermoregulation. These SNP variations may contribute to observed differences in thermoregulation among diverse ethnicities, particularly between Europeans and Africans in this analysis. It is also anticipated that some SNPs will appear in intronic or non-coding regions, which may not directly impact gene function and could be considered incidental ”byproducts.” Nevertheless, it re-

Table 1: Top ten variants in thermoregulation-related genes with highest allele frequency (AF) differences between African/African American and European (non-Finnish) populations. HGVS nomenclature of variant consequence on cDNA (c.) or protein (p.) level. Variant Effect Predictor (VEP) annotation of variant region and consequence. Contents extracted and adapted from gnomAD v4.1.0 (Karczewski et al., 2020).

Gene	HGVS Consequence	VEP Annotation	AF African/ African American	AF European (non-Finnish)
STAT3	c.1601-8dup	splice_region_variant	0.6847	0.1937
NAPEPLD	p.Asp389Asn	missense_variant	0.5586	0.9989
DRD2	p.Pro319Pro	synonymous_variant	0.1168	0.5468
MC3R	p.Val44Ile	missense_variant	0.4284	0.0839
DRD2	p.His313His	synonymous_variant	0.3622	0.7057
HSPA1A	p.Glu110Asp	missense_variant	0.4176	0.1059
TRPM2	p.Asp1360Asp	synonymous_variant	0.2808	0.0004
TRPV1	p.Thr469Ile	missense_variant	0.0741	0.3517
ADRB2	p.Glu27Gln	missense_variant	0.8239	0.5570
RBBP7	p.Arg37His	missense_variant	0.1899	0.4445

mains essential to investigate the intronic and non-coding SNPs, too. They can be located in regulatory regions with an effect on transcription rate and transcript stability or can lead to alternative splicing (Vaz-Drago et al., 2017). Furthermore, micro RNAs with key functions in pathway regulations are often located in intronic regions (Vaz-Drago et al., 2017). A key challenge, therefore, will be filtering out those SNPs with a meaningful impact on thermoregulation. A limitation of this proposed approach is the over-representation of European populations in genomic databases, while African populations remain comparatively under-studied. This imbalance may affect the generalizability of the findings. Additionally, genomic ancestry alone does not fully capture socioeconomic diversity within or between African and European populations. Socioeconomic factors can influence health outcomes through epigenetic modifications, which may impact thermoregulation and other heat-related traits. Further challenges include accounting for factors such as sex, age, and pre-existing conditions, which are likely to influence thermoregulatory responses and the risk of heat-related illnesses. Analyzing male and female participants separately may reveal sex-specific effects on thermoregulation, and considering age groups and health status will be essential for an in-depth interpretation of the results. Lastly, the applicability of these findings to clinical settings may require long-term studies, as epigentic and genetic influences on thermoregulation likely evolve over time.

4 IMPLICATIONS AND CONCLUSION

This study underscores the importance of examining genetic diversity in understanding thermoregulation and susceptibility to heat-related illnesses in addition to socioeconomic factors. By identifying genetic variations associated with heat resilience and mapping them across diverse ethnicites, we can develop more precise predictive models and preventive measures tailored to individual needs. The proposed approach will support health equity, offering insights that help to mitigate the disproportionate impact of climate change.

Just as polar bears are uniquely adapted to cold environments but face challenges as temperatures rise, different human ethnicities may too require unique adaptations as they confront a warming world. Understanding these genetic differences equips us to develop strategies to support all individuals in the face of changing climates, preserving health across the diversity of humanity.

ACKNOWLEDGEMENTS

We are particularly grateful for the financial support provided by the Federal Ministry of Education and Research (BMBF: OLCIR - 02NUK082C, MiHUBx - 01ZZ2101A).

