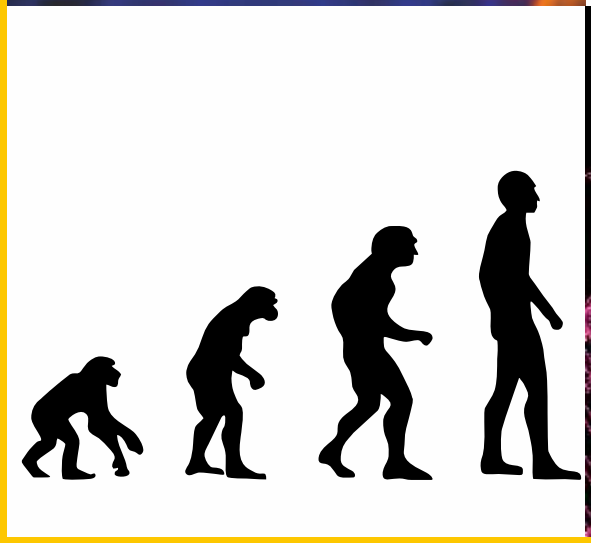
GENES, HEALTH AND ANTHROPOLOGY

KALLUR NAVA SARASWATHY
BENRITHUNG MURRY

Concept

GENES, HEALTH AND ANTHROPOLOGY

FESTSCHRIFT VOLUME
IN HONOUR OF
PROF. M.P. SACHDEVA



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Prof. K.N. Saraswathy is a professor of Biological Anthropology in the Department of Anthropology at the University of Delhi. She is a renowned expert in the field of molecular anthropology, with specializations in genome diversity and biochemical and molecular medical genetics. She obtained her M.Phil. and Ph.D. from the Department of Anthropology at the University of Delhi and completed post-doctoral research in Molecular Genetics at Albert Einstein College of Medicine in New York, USA. To date, she has successfully completed twenty major research projects in molecular and genetic anthropology, funded by the DST, DBT, and ICMR, among others. She has more than 160 research papers in high-repute journals and two books to her credit.

Prof. Benrithung Murry completed his Masters in Anthropology from North Eastern Hill University Shillong and obtained his Ph.D. from the University of Delhi with a specialization in Physical Anthropology. He joined the Department of Anthropology at the University of Delhi in 2004 as a lecturer and is presently serving as a professor. His research interests include maternal health, aged care and aged mental health, public health, and culture. Currently, he is working on studies aimed at developing region-based methodologies, approaches, and policies concerning women's health, aged care, and nutritional deficiencies. Under his supervision, nine research scholars have been awarded PhDs, and he has published more than 40 research papers in high-repute journals.

This festschrift volume has been compiled to honor the distinguished and illustrious career of Professor M.P. Sachdeva. The book was conceived to provide a comprehensive understanding of genetics in anthropology. While human genetics is studied by medical doctors, forensic geneticists, biochemists, and life science researchers, this book aims to describe genetics through an anthropological lens. Until now, there was no platform that provided a holistic approach to genetics in anthropology for students pursuing BSc or MSc in the field. This book represents a modest step towards providing a detailed description of human genetics, starting from its history to chromosomes, DNA technologies and methods, genetic epidemiology, adaptation, and genotype and phenotype interactions in understanding lifestyle diseases.

GENES, HEALTH AND ANTHROPOLOGY

About the Editors

Prof. K.N. Saraswathy is a professor of biological anthropology at the Department of Anthropology, University of Delhi. She is a renowned expert in the field of molecular anthropology. Her areas of specialization are molecular anthropology, genome diversity, and molecular medical genetics. She has completed post-doctoral in Molecular Genetics at Albert Einstein College of Medicine, New York, USA, and M.Phil. and Ph.D. from the Department of Anthropology, University of Delhi. Till now, she has successfully completed twenty research projects in the field of molecular and genetic anthropology funded by Department of Science and Technology (DST), Department of Biotechnology (DBT), Indian Council of Medical Research (ICMR), etc. She has more than 160 research papers and two books to her credit. She was felicitated by Andhra Vanitha Mandal, New Delhi, in 2010.

Prof. Benrithung Murry did his Masters in anthropology from North Eastern Hill University Shillong and Ph.D from University of Delhi with a specialization in physical anthropology. He joined the Department of Anthropology University of Delhi in 2004 as a lecturer. Prior to joining the department, he worked in the capacity of Research Officer at Law Research Institute, Gauhati High Court and as a Guest Lecturer in the Department of Anthropology, North Eastern Hill University. He teaches human evolution, biological variations and demography. His research interest includes vital anthropological dimensions such as maternal health, aged care and aged mental health, public health and culture. Presently he along with his research scholars are working on population-specific and region-specific research to develop region-based methodologies, approaches and policies with respect to women's health, aged care and nutritional deficiencies. Under his supervision nine research scholars have been awarded Ph.D.s and he has published more than 40 research papers in journals of high repute.

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Foreword

The present volume is a felicitation number in honour of Prof. M.P. Sachdeva. It is an apt collection of papers on the theme "Genes, Health and Anthropology", a topic close to the heart of Prof. Sachdeva, one of my former esteemed colleagues at the Department of Anthropology, University of Delhi. Many of the contributors have been students, colleagues, or teachers of Prof. Sachdeva.

The papers deal with almost A to Z of the themes, starting with Darwin's natural selection to gene, chromosomal, and molecular polymorphism, their causes, and maintenance in populations. The interaction of biological and cultural factors shaping human evolution is also highlighted. The paper by Prof. Saraswathy has discussed at length the methods used in molecular biology.

The significance of ancient DNA (aDNA) in explaining the extinction of different species and populations, population mobility, and ancestral relationships between populations have been emphasized in a paper by Prof. Rajan Gaur. The significance of Anthropometric measurements is also discussed in the papers on the "Genetics of Anthropometric Measures", while a related paper on genetic obesity highlights the risk of obesity determined by the interaction of genetics and environment, also well-attended by the paper on "Gene-environmental Interaction in Cardiovascular Diseases".

Chapters by Bandyopadhyay, Chandel, and Samtani have shed light on genetic and epigenetic aspects of reproductive health and mental health and the development of male external genitalia, respectively. A related chapter by Suraj Singh also highlights the genetic predisposition to alcohol dependency. The chapter on Genetics in Public Health by Priyanka Garg emphasizes the need for new born

screening programmes and precision and personalized medicine to help the development of novel treatments.

The chapter by Vani Kandpal discusses at length the status of tribal communities vis-a-vis genetic diseases and strategies to deal with the problem, while a related chapter by Simi Khan deals with genetic variance in high altitude adaptation. Jyoti Mishra, in her chapter on differences in immune response across sexes, with women exhibiting stronger humoral immune activity than men, considers it a "game changer in human reproduction".

