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UNIVERSIDADE ESTADUAL PAULISTA

“JÚLIO DE MESQUITA FILHO”

INSTITUTO DE BIOCÊNCIAS DE BOTUCATU – IBB

Programa de Pós-Graduação em Ciências Biológicas (GENÉTICA)



**Development and implementation of new reference panels for
HLA imputation from different populations to accelerate
immunogenetic association studies**

NAYANE DOS SANTOS BRITO SILVA

Botucatu, 2024



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Nayane dos Santos Brito Silva

**Development and implementation of new reference panels for
HLA imputation from different populations to accelerate
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Orientadores: Dr. Erick C. Castelli & Dr. Nicolas Vince

Tese apresentada ao Instituto de Biociências,
Universidade Estadual Paulista “Júlio de
Mesquita Filho”, *Campus* de Botucatu, para
obtenção do título de Doutora pelo Programa
de Pós-Graduação em Ciências Biológicas
(Genética).

FICHA CATALOGRÁFICA ELABORADA PELA SEÇÃO TÉC. AQUIS. TRATAMENTO DA INFORM.
DIVISÃO TÉCNICA DE BIBLIOTECA E DOCUMENTAÇÃO - CÂMPUS DE BOTUCATU - UNESP

BIBLIOTECÁRIA RESPONSÁVEL: MARIA CAROLINA A. CRUZ E SANTOS-CRB 8/10188

Silva, Nayane dos Santos Brito.

Development and implementation of new reference panels for HLA imputation from different populations to accelerate immunogenetic association studies / Nayane dos Santos Brito Silva. - Botucatu; Nantes, 2024

Tese (doutorado) - Universidade Estadual Paulista (UNESP), Instituto de Biociências, Botucatu. Nantes Université.

Orientador: Erick da Cruz Castelli

Coorientação: Nicolas Vince

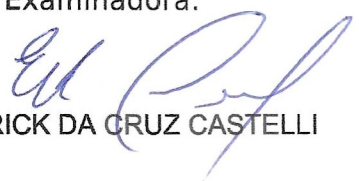
Capes: 20200005

1. HLA Antigenes. 2. Immunogenetics. 3. HLA histocompatibility antigens.

Palavras-chave: HLA; Immunogenetics; Imputation HLA; SHLARC.

ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE NAYANE DOS SANTOS BRITO SILVA, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS (GENÉTICA), DO INSTITUTO DE BIOCIÊNCIAS - CÂMPUS DE BOTUCATU.

Aos 12 dias do mês de dezembro do ano de 2024, às 9h, no(a) Anfiteatro da pós-graduação - Central de Aulas 2, realizou-se a defesa de TESE DE DOUTORADO de NAYANE DOS SANTOS BRITO SILVA, intitulada **Development and implementation of new reference panels for HLA imputation from different populations to accelerate immunogenetic association studies**. A Comissão Examinadora foi constituída pelos seguintes membros: Prof. Dr. ERICK DA CRUZ CASTELLI (Orientador(a) - Participação Presencial) do(a) Departamento de Patologia / Faculdade de Medicina de Botucatu Unesp, PhD NICOLAS VINCE (Participação Presencial) do(a) Center for Research in Transplantation and Translational Immunology / Nantes Université, Prof. Dr. LUÍS CRISTÓVÃO DE MORAES SOBRINO PÔRTO (Participação Virtual) do(a) Núcleo tecnológico em Reparo Tecidular e Histocompatibilidade / Universidade do Estado do Rio de Janeiro, PhD ANNE-LOUISE LEUTENEGGER (Participação Presencial) do(a) Departament of NeuroDiderot / Université Paris Cité, PhD FRANÇOIS CORNELIS (Participação Presencial) do(a) Departmant of Medical Genetics / Université Clermont Auvergne, Pesquisador Sênior KELLY NUNES (Participação Virtual) do(a) Departamento de Genética e Biologia Evolutiva / Universidade de São Paulo - USP, PhD SOPHIE LIMOU (Participação Virtual) do(a) Center for Research in Transplantation and Translational Immunology (CR2TI), UMR 1064, Inserm / Centrale Nantes, Nantes Université, Prof. Dr. EDUARDO ANTÔNIO DONADI (Participação Virtual) do(a) Departamento de Clínica Médica / Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo - USP. Após a exposição pela doutoranda e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, a discente recebeu o conceito final: APROVADA . Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.