REFERENCES

Aleksander, S. A., Balhoff, J., Carbon, S., Cherry, J. M., Drabkin, H. J., Ebert, D., Feuermann, M., Gaudet, P., Harris, N. L., Hill, D. P., Lee, R., Mi, H., Moxon, S., Mungall, C. J., Muruganugan, A., Mushayahama, T., Sternberg, P. W., Thomas, P. D., Van Auken, K., Ramsey, J., Siegele, D. A., Chisholm, R. L., Fey, P., Aspromonte, M. C., Nugnes, M. V., Quaglia, F., Tosatto, S., Giglio, M., Nadendla, S., Antonazzo, G., Attrill, H., dos Santos, G., Marygold, S., Strelets, V., Tabone, C. J., Thurmond, J., Zhou, P., Ahmed, S. H., Asanithong, P., Luna Buitrago, D., Erdol, M. N., Gage, M. C., Ali Kadhum, M., Li, K. Y. C., Long, M., Michalak, A., Pesala, A., Pritazahra, A., Saverimuttu, S. C. C., Su, R., Thurlow, K. E., Lovering, R. C., Logie, C., Oliferenko, S., Blake, J., Christie, K., Corbani, L., Dolan, M. E., Drabkin, H. J., Hill, D. P., Ni, L., Sitnikov, D., Smith, C., Cuzick, A., Seager, J., Cooper, L., Elser, J., Jaiswal, P., Gupta, P., Jaiswal, P., Naithani, S., Lera-Ramirez, M., Rutherford, K., Wood, V., De Pons, J. L., Dwinell, M. R., Hayman, G. T., Kaldunski, M. L., Kwitek, A. E., Laulederkind, S. J. F., Tutaj, M. A., Vedi, M., Wang, S.-J., D'Eustachio, P., Aimo, L., Axelsen, K., Bridge, A., Hyka-Nouspikel, N., Morgat, A., Aleksander, S. A., Cherry, J. M., Engel, S. R., Karra, K., Miyasato, S. R., Nash, R. S., Skrzypek, M. S., Weng, S., Wong, E. D., Bakker, E., Berardini, T. Z., Reiser, L., Auchincloss, A., Axelsen, K., Argoud-Puy, G., Blatter, M.-C., Boutet, E., Breuza, L., Bridge, A., Casals-Casas, C., Coudert, E., Estreicher, A., Livia Famiglietti, M., Feuermann, M., Gos, A., Gruaz-Gumowski, N., Hulo, C., Hyka-Nouspikel, N., Jungo, F., Le Mercier, P., Lieberherr, D., Masson, P., Morgat, A., Pedruzzi, I., Pourcel, L., Poux, S., Rivoire, C., Sundaram, S., Bateman, A., Bowler-Barnett, E., Bye-A-Jee, H., Denny, P., Ignatchenko, A., Ishtiaq, R., Lock, A., Lussi, Y., Magrane, M., Martin, M. J., Orchard, S., Raposo, P., Speretta, E., Tyagi, N., Warner, K., Zaru, R., Diehl, A. D., Lee, R., Chan, J., Diamantakis, S., Raciti, D., Zarowiecki, M., Fisher, M., James-Zorn, C., Ponferrada, V., Zorn, A., Ramachandran, S., Ruzicka, L., and Westerfield, M. (2023). The Gene Ontology knowledgebase in 2023. *Genetics*, 224(1):iyad031.

Ashburner, M., Ball, C. A., Blake, J. A., Botstein, D., Butler, H., Cherry, J. M., Davis, A. P., Dolinski, K., Dwight, S. S., Eppig, J. T., Harris, M. A., Hill, D. P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J. C., Richardson, J. E., Ringwald, M., Rubin, G. M., and Sherlock, G. (2000). Gene Ontology: tool for the unification of biology. *Nature genetics*, 25(1):25–29.

Berberian, A. G., Gonzalez, D. J. X., and Cushing, L. J. (2022). Racial Disparities in Climate Change-Related Health Effects in the United States. *Current Environmental Health Reports*, 9(3):451–464.

Bergmann, C. (1848). *Über die Verhältnisse der Wärmeökonomie der Thiere zu ihrer Grösse*. 3.

Charlebois, D. A., Hauser, K., Marshall, S., and Balázsi, G. (2018). Multiscale effects of heating and cooling on genes and gene networks. *Proceedings of the National Academy of Sciences*, 115(45).

Cheng, J., Xu, Z., Bambrick, H., Prescott, V., Wang, N., Zhang, Y., Su, H., Tong, S., and Hu, W. (2019). Cardiorespiratory effects of heatwaves: A systematic review and meta-analysis of global epidemiological evidence. *Environmental Research*, 177:108610.

Cortés, A. J., López-Hernández, F., and Osorio-Rodriguez, D. (2020). Predicting Thermal Adaptation by Looking Into Populations' Genomic Past. *Frontiers in Genetics*, 11.

Cramer, M. N., Gagnon, D., Laitano, O., and Crandall, C. G. (2022). Human temperature regulation under heat stress in health, disease, and injury. *Physiological Reviews*, 102(4):1907–1989.

Duello, T. M., Rivedal, S., Wickland, C., and Weller, A. (2021). Race and genetics versus 'race' in genetics: A systematic review of the use of African ancestry in genetic studies. *Evolution, Medicine, and Public Health*, 9(1):232.

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V., D'Eustachio, P., Stein, L., and Hermjakob, H. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC Bioinformatics*, 18:142.

Huang, T., Shu, Y., and Cai, Y.-D. (2015). Genetic differences among ethnic groups. *BMC Genomics*, 16(1):1093.

