

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Liu E, Lee H-S, Aronsson CA, et al. Risk of pediatric celiac disease according to HLA haplotype and country. *N Engl J Med* 2014;371:42-9. DOI: 10.1056/NEJMoa1313977

Supplementary Appendix

Table of Contents

Page 1-3 TEDDY study group member list

Page 4 Supplementary Table S1

Page 5 Supplementary Table S2

TEDDY Study Acknowledgements

The TEDDY Study Group (See appendix)

Funded by U01 DK63829, U01 DK63861, U01 DK63821, U01 DK63865, U01 DK63863, U01 DK63836, U01 DK63790, UC4 DK63829, UC4 DK63861, UC4 DK63821, UC4 DK63865, UC4 DK63863, UC4 DK63836, and UC4 DK95300 and Contract No. HHSN267200700014C from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Juvenile Diabetes Research Foundation (JDRF), and Centers for Disease Control and Prevention (CDC). This work supported in part by the NIH/NCATS Clinical and Translational Science Awards to the University of Florida (UL1 TR000064) and the University of Colorado (UL1 TR001082).

The TEDDY Study Group

Colorado Clinical Center: Marian Rewers, M.D., Ph.D., PI^{1,4,5,6,10,11}, Kimberly Bautista¹², Judith Baxter^{9,10,12,15}, Ruth Bedoy², Patricia Gesualdo^{2,6,12,14,15}, Michelle Hoffman^{12,13,14}, Rachel Karban¹², Edwin Liu, M.D.¹³, Jill Norris, Ph.D.^{2,3,12}, Kathleen Waugh^{6,7,12,15}, Adela Samper-Imaz, Andrea Steck, M.D.^{3,14}. University of Colorado, Anschutz Medical Campus, Barbara Davis Center for Childhood Diabetes.

Georgia/Florida Clinical Center: Jin-Xiong She, Ph.D., PI^{1,3,4,11}, †, Desmond Schatz, M.D.*^{4,5,7,8}, Diane Hopkins¹², Leigh Steed^{12,13,14,15}, Jamie Thomas*^{6,12}, Katherine Silvis², Michael Haller, M.D.*¹⁴, Meena Shankar*², Eleni Sheehan*, Melissa Gardiner, Richard McIndoe, Ph.D., Haitao Liu, M.D.†, John Nechtman†, Ashok Sharma, Joshua Williams, Gabriela Foghis, Stephen W. Anderson, M.D.^. Medical College of Georgia, Georgia Regents University. *University of Florida, †Jinfiniti Biosciences LLC, Augusta, GA, ^Pediatric Endocrine Associates, Atlanta, GA.

Germany Clinical Center: Anette G. Ziegler, M.D., PI^{1,3,4,11}, Andreas Beyerlein Ph.D.², Ezio Bonifacio Ph.D.*⁵, Michael Hummel, M.D.¹³, Sandra Hummel, Ph.D.², Kristina Foterek^{¥2}, Mathilde Kersting, Ph.D.^{¥2}, Annette Knopff⁷, Sibylle Koletzko, M.D.^{¶13}, Claudia Peplow¹², Roswith Roth, Ph.D.⁹, Joanna Stock^{9,12}, Elisabeth Strauss¹², Katharina Warncke, M.D.¹⁴, Christiane Winkler, Ph.D.^{2,12,15}. Forschergruppe Diabetes e.V. and Institute of Diabetes Research, Helmholtz Zentrum München, and Klinikum rechts der Isar, Technische Universität München. *Center for Regenerative Therapies, TU Dresden, ¶Dr. von Hauner Children's Hospital, Department of Gastroenterology, Ludwig Maximilians University Munich, ¥Research Institute for Child Nutrition, Dortmund.

