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Supplementary information

A saturated map of common genetic variants associated with human height

In the format provided by the authors and unedited

A Saturated Map of Common Genetic Variants Associated with Human Height

Yengo L., Vedantam S., Marouli E., et al.

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MVP Executive Committee

Co-Chair: J. Michael Gaziano, M.D., M.P.H., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130

Co-Chair: Sumitra Muralidhar, Ph.D., US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

Rachel Ramoni, D.M.D., Sc.D., Chief VA Research and Development Officer, US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

Jean Beckham, Ph.D., Durham VA Medical Center, 508 Fulton Street, Durham, NC 27705

Kyong-Mi Chang, M.D., Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104

Philip S. Tsao, Ph.D., VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304

James Breeling, M.D., Ex-Officio, US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

Grant Huang, Ph.D., Ex-Officio, US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

Juan P. Casas, M.D., Ph.D., Ex-Officio, VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130

MVP Program Office

Sumitra Muralidhar, Ph.D., US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

Jennifer Moser, Ph.D., US Department of Veterans Affairs, 810 Vermont Avenue NW, Washington, DC 20420

MVP Recruitment/Enrollment

MVP Cohort Management Director/Recruitment/Enrollment Director, Boston – Stacey B. Whitbourne, Ph.D.; Jessica V. Brewer, M.P.H., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130

VA Central Biorepository, Boston – Mary T. Brophy M.D., M.P.H.; Donald E. Humphries, Ph.D.; Luis E. Selva, Ph.D., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130

MVP Informatics, Boston – Nhan Do, M.D.; Shahpoor (Alex) Shayan, M.S., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130

MVP Data Operations/Analytics, Boston – Kelly Cho, M.P.H., Ph.D., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130

Director of Regulatory Affairs – Lori Churby, B.S., VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304

MVP Coordinating Centers

- Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque – Todd Connor, Pharm.D.; Dean P. Argyres, B.S., M.S., New Mexico VA Health Care System, 1501 San Pedro Drive SE, Albuquerque, NM 87108
- Genomics Coordinating Center, Palo Alto – Philip S. Tsao, Ph.D., VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
- MVP Boston Coordinating Center, Boston - J. Michael Gaziano, M.D., M.P.H., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
- MVP Information Center, Canandaigua – Brady Stephens, M.S., Canandaigua VA Medical Center, 400 Fort Hill Avenue, Canandaigua, NY 14424

MVP Science

Saiju Pyarajan Ph.D., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
Philip S. Tsao, Ph.D., VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304
Data Core - Kelly Cho, M.P.H, Ph.D., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
VA Informatics and Computing Infrastructure (VINCI) – Scott L. DuVall, Ph.D., VA Salt Lake City Health Care System, 500 Foothill Drive, Salt Lake City, UT 84148
Data and Computational Sciences – Saiju Pyarajan, Ph.D., VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130
Statistical Genetics – Elizabeth Hauser, Ph.D., Durham VA Medical Center, 508 Fulton Street, Durham, NC 27705; Yan Sun, Ph.D., Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033; Hongyu Zhao, Ph.D., West Haven VA Medical Center, 950 Campbell Avenue, West Haven, CT 06516