Hüsing, J., Beiderbeck, M., Berressem, S., Kajüter, H., Stang, A., and Zander, T. (2024). Hitzebedingte Übersterblichkeit unter in Nordrhein-Westfalen Krebserkrankten im fortgeschrittenen Stadium. page DocAbstr. 596. German Medical Science GMS Publishing House.

Jackson, P., Larkin, D., Kinnie, K. R., and Aroke, E. N. (2022). Heat Islands and Chronic Disease: Could African Americans Be More Vulnerable to Heat-Related Health Impacts? *Journal of National Black Nurses' Association : JNBNA*, 33(1):33.

Kanehisa, M. and Goto, S. (2000). KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Research*, 28(1):27.

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alföldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., Walters, R. K., Tashman, K., Farjoun, Y., Banks, E., Poterba, T., Wang, A., Seed, C., Whiffin, N., Chong, J. X., Samocha, K. E., Pierce-Hoffman, E., Zappala, Z., O'Donnell-Luria, A. H., Minikel, E. V., Weisburd, B., Lek, M., Ware, J. S., Vittal, C., Armean, I. M., Bergelson, L., Cibulskis, K., Connolly, K. M., Covarrubias, M., Donnelly, S., Ferriera, S., Gabriel, S., Gentry, J., Gupta, N., Jeandet, T., Kaplan, D., Llanwarne, C., Munshi, R., Novod, S., Petrillo, N., Roazen, D., Ruano-Rubio, V., Saltzman, A., Schleicher, M., Soto, J., Tibbetts, K., Tolonen, C., Wade, G., Talkowski, M. E., Neale, B. M., Daly, M. J., and MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*, 581(7809):434–443.

Lambert, M. I., Mann, T., and Dugas, J. P. (2008). Ethnicity and Temperature Regulation. *Medicine and sport science*, 53.

Lim, C. L. (2020). Fundamental Concepts of Human Thermoregulation and Adaptation to Heat: A Review in the Context of Global Warming. *International Journal of Environmental Research and Public Health*, 17(21):7795.

McLaren, W., Gil, L., Hunt, S. E., Riat, H. S., Ritchie, G. R. S., Thormann, A., Flicek, P., and Cunningham, F. (2016). The Ensembl Variant Effect Predictor. *Genome Biology*, 17(1):122.

Pinero, J., Bravo, A., Queralt-Rosinach, N., Gutierrez-Sacristán, A., Deu-Pons, J., Centeno, E., Garcia-Garcia, J., Sanz, F., and Furlong, L. I. (2017). DisGeNET: a comprehensive platform integrating information on human disease-associated genes and variants. *Nucleic Acids Research*, 45(Database issue):D833–D839.

Rinker, D. C., Specian, N. K., Zhao, S., and Gibbons, J. G. (2019). Polar bear evolution is marked by rapid changes in gene copy number in response to dietary shift. *Proceedings of the National Academy of Sciences of the United States of America*, 116(27):13446.

Sherry, S. T., Ward, M., and Sirotkin, K. (1999). dbSNP—Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. *Genome Research*, 9(8):677–679.

Taylor, N. A. S. (2006). Ethnic differences in thermoregulation: Genotypic versus phenotypic heat adaptation. *Journal of Thermal Biology*, 31(1):90–104.

Thiel, J., Seim, A., Grummt, S., Nesterow, I., Penesch, F., Sedlmayr, M., and Weidner, J. (2024). Tools for optimizing healthcare resource allocation in response to climate impacts and heat action planning. *Journal of Public Health*.

Valero, K. C. W., Pathak, R., Prajapati, I., Bankston, S., Thompson, A., Usher, J., and Isokpehi, R. D. (2014). A candidate multimodal functional genetic network for thermal adaptation. *PeerJ*, 2:e578.

Vaz-Drago, R., Custódio, N., and Carmo-Fonseca, M. (2017). Deep intronic mutations and human disease. *Human Genetics*, 136(9):1093–1111.

Welch, A. J., Bedoya-Reina, O. C., Carretero-Paulet, L., Miller, W., Rode, K. D., and Lindqvist, C. (2014). Polar Bears Exhibit Genome-Wide Signatures of Bioenergetic Adaptation to Life in the Arctic Environment. *Genome Biology and Evolution*, 6(2):433.

WHO (2023). Climate change.

Xu, Z., Watzek, J. T., Phung, D., Oberai, M., Rutherford, S., and Bach, A. J. E. (2023). Heat, heatwaves, and ambulance service use: a systematic review and meta-analysis of epidemiological evidence. *International Journal of Biometeorology*, 67(10):1523–1542.