Finland Clinical Center: Olli G. Simell, M.D., Ph.D., PI^{¥^1,4,11,13}, Jorma Toppari, M.D., Ph.D., Co-PI⁴, Heikki Hyöty, M.D., Ph.D.*^{±6}, Jorma Ilonen, M.D., Ph.D.^{¥¶13}, Miia Kähönen^{μx}, Mikael Knip, M.D., Ph.D.*^{±5}, Annika Koivu^{¥^}, Mirva Kearsalo*^{±§2}, Kalle Kurppa, M.D., Ph.D.*^{±13}, Maria Lönnrot, M.D., Ph.D.*^{±6}, Elina Mäntymäki^{¥^}, Katja Multasuo^{μx}, Juha Mykkänen, Ph.D.^{^¥3}, Tiina Niininen^{±*12}, Mia Nyblom*[±], Jenna Rautanen^{±§}, Anne Riikonen*[±], Minna Romo^{¥^},

Aaro Simell^{¥^}, Barbara Simell^{¥^9,12,15}, Satu Simell, M.D., Ph.D.^{*±13}, Tuula Simell, Ph.D.^{¥^9,12}, Ville Simell^{^¥13}, Maija Sjöberg^{¥^12,14}, Aino Stenius^{μx12}, Eeva Varjonen^{¥^12}, Riitta Veijola, M.D., Ph.D.^{μx14}, Suvi M. Virtanen, M.D., Ph.D.^{*±§2}, Mari Åkerlund^{*±§}. [¥]University of Turku, ^{*}University of Tampere, ^μUniversity of Oulu, [^]Turku University Hospital, [±]Tampere University Hospital, ^xOulu University Hospital, [§]National Institute for Health and Welfare, Finland, [¶]University of Kuopio.

Sweden Clinical Center: Åke Lernmark, Ph.D., PI^{1,3,4,5,6,8,10,11,15}, Daniel Agardh, M.D., Ph.D.¹³, Carin Andrén Aronsson^{2,13}, Maria Ask, Jenny Bremer, Ulla-Marie Carlsson, Corrado Cilio, Ph.D., M.D.⁵, Camilla Ekstrand, Emelie Ericson-Hallström², Lina Fransson, Thomas Gard, Joanna Gerardsson, Rasmus Håkansson, Monica Hansen, Gertie Hansson^{12,14}, Susanne Hyberg, Fredrik Johansen, Berglind Jonasdottir M.D., Linda Jonsson, Helena Larsson M.D., Ph.D.^{6,14}, Barbro Lernmark, Ph.D., Maria Månsson-Martinez, Maria Markan, Theodosia Massadakis, Jessica Melin¹², Zeliha Mestan, Kobra Rahmati, Anita Ramelius, Monica Sedig Järvirova, Sara Sibthorpe, Birgitta Sjöberg, Ulrica Swartling, Ph.D.^{9,12}, Erika Trulsson, Carina Törn, Ph.D.^{3,15}, Anne Wallin, Åsa Wimar¹², Sofie Åberg. Lund University.

Washington Clinical Center: William A. Hagopian, M.D., Ph.D., PI^{1,3,4,5,6,7,11,13,14}, Xiang Yan, M.D., Michael Killian^{6,7,12,13}, Claire Cowen Crouch^{12,14,15}, Jennifer Skidmore², Stephen Ayres, Kayleen Dunson, Diana Heaney, Rachel Hervey, Renee Kindschi, Arlene Meyer, Denise Mulenga, Elizabeth Scott, Joshua Stabbert, Nancy Williams, John Willis. Pacific Northwest Diabetes Research Institute.

Pennsylvania Satellite Center: Dorothy Becker, M.D., Margaret Franciscus¹², MaryEllen Dalmagro-Elias Smith², Ashi Daftary, M.D., Mary Beth Klein. Children's Hospital of Pittsburgh of UPMC.