Current MVP Local Site Investigators

Atlanta VA Medical Center (Peter Wilson, M.D.), 1670 Clairmont Road, Decatur, GA 30033
Bay Pines VA Healthcare System (Rachel McArdle, Ph.D.), 10,000 Bay Pines Blvd Bay Pines, FL 33744
Birmingham VA Medical Center (Louis Dellitalia, M.D.), 700 S. 19th Street, Birmingham AL 35233
Central Western Massachusetts Healthcare System (Kristin Mattocks, Ph.D., M.P.H.), 421 North Main Street, Leeds, MA 01053
Cincinnati VA Medical Center (John Harley, M.D., Ph.D.), 3200 Vine Street, Cincinnati, OH 45220
Clement J. Zablocki VA Medical Center (Jeffrey Whittle, M.D., M.P.H.), 5000 West National Avenue, Milwaukee, WI 53295
VA Northeast Ohio Healthcare System (Frank Jacono, M.D.), 10701 East Boulevard, Cleveland, OH 44106
Durham VA Medical Center (Jean Beckham, Ph.D.), 508 Fulton Street, Durham, NC 27705
Edith Nourse Rogers Memorial Veterans Hospital (John Wells., Ph.D.), 200 Springs Road, Bedford, MA 01730
Edward Hines, Jr. VA Medical Center (Salvador Gutierrez, M.D.), 5000 South 5th Avenue, Hines, IL 60141
Veterans Health Care System of the Ozarks (Kathrina Alexander, M.D.), 1100 North College Avenue, Fayetteville, AR 72703
Fargo VA Health Care System (Kimberly Hammer, Ph.D.), 2101 N. Elm, Fargo, ND 58102
VA Health Care Upstate New York (James Norton, Ph.D.), 113 Holland Avenue, Albany, NY 12208
New Mexico VA Health Care System (Gerardo Villareal, M.D.), 1501 San Pedro Drive, S.E. Albuquerque, NM 87108
VA Boston Healthcare System (Scott Kinlay, M.B.B.S., Ph.D.), 150 S. Huntington Avenue, Boston, MA 02130
VA Western New York Healthcare System (Junzhe Xu, M.D.), 3495 Bailey Avenue, Buffalo, NY 14215-1199
Ralph H. Johnson VA Medical Center (Mark Hamner, M.D.), 109 Bee Street, Mental Health Research, Charleston, SC 29401