Vipin Gupta talks about an out-of-the-box concept of big research referring to large-scale multinational and interdisciplinary research initiatives that aim to advance our understanding of complex systems such as the Genome. He has given some examples of such projects that have a significant impact in the fields of medicine, biology, and computer science. The dataset from such projects allows smaller-scale studies to seek insights into specific questions.

In all, the present volume is a befitting felicitation number in honour of Professor M.P. Sachdeva, whom I have always considered the highly read anthropologist in the field of human genetics, who has made pioneering contributions to advancing teaching and research in Human Genetics in the department. I compliment all the authors for their respective contributions in this felicitation volume in honour of the superannuating Professor. I hope the volume will have a wide circulation.

Delhi **Prof. A.K. Kalla**

Acknowledgements

We would like to extend our deepest gratitude to all the contributors of this festschrift, whose insightful and thought-provoking essays have made this volume possible. This book was made possible through articles written in honour of Prof. M.P. Sachdeva by his friends, students, and colleagues. Prof. Sachdeva has excelled in every role he has played, whether as a mentor to his students, Ph.D. supervisor, friend, or colleague.

This volume is a testament to Prof. Sachdeva's enduring legacy and his continued impact on our understanding of the complex interplay between genes, health, and anthropology. We initially conceptualized this work with Dr. Vipin, and together, we drew the blueprint for the book. Many sessions with cups of coffee discussing Prof. Sachdeva's academic contributions and the central role of gene-culture interaction helped us to realize this work. Prof. Manoj Kumar Singh and Prof. R. P. Mitra have been a tremendous source of encouragement and support from the book's inception, acting as morale boosters and bringing positivity throughout the journey of making this book.

Though enlisting everyone who has contributed to making this reality would be a daunting task, we are making this humble effort to acknowledge some key contributors. To begin with, we would like to express our deepest gratitude towards the present head of the department, Prof. S.M. Patnaik, for his constant support and appreciation for the book. Although the book was conceptualized before his headship, it took its final shape during his tenure.

We would like to thank several distinguished professors and scholars who contributed chapters to this book, including Professors Rajan Gaur, Indu Talwar, Sukh Mohinder Singh Chahal, and Arup

Ratan Bandyopadhyay, whose contributions greatly enhanced the book's worth. Their insights and expertise in genetics, paleo genetics, human evolution, and human population genetics will undoubtedly benefit students studying anthropology and population genetics. We also extend our gratitude to Dr. Harpreet, Dr. Yaiphaba, Dr. Vani, Dr. Gagandeep, Dr. Priyanka, Dr. Ratika, Dr. Jyoti, Dr. Simi, and Dr. Suraj, who not only contributed as authors but also as reviewers of chapters in the book. We are also grateful to Dr. Sonal, Dr. Rajeev, and Dr. Abhilasha for their timely submissions and contributions.

We must also acknowledge the former students of Prof. Sachdeva, who participated enthusiastically and brought much-needed dynamism to the project. We would like to extend a special debt of gratitude to our dear colleagues Dr. Vipin, Dr. Kiranmala, and Dr. Shivani for their efforts, skills, unstinted support, and willing cooperation from time to time.

We would also like to appreciate the contributions of Vineet Chaudhary, one of the research scholars, who was a continuous motivation in terms of correspondence with the publishers, reviewers, and authors and running plagiarism checks. Additionally, he has co-authored two chapters for the volume and reviewed almost all the manuscripts. But for his hard work, consistent efforts, patient thinking, and passion for Anthropology, this volume would not have seen the day.

We also thank Mr. Ashok Mittal, Managing Director of Concept Publishing Company (P) Ltd., for sticking to a very tight timeline and finally publishing the book despite many obstacles. Their contributions helped shepherd this project into reality.

Finally, we must acknowledge the indirect contribution of Prof. M.P. Sachdeva, who was the inspiration and driving force behind this book.

K.N. Saraswathy
Benrithung Murry

Introduction

This festschrift volume has been compiled to honour the distinguished and illustrious career of Prof. M.P. Sachdeva, a renowned academician, revered scientist, and extremely honorable human being. As remarkable as his academic and scientific achievements are, his journey has a very humble beginning. Starting from a small village in Punjab, Prof. Sachdeva went on to become a professor and later the Head of the Department at the Department of Anthropology, University of Delhi. His academic life began at a small school in rural Punjab. After his school education, he pursued his graduation and post-graduation from Panjab University. He completed his B.Sc (Hon) in 1979 with Anthropology, Geology, and Biochemistry and obtained an M.Sc degree in Anthropology in 1980 from Panjab University, Chandigarh, where he was awarded a Gold Medal. To pursue his doctoral research, he received a Bureau of Police Research and Development, Ministry of Home Affairs Fellowship. He pursued his doctoral research in Forensic Anthropology on the topic "Analysis of some genetic markers in blood and semen stains and their distribution in Indian populations."

His passion for Forensic Anthropology made him associated with the Regional Forensic Science Laboratory in Rohini, Delhi. He also completed LLB from the University of Delhi to strengthen his understanding of Forensic Science. He is widely revered as a pioneer in Forensic Anthropology, which he had been pursuing and teaching in the Department of Anthropology, University of Delhi, since 1986, when joined the Department as a lecturer.

Prof. Sachdeva started his teaching career in 1986 in the Department of Anthropology, University of Delhi. Apart from forensic anthropology, he had been teaching papers on population

genetics, serology, palaeoanthropology, biochemical genetics, human biological diversity, ethnic and cultural diversity, and Primate Biology. He supervised over 25 Ph.D. theses and numerous M.Phil and M.Sc dissertations during his career. He also led several fieldwork expeditions to places such as Daman, Sunder Nagar, and Mount Abu.

He is well known for his teaching prowess and dedication, which ensured that no students left his class without grasping what he taught. His concepts were so clear that even the then-new faculty members like Prof. Benrithung Murry and I used to consult him frequently to have clarity on certain topics. He is a person who would not venture into anything unless he knew it thoroughly. His par excellent knowledge in the field of Biological Anthropology is hard to match, which has earned him great recognition and respect in academic circles.

Besides teaching, he is a researcher of international repute. He has successfully completed several research projects funded by reputed funding agencies like DBT, DST, and UGC. Among his early major research endeavours is a government-funded project on the biogenetic aspects of Himachal populations, which he initiated in association with Prof. A.K. Kalla in the year 2004. The project greatly benefited from his expertise in various techniques like agglutination and electrophoresis through which several traditional genetic markers like blood groups, serum proteins, and red cell enzymes could be successfully typed.

