

METHODS IN MOLECULAR BIOLOGY

Series Editor

John M. Walker

School of Life and Medical Sciences

University of Hertfordshire

Hatfield, Hertfordshire, AL10 9AB, UK

For further volumes:

<http://www.springer.com/series/7651>

HLA Typing

Methods and Protocols

Edited by

Sebastian Boegel

Johannes Gutenberg University of Mainz, Mainz, Germany

Editor

Sebastian Boegel
Johannes Gutenberg University of Mainz
Mainz, Germany

ISSN 1064-3745 ISSN 1940-6029 (electronic)
Methods in Molecular Biology
ISBN 978-1-4939-8545-6 ISBN 978-1-4939-8546-3 (eBook)
<https://doi.org/10.1007/978-1-4939-8546-3>

Library of Congress Control Number: 2018943706

© Springer Science+Business Media, LLC, part of Springer Nature 2018

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

This Humana Press imprint is published by the registered company Springer Science+Business Media, LLC part of Springer Nature.

The registered company address is: 233 Spring Street, New York, NY 10013, U.S.A.

Preface

The human leukocyte antigens (HLA) complex is located on chromosome 6 and encodes a series of genes, including its most prominent members, i.e., the highly polymorphic classical HLA class I (HLA-A, -B, -C) and class II (HLA-DR, -DQ, -DP) molecules. These molecules are glycoproteins with the primary task to bind and present self, abnormal self (e.g., neo-epitopes arising from mutations), and foreign peptide antigens derived from intracellular (mainly HLA class I) or from extracellular proteins (mainly HLA class II) on the surface of nucleated cells. HLA-dependent peptide presentation is critical to an effective adaptive immune system in which the antigens bound to HLA molecules are recognized by T lymphocytes, leading to an immune response.

The HLA system is characterized by a vast amount of allelic variants resulting in a wide variety of HLA allele combinations, i.e., the HLA type, that differ between individuals. Determination of an individual's composition of HLA alleles—HLA typing—is essential for clinical work: the HLA type is a key parameter in solid organ and hematopoietic cell transplantation (Chapter 1) and certain HLA alleles were shown to have a high degree of association with various autoimmune diseases (Chapter 2). Two resources, which are reviewed and described in this book, play key roles in the development and application of HLA typing methods and immunological research in general: (1) the Immuno Polymorphism Database (IPD) catalogues the vast amount of sequence variants (Chapter 3) and (2) the Allele Frequency Net database contains information about HLA allele frequencies throughout many different populations (Chapter 4).

High-throughput DNA and RNA sequencing enables the rapid generation of billions of short nucleic acid sequence fragments. In the last years, the field has seen a rapid evolution of both laboratory and *in silico* methods to determine the HLA type in a massively high-throughput fashion. As the costs of sequencing continue to fall, we anticipate that HLA typing, especially using next generation sequencing, will be the future of HLA typing.

Thus, the focus of this volume is to gather a variety of protocols using high-throughput methods for HLA typing. Chapters 5–10 describe *wet lab* protocols comprising different methodologies and sequencing platforms. Chapters 11–18 summarize *in silico* tools, which are able to determine the HLA type from high-throughput data. This comprises the imputation of the HLA type from SNPs using microarray data (Chapter 11) and identification of the HLA alleles from (standard or targeted) DNA and RNA next generation sequencing data (Chapters 12–18), including a webserver (Chapter 18), as well as a software tool for HLA haplotype frequency estimation (Chapter 19).

This volume has not been possible without the contributions of the leading experts in the fields of HLA typing using high-throughput data, HLA sequence analysis, bioinformatics, and immunogenomics. I am very grateful for the discussions I had throughout the process of editing this book and for their consent to share their expertise and knowledge with the scientific community.

I wish to thank Springer and the Series Editor Prof. John M. Walker for giving me the opportunity to assemble this outstanding collection of manuscripts and for their excellent support throughout the process of editing this book. Last but not least, I especially wish to thank my friend and mentor Dr. John C. Castle for his guidance and valuable scientific input.