Columbia VA Health Care System (Roy Mathew, M.D.), 6439 Garners Ferry Road, Columbia, SC 29209
VA North Texas Health Care System (Sujata Bhushan, M.D.), 4500 S. Lancaster Road, Dallas, TX 75216
Hampton VA Medical Center (Pran Iruvanti, D.O., Ph.D.), 100 Emancipation Drive, Hampton, VA 23667
Richmond VA Medical Center (Michael Godschalk, M.D.), 1201 Broad Rock Blvd., Richmond, VA 23249
Iowa City VA Health Care System (Zuhair Ballas, M.D.), 601 Highway 6 West, Iowa City, IA 52246-2208
Eastern Oklahoma VA Health Care System (River Smith, Ph.D.), 1011 Honor Heights Drive, Muskogee, OK 74401
James A. Haley Veterans' Hospital (Stephen Mastorides, M.D.), 13000 Bruce B. Downs Blvd, Tampa, FL 33612
James H. Quillen VA Medical Center (Jonathan Moorman, M.D., Ph.D.), Corner of Lamont & Veterans Way, Mountain Home, TN 37684
John D. Dingell VA Medical Center (Saib Gappy, M.D.), 4646 John R Street, Detroit, MI 48201
Louisville VA Medical Center (Jon Klein, M.D., Ph.D.), 800 Zorn Avenue, Louisville, KY 40206
Manchester VA Medical Center (Nora Ratcliffe, M.D.), 718 Smyth Road, Manchester, NH 03104
Miami VA Health Care System (Ana Palacio, M.D., M.P.H.), 1201 NW 16th Street, 11 GRC, Miami FL 33125
Michael E. DeBakey VA Medical Center (Olaoluwa Okusaga, M.D.), 2002 Holcombe Blvd, Houston, TX 77030
Minneapolis VA Health Care System (Maureen Murdoch, M.D., M.P.H.), One Veterans Drive, Minneapolis, MN 55417
N. FL/S. GA Veterans Health System (Peruvemba Sriram, M.D.), 1601 SW Archer Road, Gainesville, FL 32608
Northport VA Medical Center (Shing Shing Yeh, Ph.D., M.D.), 79 Middleville Road, Northport, NY 11768
Overton Brooks VA Medical Center (Neeraj Tandon, M.D.), 510 East Stoner Ave, Shreveport, LA 71101
Philadelphia VA Medical Center (Darshana Jhala, M.D.), 3900 Woodland Avenue, Philadelphia, PA 19104
Phoenix VA Health Care System (Samuel Aguayo, M.D.), 650 E. Indian School Road, Phoenix, AZ 85012
Portland VA Medical Center (David Cohen, M.D.), 3710 SW U.S. Veterans Hospital Road, Portland, OR 97239
Providence VA Medical Center (Satish Sharma, M.D.), 830 Chalkstone Avenue, Providence, RI 02908
Richard Roudebush VA Medical Center (Suthat Liangpunsakul, M.D., M.P.H.), 1481 West 10th Street, Indianapolis, IN 46202
Salem VA Medical Center (Kris Ann Oursler, M.D.), 1970 Roanoke Blvd, Salem, VA 24153
San Francisco VA Health Care System (Mary Whooley, M.D.), 4150 Clement Street, San Francisco, CA 94121
South Texas Veterans Health Care System (Sunil Ahuja, M.D.), 7400 Merton Minter Boulevard, San Antonio, TX 78229
Southeast Louisiana Veterans Health Care System (Joseph Constans, Ph.D.), 2400 Canal Street, New Orleans, LA 70119
Southern Arizona VA Health Care System (Paul Meyer, M.D., Ph.D.), 3601 S 6th Avenue, Tucson, AZ 85723
Sioux Falls VA Health Care System (Jennifer Greco, M.D.), 2501 W 22nd Street, Sioux Falls, SD 57105
St. Louis VA Health Care System (Michael Rauchman, M.D.), 915 North Grand Blvd, St. Louis, MO 63106
Syracuse VA Medical Center (Richard Servatius, Ph.D.), 800 Irving Avenue, Syracuse, NY 13210
VA Eastern Kansas Health Care System (Melinda Gaddy, Ph.D.), 4101 S 4th Street Trafficway, Leavenworth, KS 66048
VA Greater Los Angeles Health Care System (Agnes Wallbom, M.D., M.S.), 11301 Wilshire Blvd, Los Angeles, CA 90073
VA Long Beach Healthcare System (Timothy Morgan, M.D.), 5901 East 7th Street Long Beach, CA 90822
VA Maine Healthcare System (Todd Stapley, D.O.), 1 VA Center, Augusta, ME 04330
VA New York Harbor Healthcare System (Peter Liang, M.D., M.P.H.), 423 East 23rd Street, New York, NY 10010
VA Pacific Islands Health Care System (Daryl Fujii, Ph.D.), 459 Patterson Rd, Honolulu, HI 96819
VA Palo Alto Health Care System (Philip Tsao, Ph.D.), 3801 Miranda Avenue, Palo Alto, CA 94304-1290
VA Pittsburgh Health Care System (Patrick Strollo, Jr., M.D.), University Drive, Pittsburgh, PA 15240

VA Puget Sound Health Care System (Edward Boyko, M.D.), 1660 S. Columbian Way, Seattle, WA 98108-1597
VA Salt Lake City Health Care System (Jessica Walsh, M.D.), 500 Foothill Drive, Salt Lake City, UT 84148
VA San Diego Healthcare System (Samir Gupta, M.D., M.S.C.S.), 3350 La Jolla Village Drive, San Diego, CA 92161
VA Sierra Nevada Health Care System (Mostaqul Huq, Pharm.D., Ph.D.), 975 Kirman Avenue, Reno, NV 89502
VA Southern Nevada Healthcare System (Joseph Fayad, M.D.), 6900 North Pecos Road, North Las Vegas, NV 89086
VA Tennessee Valley Healthcare System (Adriana Hung, M.D., M.P.H.), 1310 24th Avenue, South Nashville, TN 37212
Washington DC VA Medical Center (Jack Lichy, M.D., Ph.D.), 50 Irving St, Washington, D. C. 20422
W.G. (Bill) Hefner VA Medical Center (Robin Hurley, M.D.), 1601 Brenner Ave, Salisbury, NC 28144
White River Junction VA Medical Center (Brooks Robey, M.D.), 163 Veterans Drive, White River Junction, VT 05009
William S. Middleton Memorial Veterans Hospital (Prakash Balasubramanian, M.D.), 2500 Overlook Terrace, Madison, WI 53705