Prof. Dr. ERICK DA CRUZ CASTELLI

“And once the storm is over, you won’t remember how you made it through. But one thing is certain. When you come out of the storm, you won’t be the same person who walked in.”

Haruki Murakami

ACKNOWLEDGMENTS

Since the beginning of this PhD journey, every moment of learning, overcoming challenges, and discovery has been illuminated by the support of special people. This work represents more than results; it is the result of countless contributions, inspirations, and the generous support of those who walked with me.

To my Brazilian supervisor, Dr. Erick Castelli, thank you for your excellent guidance, for your dedication in teaching and sharing your knowledge, and for all the opportunities you provided throughout my PhD. I am deeply grateful for your attention and patience.

I would also like to express my gratitude to the entire GemBio team: Viviane Ciriaco, Heloisa Andrade, Joyce Machado, Ingrid Miranda, Gabi Sato, Rapha Pereira Neto, Isa Mira, Prof. Camila, Icaro Scalisse, João Tolo, Marcel Ferreira, Lívia Ramos, and Luciana Borali. More than just colleagues, you have been true friends during every step of this journey. Thank you for all the shared moments—I will carry you all in my heart always.

À tous ceux que j'ai rencontrés en France et qui, d'une manière ou d'une autre, ont fait partie de ce magnifique séjour, m'apportant de nombreux apprentissages, tant personnels que professionnels. Ce fut une période incroyable que j'ai eu la chance de vivre aux côtés de personnes formidables, et qui m'a transformée pour le mieux.

To my French supervisor, Dr. Nicolas Vince, thank you for your trust and patience. I am deeply grateful for all the opportunities you provided throughout my PhD. Your guidance and inspiration have been invaluable in shaping my academic journey and personal growth.

To the entire 3 iTHINK team, especially the Bioinformatics group: Sonia Bourguiba-Hachemi, Venceslas Douillard, Olivia Rousseau, Julien Paris, Mitra Barzine, Morgane Gélin, Prof. Pierre-Antoine Gourraud, Afaf Tissafi, Nathalie Bouatlaoui, Mélissa Menga, Ketsia Mortant,

Mohamed Benzahi, Agathe Bugnon, Martin Morin, Vincent Mauduit, Simon Brocard, Stanislas Demuth, Killian Maudet, Adrian Lapoutge, Lisa Thiébaut, Axelle Durand, Irène Charles, Léo Boussamet, Mame Fatou, Rafaela Miranda, Assane Sylla, Alice Clément, and Romain Gautier, who were part of this journey and brought me so much learning. Thank you all so much!

A special thanks to Venceslas Douillard for all the support you gave me throughout my PhD and for teaching me everything about imputation. Thank you for keeping in touch and for your friendship.

I am also deeply grateful to the group leader, Prof. Sophie Limou, for always being available, for your valuable advice, and for making me feel welcome in the team from day one.

A heartfelt thank you to Sonia Bourguiba-Hachemi, who welcomed me and helped me with everything I needed. Your presence made all the difference, not only professionally but also personally. I love you, and I will carry you in my heart with great affection. I am grateful for all the moments we shared, and the lessons I learned from you.

To my dear friends, Igor Faddeenkov and Marielle Oloude, who brightened my days inside and outside the lab. Thank you for your support, kindness, and friendship. You made my days so much happier—thank you for the lunches, the conversations, and for simply being there. Your companionship has meant more to me than words can express. Thank you very much!

Thanks to the CR2TI and the Graduate Program in Genetics at the Institute of Biosciences of Botucatu (IBB-UNESP) for their support, and collaboration, and for providing the academic foundation and opportunities that made this work possible.

I would like to thank the São Paulo Research Foundation (FAPESP) – Process number 2021/02815-8, as well as the Pays de la Loire region and ANR PIA-Investment NEXt for their financial support, which made this research possible.