Mainz, Germany

Sebastian Boegel

Contents

<i>Preface</i>	<i>v</i>
<i>Contributors</i>	<i>ix</i>
1 The Past, Present, and Future of HLA Typing in Transplantation <i>Claire H. Edgerly and Eric T. Weimer</i>	1
2 Role of Human Leukocyte Antigens (HLA) in Autoimmune Diseases <i>Gergely Bodis, Victoria Toth, and Andreas Schwarting</i>	11
3 The IPD Databases: Cataloguing and Understanding Allele Variants <i>Jashan P. Abraham, Dominic J. Barker, James Robinson, Giuseppe Maccari, and Steven G. E. Marsh</i>	31
4 Allele Frequency Net Database <i>Faviel F. Gonzalez-Galarza, Antony McCabe, Eduardo J. Melo dos Santos, Louise Takeshita, Gurpreet Ghattaoraya, Andrew R. Jones, and Derek Middleton</i>	49
5 High-Resolution HLA-Typing by Next-Generation Sequencing of Randomly Fragmented Target DNA <i>Michael Wittig, Simonas Juzenas, Melanie Vollstedt, and Andre Franke</i>	63
6 High-Throughput Contiguous Full-Length Next-Generation Sequencing of HLA Class I and II Genes from 96 Donors in a Single MiSeq Run <i>Philip K. Ehrenberg, Aviva Geretz, and Rasmi Thomas</i>	89
7 Application of High-Throughput Next-Generation Sequencing for HLA Typing on Buccal Extracted DNA <i>Yuxin Yin, James Lan, and Qiubeng Zhang</i>	101
8 Super High Resolution for Single Molecule-Sequence-Based Typing of Classical HLA Loci Using Ion Torrent PGM <i>Takashi Shiina, Shingo Suzuki, Jerzy K. Kulski, and Hidetoshi Inoko</i>	115
9 High-Resolution Full-Length HLA Typing Method Using Third Generation (Pac-Bio SMRT) Sequencing Technology <i>Sheetal Ambardar and Malali Gowda</i>	135
10 Full-Length HLA Class I Genotyping with the MinION Nanopore Sequencer <i>Kathrin Lang, Vineeth Surendranath, Philipp Quenzel, Gerhard Schöfl, Alexander H. Schmidt, and Vinzenz Lange</i>	155
11 Imputation-Based HLA Typing with SNPs in GWAS Studies <i>Xiuwen Zheng</i>	163
12 In Silico Typing of Classical and Non-classical HLA Alleles from Standard RNA-Seq Reads <i>Sebastian Boegel, Thomas Bukur, John C. Castle, and Ugur Sabin</i>	177

13 PHLAT: Inference of High-Resolution HLA Types from RNA
and Whole Exome Sequencing 193
Yu Bai, David Wang, and Wen Fury

14 Using Exome and Amplicon-Based Sequencing Data
for High-Resolution HLA Typing with ATHLATES. 203
Chang Liu and Xiao Yang

15 HLA Typing from Short-Read Sequencing Data with OptiType 215
Andras Szolek

16 Comprehensive HLA Typing from a Current Allele Database
Using Next-Generation Sequencing Data 225
Shuji Kawaguchi, Koichiro Higasa, Ryo Yamada, and Fumihiko Matsuda

17 Accurate Assembly and Typing of HLA using a Graph-Guided
Assembler *Kourami* 235
Heewook Lee and Carl Kingsford

18 AmpliSAS and AmpliHLA: Web Server Tools for MHC Typing
of Non-Model Species and Human Using NGS Data 249
Alvaro Sebastian, Magdalena Migalska, and Aleksandra Biedrzycka

19 HLA Haplotype Frequency Estimation from Real-Life Data
with the Hapl-o-Mat Software 275
Jurgen Sauter, Christian Schafer, and Alexander H. Schmidt