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Consortium acknowledgements and detailed affiliations

23andMe Research Team

Stella Aslibekyan[12], Adam Auton[12], Elizabeth Babalola[12], Robert K. Bell[12], Jessica Bielenberg[12], Katarzyna Bryc[12], Emily Bullis[12], Daniella Coker[12], Gabriel Cuellar Partida[12], Devika Dhamija[12], Sayantan Das[12], Sarah L. Elson[12], Teresa Filshtein[12], Kipper Fletez-Brant[12], Pierre Fontanillas[12], Will Freyman[12], Pooja M. Gandhi[12], Karl Heilbron[12], Barry Hicks[12], David A. Hinds[12], Ethan M. Jewett[12], Katelyn Kukar[12], Keng-Han Lin[12], Maya Lowe[12], Jey C. McCreight[12], Matthew H. McIntyre[12], Steven J. Micheletti[12], Meghan E. Moreno[12], Joanna L. Mountain[12], Priyanka Nandakumar[12], Elizabeth S. Noblin[12], Jared O'Connell[12], Aaron A. Petrakovitz[12], G. David Poznik[12], Morgan Schumacher[12], Anjali J. Shastri[12], Janie F. Shelton[12], Suyash Shringarpure[12], Vinh Tran[12], Joyce Y. Tung[12], Xin Wang[12], Wei Wang[12], Catherine H. Weldon[12], Peter Wilton[12], Alejandro Hernandez[12], Corinna Wong[12], Christophe Toukam Tchakouté[12]

[12]23andMe, Inc., Sunnyvale, CA 94086, USA

VA Million Veteran Program

J. Michael Gaziano[506], Sumitra Muralidhar[507], Rachel Ramoni[507], Jean Beckham[508], Kyong-Mi Chang[509], Philip S. Tsao[510], James Breeling[507], Grant Huang[507], Juan P. Casas[506], Jennifer Moser[507], Stacey B. Whitbourne[506], Jessica V. Brewer[506], Mary T. Brophy[506], Donald E. Humphries[506], Luis E. Selva[506], Nhan Do[506], Shahpoor Shayan,[506], Kelly Cho[506], Lori Churby[510], Todd Connor[511], Dean P. Argyres[511], Brady Stephens[512], Saiju Pyarajan[5,57,81], Scott L. DuVall[513], Elizabeth Hauser[508], Yan Sun[493,494], Hongyu Zhao[514], Peter Wilson[515], Rachel McArdle[516], Louis Dellitalia[517], Kristin Mattocks[518], John Harley[519], Jeffrey Whittle[520], Frank Jacono[521], John Wells[522], Salvador Gutierrez[523], Kathrina Alexander[524], Kimberly Hammer[525], James Norton[526], Gerardo Villareal[511], Scott Kinlay[506], Junzhe Xu[527], Mark Hammer[528], Roy Mathew[529], Sujata Bhushan[530], Pran Iruvanti[531], Michael Godschalk[532], Zuhair Ballas[533], River Smith[534], Stephen Mastorides[535], Jonathan Moorman[536], Saib Gappy[537], Jon Klein[538], Nora Ratcliffe[539], Ana Palacio[540], Olaoluwa Okusaga[541], Maureen Murdoch[542], Peruvemba Sriram[543], Shing Shing Yeh[544], Neeraj Tandon[545], Darshana Jhala[509], Samuel Aguayo[546], David Cohen[547], Satish Sharma[548], Suthat Liangpunsakul[549], Kris Ann Oursler[550], Mary Whooley[551], Sunil Ahuja[552], Joseph Constans[553], Paul Meyer[554], Jennifer Greco[555], Michael Rauchman[556], Richard Servatius[557], Melinda Gaddy[558], Agnes Wallbom[559], Timothy Morgan[560], Todd Stapley[561], Peter Liang[562], Daryl Fujii[563], Patrick Strollo, Jr.[564], Edward Boyko[565], Jessica Walsh[513], Samir Gupta[566], Mostaqul Huq[567], Joseph Fayad[568], Adriana Hung[569], Jack Lichy[570], Robin Hurley[571], Brooks Robey[572], Prakash Balasubramanian[573]