I would also like to thank the members of my French thesis advisory committee — Dr. Diogo Meyer and Dr. Sigrid Leclerc — for following the progress of my thesis over these three years. Additionally, I extend my gratitude to Dr. Robson Carvalho, Dr. Kelly Nunes, and Dr. Celso Teixeira Mendes Junior for their valuable contributions during my Brazilian qualifying exam.

My sincere gratitude to the members of my thesis jury — Dr. Anne-Louise Leutenegger, Prof. Luis Cristóvão Porto, Dr. Kelly Nunes, Prof. François Cornelis, Prof. Sophie Limou, and Prof. Eduardo Donadi — for accepting the invitation and making themselves available to contribute to my education and to the improvement of this work. A special thank you to Anne-Louise and Luis Cristóvão for being the reviewers of this thesis.

To the Maison des Chercheurs Étrangers à Nantes, especially Nathalie Henry and Soline Puente Rodriguez, thank you for your warm welcome and support. I am grateful for all the joyful moments you gave us. With you, I experienced some of the best times of my stay in Nantes and made lifelong friends I could not have hoped for.

To my dear friends Alejandra Valasquez, Juan Gonzalez, Bruno Storti, Florência Ferrero, Mosbah Kiwan, Mansoor Chaaban, Adilson Roberto, Laura, Aravind Vel, Laura Lenglin, and Gabriel Ladera, thank you for all the laughter and the incredible moments we shared together. You certainly made my time in Nantes much lighter. Thank you for everything, my friends. Your friendship is something we will cherish for a lifetime.

À minha família, meu sincero agradecimento por todo o amor, apoio e incentivo incondicional. A presença constante de vocês, mesmo à distância, me deu forças para seguir em frente. Cada conquista que celebro hoje é, também, de vocês.

To the most important person in the world to me—my love, husband, and best friend, Leonardo Menezes—who has always been by my side, supporting and encouraging me. Thank

you for being with me throughout this entire journey, for your unconditional support, for giving me strength, for encouraging me, and for believing in me. With you, everything became easier. I love you forever and one more day.

In each challenge faced, I found strength in the words of encouragement and supportive gestures from those around me. To everyone who was present at some point, directly or indirectly, I express my sincere gratitude. May this achievement also be a tribute to the collaboration and trust I received along this journey.

LIST OF ABBREVIATIONS AND ACRONYMS

1KG	1,000 Genomes
AFR	African
AMR	American
APCs	Professional antigen-presenting cells
AS	Ankylosing spondylitis
B2M	β 2-microglobulin
BAM	Binary alignment map
BiP	Binding immunoglobulin protein
BWA	Burrows-Wheeler Aligner
CDS	Coding sequence
CIWD	Common, Intermediate, and Well-Documented
CLIP	Class II-association Invariant chain Peptide
CNV	Copy number variation
CPU	Central Processing Units
ddNTPs	Dideoxynucleotides
DNA	Deoxyribonucleic acid
EAS	East Asian
EM	Expectation-Maximization
ER	Endoplasmic reticulum
ERp57	Endoplasmic reticulum resident protein 57
EUR	European
GATK	Genome Analysis Toolkit
GPU	Graphics Processing Units
GWAS	Genome-wide association study
hg19	Homo sapiens (human) genome assembly GRCh19
hg38	Homo sapiens (human) genome assembly GRCh38

HGDP-CEPH	Human genome diversity project
HIGAB	HLA Imputation using Attribute Bagging
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
Ig	Immunoglobulin
IHWS	International HLA & Immunogenetics Workshop
ILT2	Immunoglobulin-like transcript 2
ILT4	Immunoglobulin-like transcript 4
IMGT/HLA	IMmunoGeneTics/HLA
Indels	insertions and/or deletions
IPD	Immune Polymorphism Database
KIR	Killer-cell Immunoglobulin-like Receptors
LD	linkage disequilibrium
Ii	Invariant chain
MHC	Major Histocompatibility Complex
MICA/B	MHC class I polypeptide related sequence A/B
MIIC	MHC class II compartments
NAM	Native Americans
NGS	Next-Generation Sequencing
NK	Natural Killer
PCR	Polymerase chain reaction
PCR-SSO	PCR with sequence-specific oligonucleotide
PCR-SSP	PCR with sequence-specific primers
PRGs	Population reference graphs
SABE	Saúde, Bem Estar e Envelhecimento – Health, Well-Being, and Aging
SAM	Sequence alignment map
SAS	South Asian