Data Coordinating Center: Jeffrey P. Krischer, Ph.D., PI^{1,4,5,10,11}, Michael Abbondandolo, Sarah Austin-Gonzalez, Rasheedah Brown^{12,15}, Brant Burkhardt, Ph.D.^{5,6}, Martha Butterworth², David Cuthbertson, Christopher Eberhard, Steven Fiske⁹, Dena Garcia, Veena Gowda, David Hadley, Ph.D.^{3,13}, Hye-Seung Lee, Ph.D.^{1,2,13,15}, Shu Liu, Xiang Liu, Ph.D.^{2,9,12}, Kristian Lynch, Ph.D.^{5,6,9,15}, Jamie Malloy, Cristina McCarthy^{12,15}, Wendy McLeod^{2,5,6,13,15}, Chris Shaffer, Laura Smith, Ph.D.^{9,12}, Susan Smith^{12,15}, Roy Tamura, Ph.D.^{1,2,13}, Ulla Uusitalo, Ph.D.^{2,15}, Kendra Vehik, Ph.D.^{4,5,6,14,15}, Earnest Washington, Jimin Yang, Ph.D., R.D.^{2,15}. University of South Florida.

Project scientist: Beena Akolkar, Ph.D.^{1,3,4,5,6,7,10,11}. National Institutes of Diabetes and Digestive and Kidney Diseases.

Other contributors: Kasia Bourcier, Ph.D.⁵, National Institutes of Allergy and Infectious Diseases. Thomas Briese, Ph.D.^{6,15}, Columbia University. Suzanne Bennett Johnson, Ph.D.^{9,12}, Florida State University. Steve Oberste, Ph.D.⁶, Centers for Disease Control and Prevention. Eric Triplett, Ph.D.⁶, University of Florida.

Autoantibody Reference Laboratories: Liping Yu, M.D.^{^5}, Dongmei Miao, M.D.[^], Polly Bingley, M.D., FRCP^{*5}, Alistair Williams*, Kyla Chandler*, Saba Rokni*, Joanna Boldison*, Jacob Butterfly*, Jessica Broadhurst*, Gabriella Carreno*, Claire Caygill*, Rachel Curnock*, Peter Easton*, Ivey Geoghan*, Julia Goode*, Anna Long*, Molly Payne*, James Pearson*, Charles Reed*, Sophie Ridewood*, Rebecca Wyatt*. [^]Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, ^{*}School of Clinical Sciences, University of Bristol UK.

Cortisol Laboratory: Elisabeth Aardal Eriksson, M.D., Ph.D., Ewa Lönn Karlsson. Department of Clinical Chemistry, Linköping University Hospital, Linköping, Sweden.

Dietary Biomarkers Laboratory: Iris Erlund, Ph.D.², Irma Salminen, Jouko Sundvall, Jaana Leiviskä, Mari Lehtonen, Ph.D. National Institute for Health and Welfare, Helsinki, Finland.

HbA1c Laboratory: Randie R. Little, Ph.D., Alethea L. Tennill. Diabetes Diagnostic Laboratory, Dept. of Pathology, University of Missouri School of Medicine.

HLA Reference Laboratory: Henry Erlich, Ph.D.³, Steven J. Mack, Ph.D., Anna Lisa Fear. Center for Genetics, Children's Hospital Oakland Research Institute.

Metabolomics Laboratory: Oliver Fiehn, Ph.D., Bill Wikoff, Ph.D., Tobias Kind, Ph.D., Mine Palazoglu, Joyce Wong, Gert Wohlgemuth. UC Davis Metabolomics Center.

Microbiome and Viral Metagenomics Laboratory: Joseph F. Petrosino, Ph.D.⁶. Alkek Center for Metagenomics and Microbiome Research, Department of Molecular Virology and Microbiology, Baylor College of Medicine.

OGTT Laboratory: Santica M. Marcovina, Ph.D., Sc.D., Vinod P. Gaur, Ph.D., Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington.

Repository: Heather Higgins, Sandra Ke. NIDDK Biosample Repository at Fisher BioServices.

RNA Laboratory and Gene Expression Laboratory: Jin-Xiong She, Ph.D., PI^{1,3,4,11}, Richard McIndoe, Ph.D., Haitao Liu, M.D., John Nechtman, Yansheng Zhao, Na Jiang, M.D. Jinfiniti Biosciences, LLC.