[5]Harvard Medical School, Boston, MA 02115, USA, [57]Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA, [81]Center for Data and Computational Sciences, VA Boston Healthcare System, Boston, MA, USA, [493]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA 30322, USA, [494]Atlanta VA Health Care System, Decatur, GA 30033, USA, [506]VA Boston Healthcare System, Boston, MA 02130, USA, [507]US Department of Veterans Affairs, Washington, DC 20420, USA, [508]Durham VA Medical Center, Durham, NC 27705, USA, [509]Philadelphia VA Medical Center, Philadelphia, PA 19104, USA, [510]VA Palo Alto Health Care System, Palo Alto, CA 94304, USA, [511]New Mexico VA Health Care System, Albuquerque, NM 87108, USA, [512]Canandaigua VA Medical Center, Canandaigua, NY 14424, USA, [513]VA Salt Lake City Health Care System, Salt Lake City, UT 84148, USA, [514]West Haven VA Medical Center, West Haven, CT 06516, [515]Atlanta VA Medical Center, Decatur, GA 30033, USA, [516]Bay Pines VA Healthcare System, Bay Pines, FL 33744, USA, [517]Birmingham VA Medical Center, Birmingham AL 35233, USA, [518]Central Western Massachusetts Healthcare System, Leeds, MA 01053, USA, [519]Cincinnati VA Medical Center, Cincinnati, OH 45220, USA, [520]Clement J.