He, as the principal investigator with Prof. Kalla as co-investigator, for the first time attracted funds from the Department of Biotechnology (DBT), Government of India, for a Project proposal titled "A study on the Genomic Diversity among some population groups of Andhra Pradesh" in the year 2004. Among direct achievements, this project produced two PhDs, of which one is mine, and more than 20 good publications in reputed journals like the American Journal of Physical Anthropology. He was the first one to produce a Ph.D. in DNA technology in collaboration with IGIB.

In addition to that, this project inspired several other projects on genome diversity and paved the way for the establishment of the Molecular Anthropology Laboratory in the department. From this project onwards, the DNA laboratory of the Department of Anthropology did not look back. He was one of the major pillars of the Molecular Anthropology Laboratory at Delhi University. His initiative,

along with Prof. A.K. Kalla, has led to the presently flourishing DNA Laboratory, which caters to almost 30 Ph.D. scholars.

He also ventured into clinical genetics where, as a co-investigator, he facilitated the implementation of various projects on pregnancy complications in collaboration with Dr. Manju Puri, Lady Hardinge Medical College (LHMC), Delhi. He has more than 160 research papers and two books to his credit, which speaks volumes about his extraordinary scientific output and splendid contribution to the field of biological anthropology.

Overview of the Book

The book was basically conceived to have a comprehensive understanding of genetics in Anthropology. The contributors of this book can be grouped into three broad categories: senior teachers who have worked in the field of anthropological genetics, young faculty members who have obtained Ph.D. under the noble guidance of Prof. M.P. Sachdeva, and students who have been trained in the Laboratory of Biochemical and Molecular Anthropology during their Ph.D. Though human genetics is studied by medical doctors, forensic genetics, biochemists, and life science researchers, in this book, we wanted to provide a description of genetics through the Anthropology lens.

For any student pursuing BSc or MSc in Anthropology, there was no platform that could provide a holistic approach to genetics in Anthropology. This book is a modest step towards providing a detailed description of human genetics, starting from its history to chromosomes, DNA technologies and methods, genetic epidemiology, adaptation, and genotype and phenotype interaction in understanding lifestyle diseases.

The book, in total, has 22 chapters, which have been divided in following five parts:

Part 1: Human Genetics: Concepts, Methods and Techniques
Part 2: Human Evolution: From Fossils to Genes
Part 3: Genes and Populations
Part 4: Genotype to Phenotype
Part 5: Genes and Health

Part 1 of the book develops a discussion on concepts, methods, and techniques in human genetics. The first chapter by Prof. Benrithung Murry "Milestones in Human Genetics" deals with the milestones in the history of human genetic research. The chapter discusses significant contributions to the discipline of human genetics by scientists, including Charles Darwin, Gregor Mendel, Francis Galton, and Karl Landsteiner. The chapter further elaborates on the work done in the field of human genetics since the discovery of the structure of DNA in the year 1953. The chapter concludes with an insight into the evolution of human genetics in the 21st century.

The second chapter, titled "Human Chromosome: Structure, Aberrations and Techniques "by Dr. Harpreet Kaur and Debashish Bhattacharjee, begins with a brief discussion on its discovery, followed by an elaboration on the chromosome. The chapter then proceeds to develop the discussion on the chromosome as the vehicle of inheritance, describing its cycle, size, shape, and structure. The chapter is further dedicated to the description of chromosomal banding and classification, cell division, chromosomal theory of Mendelian inheritance, non-disjunction in chromosomes, and chromosomal aberrations. This chapter also briefly touches upon concepts such as the abortion of neonates and molecular cytogenetic techniques.

Dr. Yaiphaba starts his chapter "Genetic Polymorphisms: Concepts and Techniques" with a discussion on the definition of genetic polymorphism and goes on to discuss the types of DNA polymorphisms like single nucleotide polymorphism, tandem repeat polymorphism, indel polymorphism, etc. Besides the concept of genetic polymorphism, the chapter also deals with techniques to detect DNA polymorphism, which includes polymerase chain reaction, electrophoresis, restriction fragment length polymorphism techniques, and DNA sequencing. The chapter also elaborates on classical genetic polymorphisms like blood group, ABH antigen system, MNS blood group system, HLA antigen system, haemoglobin, haptoglobin, and immunoglobulins.

The chapter "Big Science Projects for Understanding Human Genomic Variations" by Dr. Vipin Gupta and others deals with the big science projects that greatly advanced our understanding of the genome and had a significant impact on various fields like medicine, biology,

and computer science. The chapter begins with a detailed discussion of the Human Genome Project, including the goals of the project, research tools to identify genes, and the findings of the project. Apart from HGP, the chapter also discusses the Human Genome Diversity Project, the International HapMap Project, the ENCODE project, and the 1000 Genomes Project.

In the chapter "Changing Anthropological Thoughts and Methodologies in Human Genetic Research", Prof. K.N. Saraswathy reviews the evolution of aims and the scope of genetic research in the field of anthropology. She further discusses the evolution of methods with time and technology. The chapter discusses traditional as well as contemporary study designs, such as family-based study designs, twin studies, adoption studies, case studies, cross-sectional, and longitudinal studies. Towards the end of the chapter, the importance of collaborations and team building in research is highlighted through the example of the Laboratory of Biochemical and Molecular Anthropology at the University of Delhi.

The chapter, "Ethics in Anthropological Genetic Research" by Dr. Kiranmala Devi, deals with ethical issues and guidelines in genetic research. The chapter briefly describes the need for ethical guidelines against the backdrop of the eugenic movement and then goes on to discuss the core principles of ethical research. The other part of the chapter outlines some of the important ethical guidelines followed in human genetic research.

Part 2 of the book traces human evolution via fossils and genetic evidence. The chapter "Palaeogenetics and Human Evolution: An Overview" by Professor Rajan Gaur deals with genetic evidence in the field of paleoanthropology. It provides insight into human evolution and discusses paleogenetics in detail. The chapter covers the scope of paleogenomics, ancient DNA, ancient mitochondrial DNA, applications of ancient DNA, problems with ancient DNA, and ancient DNA investigation techniques in detail. Additionally, the chapter touches upon DNA studies on Indian populations, ancient DNA investigations of archaeological remains from India, and ancient DNA studies on hominin evolution.

The chapter "Human Evolution and Molecular Evidence" by Dr. Kiranmala Devi starts with a brief discussion of the concept

of evolution. The chapter discusses the fossil evidence of human evolution and the association of humans with other non-human primates, including the chimpanzee. The chapter elaborates on the relationship between humans and chimpanzees, as well as distinct genes in humans compared to chimpanzees. The chapter also discusses the genetic similarities between humans and their closest ancestors, the Neanderthals.