SNP Laboratory: Stephen S. Rich, Ph.D.³, Wei-Min Chen, Ph.D.³, Suna Onengut-Gumuscu, Ph.D.³, Emily Farber, Rebecca Roche Pickin, Ph.D., Jordan Davis, Dan Gallo. Center for Public Health Genomics, University of Virginia.

Committees:

¹Ancillary Studies, ²Diet, ³Genetics, ⁴Human Subjects/Publicity/Publications, ⁵Immune Markers, ⁶Infectious Agents, ⁷Laboratory Implementation, ⁸Maternal Studies, ⁹Psychosocial, ¹⁰Quality Assurance, ¹¹Steering, ¹²Study Coordinators, ¹³Celiac Disease, ¹⁴Clinical Implementation, ¹⁵Quality Assurance Subcommittee on Data Quality.

Table S1. High risk HLA genotypes followed in TEDDY. In bold are the genotypes reported in this study.

HLA genotypes	Abbreviation	First-degree relative with type 1 diabetes	General Population
A. DR4-DQA1*03:0X-DQB1*03:02 / DR3-DQA1*05:01-DQB1*02:01	DR3-DQ2/DR4-DQ8	Y	Y
B. DR4-DQA1*03:0X-DQB1*03:02 / DR4-DQA1*03:0X-DQB1*03:02	DR4-DQ8/DR4-DQ8	Y	Y
C. DR4-DQA1*03:0X-DQB1*03:02 / DR8-DQA1*04:01-DQB1*04:02	DR4-DQ8/DR8-DQ4	Y	Y
D. DR3-DQA1*05:01-DQB1*02:01 / DR3-DQA1*05:01-DQB1*02:01	DR3-DQ2/DR3-DQ2	Y	Y
E. DR4-DQA1*03:0X-DQB1*03:02 / DR4- DQA1*03:0X-DQB1*02:0X	DR4/DR4b	Y	N
F. DR4-DQA1*03:0X-DQB1*03:02 / DR1- DQA1*01:01-DQB1*05:01	DR4/DR1	Y	N
G. DR4-DQA1*03:0X-DQB1*03:02 / DR13-DQA1*01:02-DQB1*06:04	DR4/DR13	Y	N
H. DR4-DQA1*03:0X-DQB1*03:02 / DR9- DQA1*03:0X-DQB1*03:03	DR4/DR9	Y	N
I. DR3-DQA1*05:01-DQB1*02:01 / DR9- DQA1*03:0X-DQB1*03:03	DR3/DR9	Y	N

Note: For general population subjects, DR4 subtyping must exclude DRB1*04:03. Acceptable alleles in the DR4 haplotype include both DQB1*03:02 (shown) and *03:04 (not shown). DR8-DQA1*04:01-DQB1*04:02 is the only low risk HLA haplotype for celiac disease present in greater than 2% of subjects in the study cohort. This table is updated from Reference #4.

Table S2. Screening and eligibility results by clinical center. Two satellite centers that screened 56 total subjects are not shown. For further details, see Reference #2.

Clinical Center	Screened	Eligible	Percent of screened by genotype								
	N	N (%)	A	B	C	D	E	F	G	H	I
Colorado	76691	4407 (5.8%)	2.00	1.39	1.19	1.07	0.00	0.05	0.02	0.00	0.01
Georgia	88544	3266 (3.7%)	1.61	0.66	0.39	0.96	0.00	0.03	0.01	0.00	0.01
Washington	114446	4826 (4.2%)	1.72	0.76	0.60	1.09	0.00	0.03	0.01	0.00	0.00
Finland	60803	3682 (6.1%)	1.97	1.05	1.89	0.92	0.00	0.14	0.03	0.03	0.02
Germany	36108	1673 (4.6%)	1.93	0.84	0.46	1.13	0.00	0.19	0.06	0.01	0.02
Sweden	48140	3724 (7.7%)	3.25	1.68	1.02	1.67	0.00	0.07	0.03	0.01	0.00
TOTAL	424732	21578 (5.1%)	1.98	1.00	0.89	1.10	0.00	0.07	0.02	0.01	0.01