Zablocki VA Medical Center , Milwaukee, WI 53295, USA, [521]VA Northeast Ohio Healthcare System, Cleveland, OH 44106, USA, [522]Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA 01730, USA, [523]Edward Hines, Jr. VA Medical Center, Hines, IL 60141, USA, [524]Veterans Health Care System of the Ozarks, Fayetteville, AR 72703, USA, [525]Fargo VA Health Care System, Fargo, ND 58102, USA, [526]VA Health Care Upstate New York, Albany, NY 12208, USA, [527]VA Western New York Healthcare System, Buffalo, NY 14215-1199, USA, [528]Ralph H. Johnson VA Medical Center, Charleston, SC 29401, USA, [529]Columbia VA Health Care System, Columbia, SC 29209, USA, [530]VA North Texas Health Care System, Dallas, TX 75216, USA, [531]Hampton VA Medical Center, Hampton, VA 23667, USA, [532]Richmond VA Medical Center, Richmond, VA 23249, USA, [533]Iowa City VA Health Care System, Iowa City, IA 52246-2208, USA, [534]Eastern Oklahoma VA Health Care System, Muskogee, OK 74401, USA, [535]James A. Haley Veterans' Hospital, Tampa, FL 33612, USA, [536]James H. Quillen VA Medical Center, Mountain Home, TN 37684, USA, [537]John D. Dingell VA Medical Center, Detroit, MI 48201, USA, [538]Louisville VA Medical Center, Louisville, KY 40206, USA, [539]Manchester VA Medical Center, Manchester, NH 03104, USA, [540]Miami VA Health Care System, Miami FL 33125, USA, [541]Michael E. DeBakey VA Medical Center, Houston, TX 77030, USA, [542]Minneapolis VA Health Care System, Minneapolis, MN 55417, USA, [543]N. FL/S. GA Veterans Health System, Gainesville, FL 32608, USA, [544]Northport VA Medical Center, Northport, NY 11768, USA, [545]Overton Brooks VA Medical Center, Shreveport, LA 71101, USA, [546]Phoenix VA Health Care System, Phoenix, AZ 85012, USA, [547]Portland VA Medical Center, Portland, OR 97239, USA, [548]Providence VA Medical Center, Providence, RI 02908, USA, [549]Richard Roudebush VA Medical Center, Indianapolis, IN 46202, USA, [550]Salem VA Medical Center, Salem, VA 24153, USA, [551]San Francisco VA Health Care System, San Francisco, CA 94121, USA, [552]South Texas Veterans Health Care System, San Antonio, TX 78229, USA, [553]Southeast Louisiana Veterans Health Care System, New Orleans, LA 70119, USA, [554]Southern Arizona VA Health Care System, Tucson, AZ 85723, USA, [555]Sioux Falls VA Health Care System, Sioux Falls, SD 57105, USA, [556]St. Louis VA Health Care System, St. Louis, MO 63106, USA, [557]Syracuse VA Medical Center, Syracuse, NY 13210, USA, [558]VA Eastern Kansas Health Care System, Leavenworth, KS 66048, USA, [559]VA Greater Los Angeles Health Care System, Los Angeles, CA 90073, USA, [560]VA Long Beach Healthcare System, Long Beach, CA 90822, USA, [561]VA Maine Healthcare System, Augusta, ME 04330, uSA, [562]VA New York Harbor Healthcare System, New York, NY 10010, USA, [563]VA Pacific Islands Health Care System, Honolulu, HI 96819, USA, [564]VA Pittsburgh Health Care System, Pittsburgh, PA 15240, USA, [565]VA Puget Sound Health Care System, Seattle, WA 98108-1597, USA, [566]VA San Diego Healthcare System, San Diego, CA 92161, USA, [567]VA Sierra Nevada Health Care System, Reno, NV 89502, USA, [568]VA Southern Nevada Healthcare System, North Las Vegas, NV 89086, USA, [569]VA Tennessee Valley Healthcare System, South Nashville, TN 37212, USA, [570]Washington DC VA Medical Center, Washington, D. C. 20422, USA, [571]W.G. (Bill) Hefner VA Medical Center, Salisbury, NC 28144, USA, [572]White River Junction VA Medical Center, White River Junction, VT 05009, USA, [573]William S. Middleton Memorial Veterans Hospital, Madison, WI 53705, USA

DiscovEHR (DiscovEHR and MyCode Community Health Initiative)

Jason E. Miller[190,191], Shefali S. Verma[67], Anne E. Justice[9,496]

[9]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27516, USA, [67]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA, [190]Biomedical and Translational Informatics Institute, Geisinger, Danville, PA 17821, USA, [191]Department of Genetics, Institute for Biomedical Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA, [496]Department of Population Health Sciences, Geisinger, Danville, PA 17822, USA

eMERGE (Electronic Medical Records and Genomics Network)

Murray Brilliant[574], Wendy Chung[575,576], Paul Crane[577], Damien Croteau-Chonka[57], Josh Denny[450,578], Todd Edwards[58,579], Geoff Hayes[580], Scott Hebbring[581], George Hripsak[582], Krzysztok Kiryluk[576], Terrie Kitchner[574], Iftikhar Kullo[583], Bahram Namjou[584], Peggy Peissig[574], Ning Shang[576], Digna Velez Edwards[578,579,585], Chunhua Weng[582]

[57]Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA, [58]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA, [450]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA, [575]Department of Pediatrics, Columbia University, New York, NY 10032, USA, [576]Department of Medicine, Columbia University, New York, NY 10032, USA, [577]Division of General Internal Medicine, Department of Internal Medicine, University of Washington School of Medicine, Seattle, WA 98195, USA, [578]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN 37232, USA, [579]Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN 37232, USA, [580]Department of Medicine (Endocrinology), Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA, [581]Center for Human Genetics, Marshfield Clinic, Marshfield, WI 54449, USA, [582]Department of Biomedical Informatics, Columbia University, New York, NY 10032, USA, [583]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905, USA, [584]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA, [585]Division of Quantitative Science, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN 37230, USA