SBT	Sanger sequencing-based typing
SHLARC	SNP-HLA Reference Consortium
SNP	Single nucleotide polymorphisms
TAP1/2	Transporter associated with antigen processing ½
UTR	Untranslated region
VCF	Variant calling format
VQSR	Variant Quality Score Recalibration
WES	Whole-exome sequencing
WGS	Whole-genome sequencing
WTCCC	Wellcome Trust Case Control Consortium

ABSTRACT

The Human Leukocyte Antigen (*HLA*) genes within the Major Histocompatibility Complex (*MHC*) region encode essential molecules for immune system activation. These molecules are involved in the antigen presentation pathway, presenting both self and non-self antigens. *HLA* gene polymorphisms are associated with many diseases and influence transplant outcomes. The analysis of *HLA* genes from second-generation sequencing data (also known as NGS) requires specialized tools to avoid alignment and genotyping errors. In this study, we applied the hla-mapper pipeline to call SNPs and haplotypes within *HLA* genes in different worldwide populations, including over 1,000 samples from Brazil. This methodology effectively analyzed *HLA* genetic diversity at multiple levels, encompassing SNPs, InDels, haplotypes, and alleles with 2- to 4-field resolution, as we demonstrated for the *HLA-B* gene (the most polymorphic *HLA* gene). After, within the SNP-*HLA* Reference Consortium (SHLARC) framework, we used the data obtained in the previous step to create and test *HLA* imputation models. These models were validated using an independent Brazilian sample and cross-validated within the reference panel by performing repetitive subsampling. The best results for imputation were obtained using the full reference panel, i.e., when we pooled together all samples (including Brazilians) in a single reference panel, highlighting the importance of including admixed samples in multiethnic panels. Moreover, our imputation accuracy outperformed those obtained with the Michigan Imputation Server, a widely used imputation platform for *HLA* genes, validating the effectiveness of our method. The findings of this work represent a significant contribution to understanding the genetic diversity of *HLA* genes and improving imputation techniques.

Keywords: *HLA*, Imputation *HLA*, SHLARC, Immunogenetics

RESUMO

Os genes *HLA* (Human Leukocyte Antigen) na região do Complexo Principal de Histocompatibilidade (*MHC*) codificam moléculas essenciais para a ativação do sistema imunológico. Essas moléculas estão envolvidas na via de apresentação de antígenos, apresentando tanto antígenos próprios quanto não próprios aos linfócitos T. Os polimorfismos dos genes *HLA* estão associados a diversas doenças e influenciam os resultados de transplantes. A análise dos genes *HLA* a partir de dados de sequenciamento de segunda geração (também conhecido como NGS) requer ferramentas especializadas para evitar erros de alinhamento e genotipagem. Neste estudo, aplicamos o programa hla-mapper para identificar SNPs e haplótipos dentro dos genes *HLA* em diferentes populações mundiais, incluindo mais de 1.000 amostras do Brasil. Essa metodologia analisou de forma eficaz a diversidade genética dos genes *HLA* em vários níveis, abrangendo SNPs, InDels, haplótipos e alelos com resolução de 2 a 4 campos, como demonstramos para o gene *HLA-B* (o gene *HLA* mais polimórfico). Posteriormente, no âmbito do SNP-*HLA* Reference Consortium (SHLARC), utilizamos os dados obtidos na etapa anterior para criar e testar modelos de imputação de *HLA*. Esses modelos foram validados usando uma amostra brasileira independente e validados de forma cruzada dentro do painel de referência, por meio de subamostragens repetidas. Os melhores resultados de imputação foram obtidos utilizando o painel de referência completo, ou seja, quando agrupamos todas as amostras (incluindo as brasileiras) em um único painel de referência, destacando a importância de incluir amostras miscigenadas em painéis multiétnicos. Além disso, nossa precisão de imputação superou os resultados obtidos com o Michigan Imputation Server, uma plataforma amplamente utilizada para imputação de genes *HLA*, validando a eficácia do nosso método. As descobertas deste trabalho representam uma contribuição significativa para a compreensão da diversidade genética dos genes *HLA* e para o aprimoramento de técnicas de imputação.