The chapter "Anthropological Applications of Ancient DNA: Problems and Prospects" by Dr. Sonal Jain deals with the importance of ancient DNA in the field of molecular evolutionary biology. Ancient DNA has allowed scientists to study the evolution and, in some cases, the extinction of species. The chapter elaborates on the steps in the analysis of ancient DNA, which includes experimentation material type, DNA extraction, mini barcode PCR amplification, multivariate analysis, population and sister modeling, and genotype imputation. The chapter further discusses the hurdles in the study of ancient DNA, with the most important hurdle pertaining to the extraction of ancient DNA, postmortem DNA decay, and contamination of DNA. The other part of the chapter deals with anthropological applications of ancient DNA, such as genetic sexing, understanding population continuity versus population replacement, maternal and paternal kinship, understanding human genomics, domestication, extinction, climate change, etc. The chapter also outlines the ethical concerns in ancient DNA research.

Part 3 of the book discusses the important concepts of population genetics, the importance of genetics in public health, and genetic adaptation in high-altitude populations. In his chapter "Some Aspects of Human Population Genetics", Prof. S.M.S. Chahal introduces Darwin's evolutionary theory and Mendel's principle of classical genetics as the foundation of population genetics. He discusses Mendel's law of inheritance in detail and then ventures into a discussion on genetic polymorphism, the Hardy-Weinberg equilibrium, evolutionary forces like mutation, natural selection, and genetic drift. The chapter further covers an elaborate discussion of the naturalist-selectionist controversy, the genetic structure of human populations, measures of genetic variations, measures of population differentiation, and measures of genetic similarity and distance.

In the chapter "Genetics in Public Health: Advances, Implications, and Ethical Considerations", Dr. Priyanka Rani Garg explores the role of genetics in public health. Genetics is a rapidly advancing field that has become increasingly important in public health. This chapter explores the role of genetics in public health, including the identification of genetic risk factors for common diseases, genetic testing and counselling, and the ethical, legal, and social implications of genetics in public health. Before the chapter delves into these areas, it gives a brief introduction to genetics and the historical background of genetics in public health.

Dr. Vani Kandpal, in the chapter "Tribal Health and Genetics: Indian Scenario", explores genetic diversity and resulting health consequences among Indian tribes. The chapter begins with a detailed discussion of the tribes of India, followed by a discussion on the health status of tribes. The chapter elaborates on genetic diseases among Tribals, including Hemoglobinopathies, G6PD deficiency, and multifactorial disorders. The chapter also briefly touches upon the need for genetic counselling and health awareness programmes.

Dr. Simi Khan, in the chapter "Genetics, Ethnicity, and High-Altitude Adaptations: An Overview" deals with genetic adaptations in ethnic groups inhabiting high altitude. The chapter starts with a discussion on ethnic groups residing at high altitudes. Over 81.6 million people reside at more than 2500 m, 14.4 million at more than 3500 m, and many of them also reside in regions over 4000 m. These populations range from Sherpas, Ladakhis, Andeans, Tibetans and Ethiopians and have developed adaptive mechanisms to respond to this hypoxic condition. The chapter outlines some of the genetic factors in high altitude adaptations, like ACE gene polymorphism, which is involved in the regulation of cardiovascular homeostasis. Insertion (I) allele of a 47-bp insertion-deletion (I/D) polymorphism contributes to higher resting and exercise SaO2 among Peruvian Quechua. Further, the contribution of the EGLN1 gene to adaptive response is also discussed in this chapter. Further, the chapter touches upon epigenetic modifications and the heritability of epigenetic marks, which also contribute to the adaptive process of human beings to different environmental conditions, including high altitude conditions like hypoxia.

Part 4 of the book explores the genetics of selected human traits. Dr. Gagandeep Kaur Walia in her chapter "Genetics of Anthropometric Measures" attempts to explore the genetic basis of anthropometric traits. The chapter presents a brief overview of anthropometry and anthropometric traits before delving into the genetics of these traits. Anthropometry can broadly be classified into two categories: Structural or Static anthropometry and Functional or Dynamic anthropometry. The chapter initially discusses the candidate genes associated with anthropometric traits like BMI and body fat, followed by a detailed discussion on genome-wide association studies from across the world.

In the chapter, "Sexual Dimorphism in Human Skeletal Remains: Forensic Anthropological Insights", Dr. Abhilasha Kapoor discusses the identification process from skeletal materials using methodological approaches such as morphological, metrical, and molecular techniques. This chapter presents forensic anthropological insights into methods to assess sexual dimorphism in skeletal remains, as well as reflections on the merits and demerits of these methods in assessing sexual dimorphism. The awareness and elaboration of methods are extremely important in the forensic identification of human skeletal remains. There are merits and demerits to both conventional morphometric and contemporary molecular methods of sex determination. Collectively, these methods seem to complement each other and deliver superlative outcomes for forensic, anthropological, and archaeological studies.

Prof. Indu Talwar, in her chapter "Genetics of Obesity", attempts to throw light on the basic understanding of the genetics of obesity based on the latest findings. Obesity is a complex disorder influenced by genetic, socio-cultural, behavioural, and environmental factors. The chapter starts with a brief discussion on the definitions of obesity and goes on to outline various genes that have been reported to be associated with obesity. The chapter also covers obesity-related genome-wide linkage and association studies in detail.

Part 5 of the book examines the role of genetics in a number of human health conditions. The chapter "Anthropological Genetics in Menstrual and Menopausal Milieu: Reproductive Health Issues" by Prof. Arup Ratan Bandyopadhyay deals with women's reproductive health and its anthropological significance. The chapter deals with menarche and menopause through an evolutionary lens. The chapter

discusses the effect of early or late menarche and menopause on women's health and their association with physical and mental health disorders like Alzheimer's disease, cardiovascular diseases, etc. The chapter concludes that the emphasis has to be shifted from curative medicine to preventive medicine.

In the chapter "Genetics of Male Genital Malformations" by Dr. Ratika Samtani deals with hypospadias, a complex genital malformation in male babies with both environmental and genetic factors having a strong influence on the development of the male external genitalia. Hypospadias condition hampers the health and fertility of a child and often has an adverse psychological and psychosocial effect on the families of the affected. The chapter reviews the findings of several epidemiologic studies to suggest that the coupling effect of multiple genes and environmental factors results in hypospadias. Further, the problem is likely to increase in the near future, thus, understanding the role of genetic and environmental factors in aetiology of hypospadias becomes important to reduce the burden of the disease.