Lifelines Cohort Study

Raul Aguirre-Gamboa[586], Patrick Deelen[586], Lude Franke[586], Jan A. Kuivenhoven[587], Esteban A. Lopera Maya[586], Ilja M. Nolte[41], Serena Sanna[586], Harold Snieder[41], Morris A Swertz[586], Peter M. Visscher[1,41], Judith M. Vonk[41], Cisca Wijmenga[586]

[1]Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD 4072, Australia, [41]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, 9700 RB, the Netherlands,[586]Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, 9700 RB, the Netherlands, [587]Department of Pediatrics, University of Groningen, University Medical Center Groningen, Groningen, 9700 RB, the Netherlands

The PRACTICAL Consortium

Rosalind A. Eeles[489,588], Zsofia Kote-Jarai[489], Kenneth R. Muir[589], Artitaya Lophatananon[589], Catherine M. Tangen[590], Phyllis J. Goodman[590], Ian M. Thompson Jr.[591], Alicja Wolk[592], Niclas Håkansson[593], Demetrius Albanes[15], Stephanie Weinstein[15], Nora Pashayan[594,595], Alison M. Dunning[595], Maya Ghoussaini[596], Jyotsna Batra[597,598], Suzanne Chambers[599,600], Judith A. Clements[597,598], Lisa Horvath[601,602], Leire Moya[597,598], Gail P. Risbridger[603,604], Wayne Tilley[605], Sonja I. Berndt[15], Stephen Chanock[15], Gerald L. Andriole[606], Robert N. Hoover[15], Stella Koutros[15], Laura Beane Freeman[15], Florence Menegaux[607], Thérèse Truong[607], Christopher A. Haiman[339], Fredrick R. Schumacher[167,608], Loic Le Marchand[391], Xin Sheng[339], Robert J. MacInnis[609,610], Melissa C. Southey[609,611,612], Graham G. Giles[609,610,611], Roger L. Milne[609,610,611], Robert J. Hamilton[613,614], Antonio Finelli[615], Manolis Kogevinas[616,617,618], Javier Llorca[619,620], Gemma Castaño-Vinyals[616,617,618], Antonio Alcaraz[621], Olivier Cussenot[622,623], Géraldine Cancel-Tassin[622,623], Janet L. Stanford[110,435], Elaine A. Ostrander[624], Adam S. Kibel[625], Bettina F. Drake[626], Hermann Brenner[627,628,629], Xin Gao[627], Bernd Holleczek[630], Ben Schöttker[627], Esther M. John[631], Jong Y. Park[632], Hui-Yi Lin[633], Nawaid Usmani[634,635], Matthew Parliament[634,635], Aswin Abraham[634], Susan L. Neuhausen[636], Yuan Chun Ding[636], Linda Steele[636], Jose Esteban Castelao[637], Manuela Gago-Dominguez[638,639], Maria Elena Martinez[639], Frank Claessens[640], Steven Joniau[641], Thomas Van den Broeck[640,641], Christiane Maier[642], Manuel Luedeke[643], Thomas Schnoeller[644], Marija Gamulin[645], Davor Lessel[646], Tomislav Kulis[647]

[15]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD 20850, USA, [110]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA, [167]Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH 44106, USA, [339]Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, CA 90089, USA, [391]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI 96813, USA, [435]Department of Epidemiology, University of Washington, Seattle, WA 98195, USA, [489]The Institute of Cancer Research, London, SM2 5NG, UK, [595]Centre for Cancer Genetic Epidemiology,