Palavras-chave: HLA, Imputação de HLA, SHLARC, Imunogenética

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1. INTRODUCTION TO THE MAJOR HISTOCOMPATIBILITY COMPLEX

The discovery of the Major Histocompatibility Complex (MHC) and the research that followed has significantly shaped our understanding of immunology, disease susceptibility, and transplantation biology. The first studies date back to the early 20th century, with initial research carried out through transplantation experiments in animals. Clarence Little was one of the pioneers, demonstrating that susceptibility and resistance to transplants were influenced by multiple genes with Mendelian inheritance(1). In the 1930s, Peter Gorer identified antigen II (later known as H-2) in mice and discovered that these antigens were associated with the rejection of tumor grafts. He introduced the concept that specific antigens determined the immune response to transplanted tissues(2). Later, Snell selectively bred two mouse strains, achieving a new strain nearly identical to one of the progenitor strains but differing in histocompatibility, which allowed for the genetic mapping of loci associated with graft rejection(3). His collaboration with Peter Gorer confirmed that the H-2 locus identified by both was the same, demonstrating the dominant influence of H-2 on graft survival(4). This H-2 locus was later proved to be very complex through many genes specifying many antigens, and it has since become established as the principal histocompatibility locus in mice—that is, central to understanding immune response and rejection of transplants(4,5).

The term MHC was adopted in the early 70s after researchers discovered that systems genetically homologous to H-2 were found in many other vertebrates(5). Since then, there have been significant advances in understanding the structure and function of MHC molecules. *MHC* genes, present in all mammals, are crucial in the immune response, especially adaptive immunity. They influence the ability to distinguish between self and non-self, as well as the susceptibility to autoimmune, infectious, neoplastic diseases(6), and their subsequent progression.

In humans, the *MHC* is located on the short arm of chromosome 6 at position 6p21.3, covering about 4Mb and containing around 250 genes, most of which regulate immune responses(7). The *MHC* region is considered the most gene-dense region of the human genome, with an average of 1 gene every 16Kb(8), containing 1% of the human coding genes within just 0.1% of the genome's length(9). It consists of highly polymorphic blocks originated through duplications, deletions, and various genomic recombination events during the evolution of

mammals and primates(10). The MHC is the most variable region in the human genome, mainly because of the high diversity of a specific group of genes known as Human Leukocyte Antigens (*HLA*) genes(11).

The *MHC* is divided into three regions or classes: classes I, II, and III(7) (Figure 1). Focusing on the immune-related genes, the class I and II regions comprise the *HLA* system, with genes encoding membrane glycoproteins responsible for presenting protein antigens(12). The class I region also harbors the *MIC* (MHC class I chain-related genes) genes, whose products modulate the Natural Killer (NK) cell activity by interacting with NKG2D receptors in cells upon stress(13). In the class II region, *TAP1* and *TAP2* form heterodimers that are associated with the transport and processing of peptides from class I HLA molecules(14). The class III region, located between class I and II, does not encode molecules involved in antigen presentation but has other essential components of the immune system, such as proteins of the complement system (e.g., C2 and C4), hormones, and cytokines (e.g., Tumor Necrosis Factor, Lymphotoxin alpha and beta)(7,12).

The extensive variability and gene density of the *MHC* highlights its evolutionary importance and essential role in both innate and adaptive immunity(12,14). This variability has clinical significance in transplantation and autoimmune diseases(6). Advances in molecular biology have helped researchers better understand the complex interactions between MHC molecules and immune cells, which are essential for distinguishing between self and non-self, a key in the development of many diseases(9). *HLA* typing is a standard procedure for organ and bone marrow transplants, significantly impacting the transplant success rates(15). Therefore, the intricate genetic organization and polymorphism of the *MHC*, especially the *HLA* genes, underscore its vital role in modulating immune responses.