Index. 285

Contributors

- JASHAN P. ABRAHAM • *Anthony Nolan Research Institute, London, UK*
- SHEETAL AMBARDAR • *Centre for Functional Genomics and Bioinformatics, Institute of TransDisciplinary Health Sciences and Technology, Bangalore, Karnataka, India*
- YU BAI • *Regeneron Pharmaceuticals, Tarrytown, NY, USA*
- DOMINIC J. BARKER • *Anthony Nolan Research Institute, London, UK*
- ALEKSANDRA BIEDRZYCKA • *Institute of Nature Conservation, Polish Academy of Sciences, Kraków, Poland*
- GERGELY BODIS • *Bioscientia Institut für Medizinische Diagnostik GmbH, Ingelheim, Germany; Acura Rheumatology Center Rhineland Palatine, Bad Kreuznach, Germany*
- SEBASTIAN BOEGEL • *TRON gGmbH–Translational Oncology at Johannes Gutenberg-University Medical Center gGmbH, Mainz, Germany*
- THOMAS BUKUR • *TRON gGmbH–Translational Oncology at Johannes Gutenberg-University Medical Center gGmbH, Mainz, Germany*
- JOHN C. CASTLE • *TRON gGmbH–Translational Oncology at Johannes Gutenberg-University Medical Center gGmbH, Mainz, Germany; Agenus Inc, Lexington MA, USA*
- CLAIRE H. EDGERLY • *Department of Pathology and Laboratory Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*
- PHILIP K. EHRENBERG • *U.S. Military HIV Research Program (MHRP), Walter Reed Army Institute of Research, Silver Spring, MD, USA*
- ANDRE FRANKE • *Institute of Clinical Molecular Biology, Kiel University, Kiel, Germany*
- WEN FURY • *Regeneron Pharmaceuticals, Tarrytown, NY, USA*
- AVIVA GERETZ • *U.S. Military HIV Research Program (MHRP), Walter Reed Army Institute of Research, Silver Spring, MD, USA; Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF), Bethesda, MD, USA*
- GURPREET GHATTAORAYA • *Institute of Integrative Biology, University of Liverpool, Liverpool, UK*
- FAVIEL F. GONZALEZ-GALARZA • *Department of Molecular Immunobiology, Faculty of Medicine, Centre for Biomedical Research, Autonomous University of Coahuila, Torreón, Coahuila, Mexico*
- MALALI GOWDA • *Centre for Functional Genomics and Bioinformatics, Institute of TransDisciplinary Health Sciences and Technology, Bangalore, Karnataka, India*
- KOICHIRO HIGASA • *Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan*
- HIDETOSHI INOKO • *Department of Molecular Life Science, Division of Basic Medical Science and Molecular Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan*
- ANDREW R. JONES • *Institute of Integrative Biology, University of Liverpool, Liverpool, UK*
- SIMONAS JUZENAS • *Institute of Clinical Molecular Biology, Kiel University, Kiel, Germany; Laboratory of Clinical and Molecular Gastroenterology, Institute for Digestive Research, Lithuanian University of Health Sciences, Kaunas, Lithuania*