In the chapter "Immune System: A Game Changer in Human Reproduction" Dr. Jyoti Mishra discusses the complex but crucial role of the immune system in successful reproduction. The chapter presents a discussion on the role that the immune system plays at various stages of reproduction, including fertilization, implantation, and pregnancy. In the female reproductive tract, substances are produced to promote the movement and survival of sperm toward the egg. After fertilization, the developing embryo must be tolerated by the immune system, which contains foreign genetic material from the father. During pregnancy, the immune system undergoes changes to tolerate foreign tissue and maintain a balance between tolerance and defence against infections. However, immune system dysfunction can lead to complications such as infertility, miscarriage, or preterm labour. The chapter briefly touches upon autoimmune disorders, which can also affect reproductive health by causing the immune system to attack the body's own tissues. The chapter concludes that understanding the complex interactions between immunology and reproduction is essential for developing effective therapies for reproductive disorders.

Dr. H. Suraj Singh, in his chapter "Genetics and Epigenetics of Alcohol Dependence", attempts to understand genetics and

epigenetic factors involved in predisposing to Alcohol Dependence (AD). AD is a complex trait with variable phenotypes in terms of both risk and adverse outcome. Both socio-cultural and biological variables govern predisposition to alcohol consumption and its adverse health effects. Therefore, the etiology of AD can effectively be explained by gene-environmental interactions, which influence gene expression substantially in large population-specific studies. The chapter concludes that a comprehensive study on genetic regulation and transcriptional factors and analysis of the network of genes and its interaction with environmental factors may contribute to the initiation and maintenance of alcohol addictive mechanism rather than emphasizing individually. Such research may also contribute to formulating effective public health policies to prevent AD and lessen the associated morbidity and mortality burden.

The chapter "Mental Health and Genes: A Review on Epigenetics of Mental Health Among Adolescents" by Dr. Shivani Chandel attempts to collate information on the epigenetics of mental health among adolescents and aims to examine the association between mental health and genes. The chapter presents a discussion on FKBP5 and SLC6A4 genes, which were found to be associated with stress-causing symptoms. Additionally, the chapter highlights that there are various genes that may contribute to mental health among adolescents. Based on the discussion, the chapter concludes that these observations have the potential to provide a framework for precision medicine that utilizes both genetic variation and phenotypic markers for early intervention and treatment.

In the chapter "Gene-environment Interactions in Cardiovascular Diseases: Special Reference to ACE and Tobacco Consumption", Dr. Rajeev Ahirwar discusses the importance of angiotensin-converting enzymes in regulating the fluid volume and influencing blood pressure. The chapter discusses that the association between these gene-environmental interactions can directly influence cardiovascular adversities. The available literature reveals that the homozygous DD genotype of ACE In/Del polymorphism, along with tobacco consumption, may result in an increased risk of cardiovascular diseases. The chapter concludes that there is a need to conduct research studies of this type for a better understanding of gene-environmental

interactions, which can be helpful in taking necessary steps at the earliest.

Overall, the present book provides a comprehensive and in-depth discussion on key topics pertaining to genetics in anthropology. This book would immensely be helpful not only to students and teachers of Genetic Anthropology but anyone who is interested in exploring anthropological approaches to human genetics. We hope to receive readers' feedback on both the content and the coverage of the topics for improving future editions.

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HUMAN EVOLUTION: FROM FOSSILS TO GENES

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GENES AND HEALTH

About the Contributors

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Genetics of Male Genital Malformation

Ratika Samtani and *Kevingan Khate*

Introduction

Hypospadias (OMIM# 146450) is one of the most common congenital anomalies occurring in 1 out of 300 to 1 out of 125 male infants in different ethnic populations (Bacchelli, 2005), and has apparently increased during the last decades. It's a defect of male external genital development in which the urethral orifice or the urethral opening is found on the ventral surface of the phallus (i.e. penis—the genital organ) rather than at the tip of the glans. It may be classified as 1st degree (anterior), 2nd degree (middle), or 3rd degree (posterior) depending on the position of the urethral meatus; 3rd degree hypospadias is the most severe and difficult to correct.

Hypospadias condition hampers the health and fertility of a child and often has an adverse psychological and psychosocial effect on the families of the affected. Uncorrected hypospadias can cause difficulties in urination, abnormal sexual function, and adverse psychological and psychosocial consequences. Acute surgical complication rates for hypospadias repair are high, and can lead to failure of the repair. Moreover, repeated surgical procedures may not yield normal function and appearance. Depending on the degree of anatomical defect, affected patients may be unable to urinate while standing and

can experience issues regarding body image, sexual intercourse, and relationships (Bhat & Mandal, 2008).

Since both environmental and genetic factors have a strong influence on the development of Hypospadias, this malformation is considered as a complex disease and ongoing investigation has implicated many factors which include testosterone biosynthesis defects, 5 alpha-reductase type 2 mutations, androgen receptor mutations, IVF (progesterone administration) or endocrine abnormalities associated with fertility and environmental agents, epigenetic mechanisms may disrupt the male hormonal axis leading to hypospadias.

Genetic Predisposition of Hypospadias

Hedgehog family genes

Hedgehog plays a pivotal role in various tissues during embryonic development, tissue homeostasis and tumorigenesis (Riobo-Del Galdo *et al.*, 2019). In mammals, Hedgehog exists in three homologs: Sonic Hedgehog (Shh), Desert hedgehog (Dhh) and Indian hedgehog (Ihh). Shh is expressed in the developing urethral plate. In mouse models, Sonic Hedgehog (Shh) has been shown to be crucial for the normal genital development (Loo *et al.*, 2021), but no Shh mutations in boys with hypospadias have been reported. Shh mutations may be lethal as in the absence of Shh signaling, Ptch1, Fgf8, Fgf10, Bmp2, Bmp4 and

Wnt5a are down regulated, and apoptosis is enhanced in genitalia. (Reynolds *et al.*, 2020) These results identify the urethral epithelium as a signaling center of the genital tubercle, and demonstrate that Shh is required for the initiation of GT outgrowth and subsequent tissue differentiation, including patterning and cell survival in the developing external genitalia.

The Gli family of transcription factors, which are targets of the Shh signal pathway, are also required for GT development (Haraguchi *et al.*, 2001). Gil2 knockout mice exhibited ventral malformations of the GT. The failure of the fetal Leydig cell differentiation provided an explanation for the hypospadiac phenotype of male Dhh knockout mice (Kojima *et al.*, 2010). Dhh (Desert hedgehog) may play a role in external genitalia formation mainly in the late hormone-independent phase (Johanssen & Svingen, 2020).