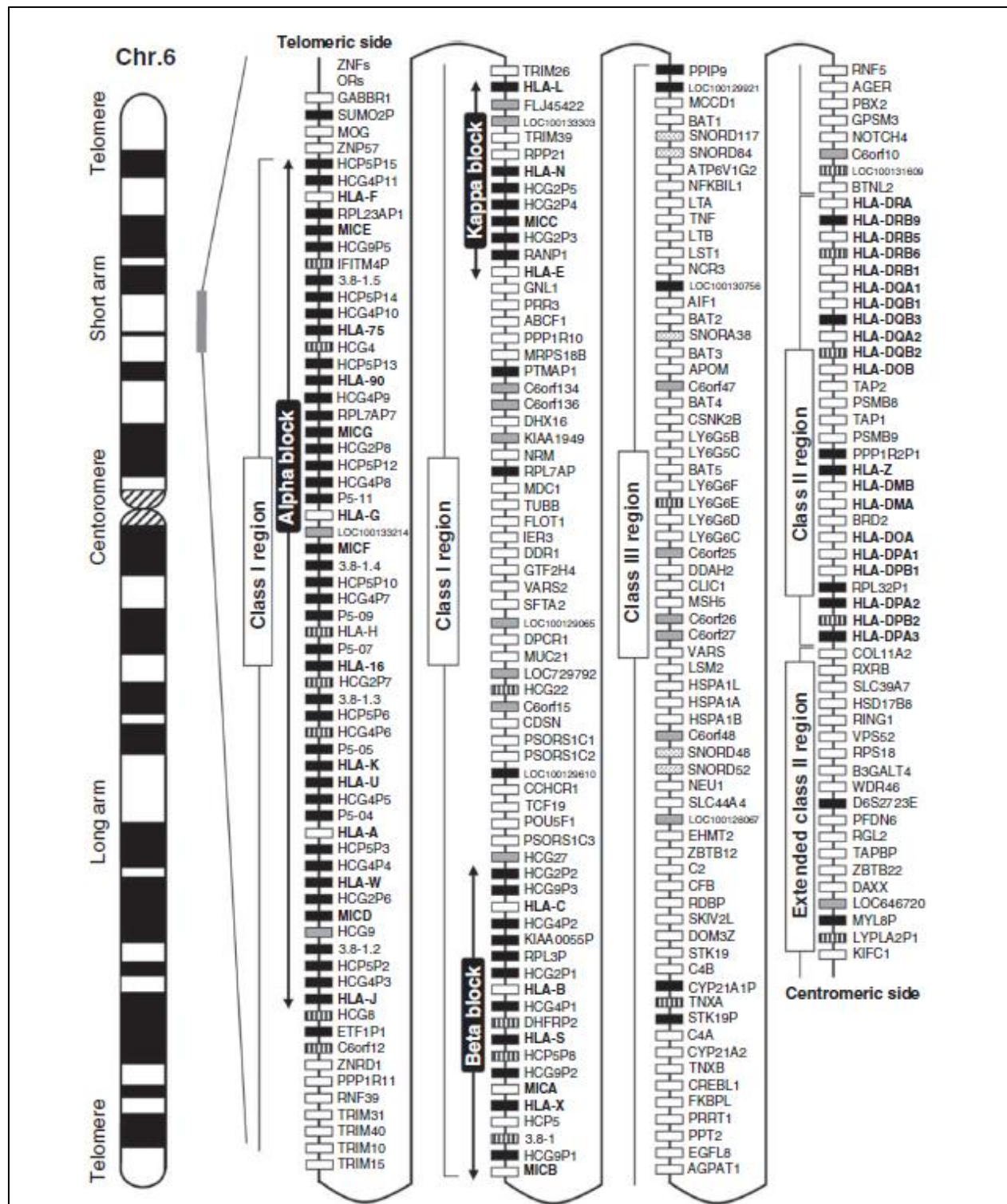


Figure 1: Location and organization of the MHC complex on chromosome 6. The MHC complex is divided into three regions: I, II, and III. White, gray, striped, and black boxes represent expressed genes, gene candidates, non-coding genes, and pseudogenes, respectively. Figure adapted from Shiina et al(12).

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