- SHUJI KAWAGUCHI • *Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan*
- CARL KINGSFORD • *Computational Biology Department, School of Computer Science, Carnegie Mellon University, Pittsburgh, PA, USA*
- JERZY K. KULSKI • *Department of Molecular Life Science, Division of Basic Medical Science and Molecular Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan; School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Crawley, WA, Australia*
- JAMES LAN • *Nephrology and Kidney Transplantation, University of British Columbia, Vancouver General Hospital, Vancouver, BC, Canada*
- KATHRIN LANG • *DKMS Life Science Lab, Dresden, Germany*
- VINZENZ LANGE • *DKMS Life Science Lab, Dresden, Germany*
- HEEWOOK LEE • *Computational Biology Department, School of Computer Science, Carnegie Mellon University, Pittsburgh, PA, USA*
- CHANG LIU • *Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA*
- GIUSEPPE MACCARI • *Anthony Nolan Research Institute, London, UK; The Pirbright Institute, Surrey, UK*
- STEVEN G. E. MARSH • *Anthony Nolan Research Institute, London, UK; UCL Cancer Institute, University College London, London, UK*
- FUMIHIKO MATSUDA • *Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan*
- ANTONY McCABE • *Institute of Integrative Biology, University of Liverpool, Liverpool, UK*
- EDUARDO J. MELO DOS SANTOS • *Human and Medical Genetics, Institute of Biological Sciences, Federal University of Para, Belém, PA, Brazil*
- DEREK MIDDLETON • *Transplant Immunology Laboratory, Royal Liverpool and Broadgreen University Hospital, Liverpool, UK; Institute of Infection and Global Health, University of Liverpool, Liverpool, UK*
- MAGDALENA MIGALSKA • *Evolutionary Biology Group, Faculty of Biology, Adam Mickiewicz University, Poznan, Poland*
- PHILIPP QUENZEL • *DKMS Life Science Lab, Dresden, Germany*
- JAMES ROBINSON • *Anthony Nolan Research Institute, London, UK; UCL Cancer Institute, University College London, London, UK*
- UGUR SAHIN • *TRON gGmbH—Translational Oncology at Johannes Gutenberg-University Medical Center gGmbH, Mainz, Germany*
- JÜRGEN SAUTER • *DKMS gemeinnützige GmbH, Tübingen, Germany*
- CHRISTIAN SCHÄFER • *DKMS gemeinnützige GmbH, Tübingen, Germany*
- ALEXANDER H. SCHMIDT • *DKMS Life Science Lab, Dresden, Germany; DKMS, Tübingen, Germany; DKMS gemeinnützige GmbH, Tübingen, Germany*
- GERHARD SCHÖFL • *DKMS Life Science Lab, Dresden, Germany*
- ANDREAS SCHWARTING • *Acura Rheumatology Center Rhineland Palatine, Bad Kreuznach, Germany; Division of Rheumatology and Clinical Immunology, Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany*
- ALVARO SEBASTIAN • *Sixth Researcher, Poznan, Poland; Instituto Aragonés de Empleo (INAEM), Zaragoza, Spain; Evolutionary Biology Group, Faculty of Biology, Adam Mickiewicz University, Poznan, Poland*

- TAKASHI SHIINA • *Department of Molecular Life Science, Division of Basic Medical Science and Molecular Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan*
- VINEETH SURENDRANATH • *DKMS Life Science Lab, Dresden, Germany*
- SHINGO SUZUKI • *Department of Molecular Life Science, Division of Basic Medical Science and Molecular Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan*
- ANDRÁS SZOLEK • *Applied Bioinformatics, Department for Computer Science, University of Tübingen, Tübingen, Germany*
- LOUISE TAKESHITA • *Institute of Integrative Biology, University of Liverpool, Liverpool, UK*
- RASMI THOMAS • *U.S. Military HIV Research Program (MHRP), Walter Reed Army Institute of Research, Silver Spring, MD, USA; Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF), Bethesda, MD, USA*
- VICTORIA TOTH • *Bioscientia Institut für Medizinische Diagnostik GmbH, Ingelheim, Germany; Acura Rheumatology Center Rhineland Palatine, Bad Kreuznach, Germany*
- MELANIE VOLLSTEDT • *Institute of Clinical Molecular Biology, Kiel University, Kiel, Germany*
- DAVID WANG • *Department of Biological Statistics and Computational Biology, Cornell University, Ithaca, NY, USA*
- ERIC T. WEIMER • *Department of Pathology and Laboratory Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*
- MICHAEL WITTIG • *Institute of Clinical Molecular Biology, Kiel University, Kiel, Germany*
- RYO YAMADA • *Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan*
- XIAO YANG • *Grail, Inc., Menlo Park, CA, USA*
- YUXIN YIN • *Department of Pathology & Laboratory Medicine, UCLA Immunogenetics Center, Los Angeles, CA, USA*
- QIUHENG ZHANG • *Department of Pathology & Laboratory Medicine, UCLA Immunogenetics Center, Los Angeles, CA, USA*
- XIUWEN ZHENG • *Department of Biostatistics, University of Washington, Seattle, WA, USA*