Fibroblast Growth Factor

Members of Fibroblast Growth Factor (Fgf) gene families have been suggested to regulate various epithelial-mesenchymal interactions during Genital Tubercle (GT) growth (Kojima Y *et al.*, 2009). Expression of Fibroblast Growth Factor (FGF) 8 and Bone Morphogenetic Protein 7 (Bmp7) in the developing urethra depends on Homebox genes (HOXA13), which also influences vascularization and androgen receptor expression. In addition to FGF 8, FGF 10 and FGF receptor 2 have been associated to the risk of hypospadias in humans (Morgan *et al.*, 2003). Fgf8 is expressed in the Distal Urethral Epithelium (DUE) of Genital tubercle (GT) together with other markers, such as Fgf10, Bmp4, Hoxd13 and Msx1, expressed in the mesenchyme, and augments these expressions. Haraguchi reported that the DUE of GT, the Fgf8-expressing region, regulates GT outgrowth using an *in vitro* organ culture system. (Haraguchi *et al.*, 2001) According to Beleza-Meireles *et al.*., mutations are rare but gene variants may influence the risk of hypospadias (Beleza- Meireles *et al.*, 2007).

On the other hand, Fgf10/Fgfr2IIIb signals play important roles in the developmental processes of prepuce fusion and urethral formation, but they are not essential for the early phase of GT outgrowth. According to Haraguchi *et al.*, Fgf10 knockout mice showed abnormal external genital development (Haraguchi *et al.*, 2001). Fgfr2IIIb knockout mice exhibited severe hypospadias, and failed to maintain the progenitor cell population required for uroepithelial renewal during tubular morphogenesis (Petiot *et al.*, 2005). In addition, according to Petiot *et al.*, antagonism of the androgen receptor (AR) leads to loss of fgfr2IIIb expression in the urethra, and an associated hypospadias phenotype, suggesting that this is a downstream target of AR during external genital development (Petiot *et al.*, 2005). According to Beleza-Meireles *et al.*, genetic variants in FGFR2 were also found in patients with hypospadias (Beleza- Meireles *et al.*, 2007).

***Bone Morphogenetic Protein* (*BMP*)**

The essential role of Bmp signalling in organogenesis and the coordinated action of their antagonists had been demonstrated in many

developmental processes (Wang *et al.*, 2014). Several Bmp signalling molecules were found to be dynamically expressed in and adjacent to the DUE, and to regulate various epithelial-mesenchymal interactions during GT outgrowth (Tarulli *et al.*, 2022). Bmp2 expression was localized to the urethral epithelium and proximolateral mesenchyme of the Genital Tubercle (Tarulli *et al.*, 2022).The expression of Bmp4 was detected in the mesenchyme along the urethral plate and also around the DUE. Exogenous Bmp4 down-regulated the expression of fgf8 and Wnt5a and suppressed cell proliferation. Bmp7 was expressed in the DUE and in the urethral epithelium with its expression level moderately higher in the distal and lower in the proximal regions (Tarulli *et al.*, 2022). During GT outgrowth, the expression pattern of Bmp7 in the DUE overlapped with that of fgf8 (Suzuki *et al.*, 2003), suggesting that Bmp- fgf crosstalk may function during GT outgrowth. According to Kojima Y. *et al.*, the activity of Bmp4 and Bmp7 was found to be associated with the developmentally regulated onset of apoptosis and the output of Bmp signalling affected GT outgrowth through a mechanism including apoptosis (Kojima *et al.*, 2010). These findings suggest that some Bmp genes could negatively affect proximodistally oriented GT outgrowth with regulatory functions in cell proliferation and apoptosis. Chen *et al.*, reported nucleotide sequence variations in BMP4 and BMP7 among Hypospadias patients (Suzuki *et al.*, 2003).

HOX Genes

According to Morgan *et al.* (2003), Home box genes HOXA and HOXD are mainly involved in the development of urogenital structures, and genetic defects in them lead to agenesis or malformations of genitalia. Hoxa13 and Hoxd13 are expressed in the mesenchyme of the GT.In Hoxa13 knockout mice, hypospadias occurred as a result of the combined loss of Fgf8 and Bmp7 expression in the urethral plate epithelium, as well as the ectopic expression of noggin in the flanking mesenchyme. Shaut *et al.*, reported that Hoxa13 knockout mice also exhibited changes in AR expression, providing a developmental link between Hoxa13-associated hypospadias and that produced by antagonists to androgen signaling (Shaut *et al.*, 2007). Hoxd13/

Hoxd13 double knockout mice failed to develop a GT or cloaca (Klonisch *et al.*, 2004). These results suggest that Hox genes play a role in the requirement of the coordinated control of GT outgrowth in the early hormone–independent phase and urethral fusion in the late hormone–dependent sexual differentiation phase. Recent genome wide analysis study depicted an increased expression of HOX A4 in hypospadias (Geller *et al.*, 2014).

WNT/β-catenin

According to Kojima, Y. *et al.*, the Wnt family can be classified into two subfamilies: the Wnt 1 class, which activates the canonical WNT/β-catenin pathway, and the Wnt5a class, which activates the non-canonical Wnt pathway (Kojima *et al.*, 2010). According to Yamaguchi *et al.*, Wnt5a knockout mice showed an absence of GT (Yamaguchi *et al.*, 1999). Lin *et al.*, reported that Wnt/β-catenin signaling is required in the endodermal urethra to activate and maintain Fgf8 expression and direct GT outgrowth, as well as to maintain homoestasis of the urethra (Lin *et al.*, 2008). Moreover, it was observed that β-catenin is required not only in the mesenchyme to promote cell proliferation, but also in the ectoderm to maintain tissue integrity, possibly through cell-cell adhesion during GT outgrowth. In addition, β-catenin knockout animals developed severe hypospadias (Lin *et al.*, 2008). Recent reports have shown that Wnt/β-catenin signaling pathway is necessary for orchestrated genital development and masculinization of the external genitalia (Geller *et al.*, 2014).

Androgen- Related Genes

Androgens have been thought to play a central role in male external genital development. Welsh *et al.*, showed that androgen-driven masculinization is programmed by androgen action earlier in fetal life (10-14 gestational weeks) before morphological differentiation occurs, and deficient androgen action with this programming window can induce Hypospadias (Welsh *et al.*, 2008).

According to Kojima, Y. *et al.*, several androgens related genes such as AR, SRD5A2, HSD17B3, FKBP52, MAMLD1/CXorf6, are associated with the regulation of external genitalia formation and become causative or risk factors for Hypospadias (Kojima *et al.*, 2009).

Androgen Receptor Gene

Mutations in the androgen receptor gene are carried by subset of patients with genital ambiguity presenting primarily with Hypospadias. However, according to Sutherland *et al.*, though Androgen receptor gene mutations are found in certain isolated cases of distal shaft hypospadias, these mutations however appear to be a rare cause (Sutherland *et al.*, 1996).

Steroid 5 Alpha Reductase Type 2 Gene

Normal growth and function of the external genitalia are contingent on the reduction of Testosterone (T) to Dihydrotestosterone (DHT) by 5 alpha reductase. 5 alpha reductase deficiency is an uncommon autosomal recessive disorder resulting from impaired conversion of T to DHT due to mutations in 5 alpha reductase type 2 gene (SRD5A2). Silver and Russell, reported three mutations (L113V, H231R, A49T), of which A49T was observed to be present in less severe forms of hypospadias (Silver & Russell, 1999).Thai *et al.*, also reported that the V89 allele of the SRD5A2 gene in the homozygous form reduces the risk of mild and severe Hypospadias (Thai *et al.*, 2005). Studies on candidate gene, SRD5A2, have evidenced that polymorphisms in these genes may individually increase the risk to hypospadias. According to Xu *et al.*, Exon-4 is a hot spot region of mutation within SRD5A2 gene resulting in about 10 per cent of hypospadiac patients complicated with SRD5A2 dysfunction or deficiency (Xu *et al.*, 2019).

17B Hydroxysteroid Dehydrogenase Type 3 (HSD17B3 Gene)

This enzyme catalysing the conversion of Androstenedione to Testosterone is also required to produce testosterone for male sex differentiation. Sata *et al.*, reported HSD17B3 G289S polymorphism to be a potential risk modifier of Hypospadias among Japanese cases, thereby suggesting that a certain genotype related to androgen production may potentiate the risk of Hypospadias (Sata *et al.*, 2010).

FKBP52

According to Beleza-Meireles, a co-chaperone of the AR gene, FKBP52, is likely to play a role in the growth and development of male

genitalia since it is expressed in the genital skin of prepubertal boys; however, alterations in the sequence and expression of the FKBP52 gene are not a common cause of isolated hypospadias (Beleza-Meireles *et al.*, 2007).

MAMLD1 (Or CXorf6)

Mutations in chromosome X open reading frame 6 (CXorf6), a recently described candidate gene involved in the development of male genitalia, have been found in patients with complex 46, XY disorders of sexual development (46, XY DSD) including micropenis, bifid scrotum, and penoscrotal hypospadias (Kalfa *et al.*, 2008). The underlying mechanism may involve disruption of androgen production, because the gene affects hormone synthesis and has the SF1 target sequence (Val *et al.*, 2003). Although MAMLD1 mutations are rare in patients with hypospadias, the gene may be involved in the cascade of events leading to this disorder (Fluck *et al.*, 2019).

Estrogen-Related Genes

Although male external genitalia formulation is mediated by androgens, estrogen can modify these androgen effects. According to Staib *et al.*, elevated estrogen formation in male genital tissue might be a causative or risk factor for hypospadias (Staib *et al.*, 1994). There is an increased risk of hypospadias in the sons of women exposed to diethylstilbestrol, a potent synthetic estrogen, in utero. Estrogen receptors (ERs) and the estrogen-responsive gene (ATF) could also be risk factors for Hypospadias.

Estrogen Receptors

ER alpha and beta are differentially distributed and activated in mouse fetal Genital tubercle (GT) (Agras *et al.*, 2007). Genetic polymorphisms of ESR1 and ESR2 may influence estrogen activity and the risk of hypospadias. Studies have reported that the G allele containing variants of ER alpha (*ESR1*) XbaI and the G allele containing variants of ER beta (*ESR2*) 2681-4A>G may decrease the risk of hypospadias, whereas the *ESRI C-A* haplotype may increase the risk.

Activating transcription factor (ATF) 3

Wang *et al.*. performed microarray analysis on tissue from patients with and without hypospadias and found significant differences in gene expression, specifically with a group of genes, including *ATF3, CYR61, CTGF and GADDD45*, known to be responsive to estrogen or to interact with ER (Wang *et al.*, 2007).

ATF3 is an estrogen-responsive gene and it is involved in TGF-beta signaling, offering a plausible hypothesis how estrogens might bring about hypospadias (Liu *et al.*, 2006). In addition to ATF3, any of the above mentioned genes may also be targets of environmental endocrine disruptors that can disturb their regulation at critical windows of their expression. ATF3 was suspected to be linked to hypospadias, because it was up-regulated in the foreskin samples in 86% of patients operated on for hypospadias, whereas in samples from circumcision patients it was up only in 13%. Estradiol up regulates ATF3 expression in the foreskin *in vitro* and *in vivo*. Recently, two groups reported that genetic variants of ATF3 are associated with some patients with hypospadias. Beleza-Meireles *et al.*, reported three single nucleotide polymorphisms (SNPs) in the ATF3 sequence, spanning a region of about 16kb in intron 1, which affects the risk for hypospadias (Beleza-Meireles *et al.*, 2007). Additionally, a missense mutation in exon 3 and a sequence variant in the 3'-UTR region of this gene were found to be present in three non-related boys with hypospadias. Kalfa *et al.*, reported that genetic variants of ATF3, including a missense variant (L23M) or three genetic variants (C53070T, C53632A, Ins53943A), was found in 10% of patients with hypospadias, however, none of these genomic variants were observed in control patients with hypospadias (Kalfa *et al.*, 2008). According to the same author, ATF3 was found to be overexpressed in the urethral plate and subcutaneous tissue, especially around the ectopic orifice of the urethra of human fetuses with hypospadias, although it was not found to be expressed in and around the urethra in normal fetuses.

Environmental Risk Factors

Recent findings indicated low birth weight, being a twin or a triplet, mother being a diethylstilbestrol-daughter, fertility treatments,

paternal sub-fertility, obesity, prescriptive drug use, familial occurrence of hypospadias and testicular cancer to be associated with hypospadias. Several studies have observed that male infants with Hypospadias have lower birth weight, shorter length of gestation and/or evidence of growth retardation in utero (Chen *et al.*, 2014).

On maternal and perinatal data of hypospadias in a 25- year period by Zalabardo *et al.*, also suggested low birth weight, intrauterine growth restriction and preterm births to be associated with Hypospadias (Zalabardo *et al.*, 2004). Up to a 10-fold increase of Hypospadias has been reported in infants small for gestational age (Pinborg *et al.*, 2004). The decrease in some growth parameters including birth weight and duration of gestation in hypospadias infants suggested that the primary cause occurs early, during the first trimester of pregnancy. Therefore, poor intrauterine growth is indicated as risk factor for Hypospadias (Chen *et al.*, 2014). However, it is still elusive to date whether growth retardation in itself has an impact on the formation of urethra, or if other environmental factors that influence the intrauterine growth and morphogenesis of the urogenital tract are considered to be the cause.

One hypothesis is that disturbance of placental function early in pregnancy is a key mechanism underlying both low birth weight and the improper closure of the urethra, since the placenta is involved in the differentiation and development of the fetal organs in this period. According to several authors, reported associations between Hypospadias and low birth weight, preterm birth and signs of preeclampsia indicate that placental malfunction and subsequent abnormalities in hormone regulation and/or the provision of the nutrients to the fetus may play a role in the maldevelopment of the urethra (Brnataester *et al.*, 2014).

Maternal Risk Factors

Advanced maternal age was found to be associated with increased severity of hypospadias (Carlson *et al.*, 2009). Maternal risk factors for Hypospadias include maternal history of spontaneous, threatened abortions in the first or second trimester, maternal common cold accompanied fever in the first trimester, maternal drug exposure during the second trimester, paternal occupational exposure to pesticides and neonatal low birth weight.

Several authors have suggested that Hypospadias may be caused by abnormal levels of pregnancy hormones resulting from impaired placental function or exposure to disruptive exogenous hormones (Akre *et al.*, 2008). Iron supplementation in mothers immediately prior to contraception and/or during the first trimester of gestation has also been suggested as a risk factor for Hypospadias (Nazmy *et al.*, 2008). A possible explanation is that this supplementation may increase the blood viscosity which subsequently impairs placental blood flow and then results in malfunction of the placenta, leading to both low birth weight and Hypospadias. As suggested by Skakkebaek *et al.*, because Hypospadias and male sub-fertility may share the same embryonic origin with genetic and environmental components, the affected fathers may transmit a certain predisposition to their sons (Skakkebaek *et al.*, 2001).

Vegetarian Diet

According to Akre *et al.*, a pregnancy diet devoid of meat and fish is an independent risk factor for Hypospadias (Akre *et al.*, 2008). It has been previously suggested that the risk of genital anomalies in male offspring may be increased by intake of different soy proteins frequently ingested by vegetarians. It has also been suggested that phytoestrogens from soybeans disrupt the masculinization of the male through interference with the pituitary-gonadal axis.

In-Vitro Fertilization

Many studies have suggested an increased risk for Hypospadias following in-vitro fertilization and intra-cytoplasmic sperm injection. According to Silver *et al.*, this may be explained by the high doses of gestagens interfering with androgen production in the male fetus (Silver *et al.*, 1999). In other words, hormone administration as part of pregnancy support interferes with androgen production in early gestation and thereby disturbs normal genital development.

Role of Endocrine Disrupting Chemicals

According to White *et al.*, prenatal exposure to heavy metal hazardous air pollutants (HMHAPs) is associated with an increased risk of

hypospadias. Haraux *et al.*, suggest that maternal occupational exposure to EDCs is a risk factor for hypospadias and suggests a possible influence of household use of hair cosmetics during early pregnancy on the incidence of hypospadias in the offspring (Haraux *et al.*, 2017). According to Winston *et al.*, a possible association between atrazine and hypospadias occurrence was observed (Winston *et al.*, 2016). In a meta-analysis of nine studies assessing the relationship between pesticide exposure and hypospadias, elevated but marginally significant risks were associated with maternal occupational exposure (pooled risk ratio [PRR] of 1.36, CI 1.04–1.77) and paternal occupational exposure (PRR of 1.19, CI 1.00–1.41) (Rocheleau *et al.*, 2009). Fungicides vinclozolin and procymidone and DDE, the persistent congener of estrogenic DDT were observed to act as androgen receptor antagonists, while some phthalate esters, such as dibutyl phthalate and diethyl hexyl phthalate, disturb androgen biosynthesis. Poon *et al.*, suggested that level of exposure to PBDEs during gestation may have a role in the etiology of hypospadias (Poon *et al.*, 2018). Some PBDE metabolites were observed to induce aromatase activity in cell cultures from human adrenocortical carcinoma (Stapleton *et al.*, 2009). Giordano F. *et al.*, provides evidence of an association between maternal exposures to Endocrine disrupting chemicals, in particular elevated plasma hexachlorobenzene concentration and the development of Hypospadias in the offspring (Giordano F. *et al.*, 2010). Nassar *et al.*, provided evidence of an association between maternal exposure to EDCs with oestrogenic or anti-androgenic properties and increased risk of hypospadias (Nassar *et al.*, 2010).

Epigenetic Approach to Investigate Hypospadias

The term epigenetics refers to the overall molecular phenomenon which is inherited from parents to offspring and that regulates gene expression without any alteration of the genomic DNA sequence. Since certain endogenous or exogenous factors such as hormone levels, diet and exposure to chemical substances can cause epigenetic alterations, particularly maternal exposure during fetal development, it is likely that epigenetic alterations are involved in the etiology of hypospadias. Vottero *et al.* found increased DNA methylation of the AR gene in foreskin from children with hypospadias, resulting in

decreased expression of AR (Vottero *et al.*, 2011). Wu *et al.*, analysed that mice fetal testis exposed to diethylhexyl phthalate had 10% relative increase in global DNA methylation as well as increased DNA methyltransferase expression (Wu *et al.*, 2009).Choudhry *et al.*, suggested that DNA methylation patterns are useful in identifying new genes such as SCARB1 and MYBPH that may be involved in the etiology of hypospadias (Choudhry *et al.*, 2012).

Perspective

Improvement in hypospadias surgery and assisted reproductive technologies over the last 50 years has led to improved reproductive performance of Hypospadias cases. However, several epidemiologic studies have suggested various genetic, epigenetic and environmental risk factors as a possible cause for the observed increased incidence of Hypospadias. Uncorrected hypospadias can cause difficulties in urination, abnormal sexual function, and adverse psychological and psychosocial consequences. Studies have pointed out that people who have hypospadias treated are twice as likely to have problems with their lower urinary tract. These problems can last for years after the initial repair (Halaseh *et al.*, 2022).

Since ambiguity of the genitalia is a sensitive topic of discussion, its information in many communities across the world is often kept a secret within families. Awareness among the general public and management strategies need to be devised and implemented by the health planners in order to curb this disorder which is on a rise worldwide.

To conclude, with the advancements in surgical techniques in treatment for hypospadias, the problem is mended to give a normal life to the patient, however, the coupling effect of multiple genes and environmental factors results in hypospadias, the load shall increase in the populations through subsequent generations. In days to come, the problem is likely to increase and thus by knowing its genetic/environmental/epigenetic role one can pilot to counselling and controlling the propagation of the disorder.

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