Department of Oncology, University of Cambridge, Strangeways Laboratory, Cambridge, CB1 8RN, UK, [596]Open Targets, Wellcome Sanger Institute, Hinxton, Saffron Walden, CB10 1SA, UK, [597]Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and School of Biomedical Sciences, Queensland University of Technology, Brisbane QLD 4059, Australia, [598]Translational Research Institute, Brisbane, QLD 4102, Australia, [599]Faculty of Health Sciences, Australian Catholic University, Banyo ALD 4014, Australia, [600]Cancer Council Queensland, Fortitude Valley, QLD 4006, Australia, [601]Chris O'Brien Lifehouse (COBLH), Camperdown, Sydney, NSW 2010, Australia, [602]Garvan Institute of Medical Research, Sydney NSW 2010, Australia, [603]Department of Anatomy and Developmental Biology, Biomedicine Discovery Institute, Monash University, Melbourne,Victoria 3800, Australia, [604]Prostate Cancer Translational Research Program, Cancer Research Division, Peter MacCallum Cancer Centre, Melbourne, VIC 3000, Australia, [605]Dame Roma Mitchell Cancer Research Laboratories, University of Adelaide, Adelaide, South Australia, Australia, [606]Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA, [607]"Exposome and Heredity", CESP (UMR 1018), Faculté de Médecine, Université Paris-Saclay, Inserm, Gustave Roussy, Villejuif, France, [608]Seidman Cancer Center, University Hospitals, Cleveland, OH 44106, USA, [609]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, VIC 3004, Australia, [610]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, VIC 3010, Australia, [611]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC 3168, Australia, [612]Department of Clinical Pathology, The Melbourne Medical School, The University of Melbourne, Melbourne, VIC 3010, Australia., [613]Dept. of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada, [614]Dept. of Surgery (Urology), University of Toronto, Toronto, ON M5G 2M9, Canada, [615]Division of Urology, Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada, [616]ISGlobal, 08036 Barcelona, Spain, [617]IMIM (Hospital del Mar Medical Research Institute), 08003 Barcelona , Spain, [618]Universitat Pompeu Fabra (UPF), 08002 Barcelona, Spain, [619]University of Cantabria, 39005 Santander, Spain, [620]CIBER Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain, [621]Department and Laboratory of Urology, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, 08036 Barcelona, Spain, [622]Sorbonne Universite, GRC n°5 , AP-HP, Tenon Hospital, F-75020 Paris, France, [623]CeRePP, Tenon Hospital, F-75020 Paris, France., [624]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA, [625]Division of Urologic Surgery, Brigham and Womens Hospital, Boston, MA 02115, USA, [626]Department of Surgery, Washington University School of Medicine, St. Louis, MO 63110, USA, [627]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), D-69120, Heidelberg, Germany, [628]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), D-69120 Heidelberg, Germany, [629]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), 69120 Heidelberg, Germany, [630]Saarland Cancer Registry, 66119 Saarbrücken, Germany, [631]Departments of Epidemiology & Population Health and of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA 94304, USA, [632]Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL 33612, USA, [633]School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA, [634]Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta T6G 1Z2, Canada, [635]Division of Radiation Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta T6G 1Z2, Canada, [636]Department of Population Sciences, Beckman Research Institute of the City of Hope, Duarte, CA 91010, USA, [637]Genetic Oncology Unit, CHUVI Hospital, Complexo Hospitalario Universitario de Vigo, Instituto de Investigación Biomédica Galicia Sur (IISGS), 36204, Vigo (Pontevedra), Spain, [638]Genomic Medicine Group, Galician Foundation of Genomic Medicine, Instituto de Investigacion Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, Servicio Galego de Saúde, SERGAS, 15706, Santiago de Compostela, Spain, [639]University of California San Diego, Moores Cancer Center, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA 92093, USA, [640]Molecular Endocrinology Laboratory, Department of Cellular and Molecular Medicine, KU Leuven, BE-3000, Belgium, [641]Department of Urology, University Hospitals Leuven, BE-3000 Leuven, Belgium, [642]Humangenetik Tuebingen, D-72076 Tuebingen, Germany, [643]genetikum, D-89231 Neu-Ulm, Germany, [644]Department of Urology, University

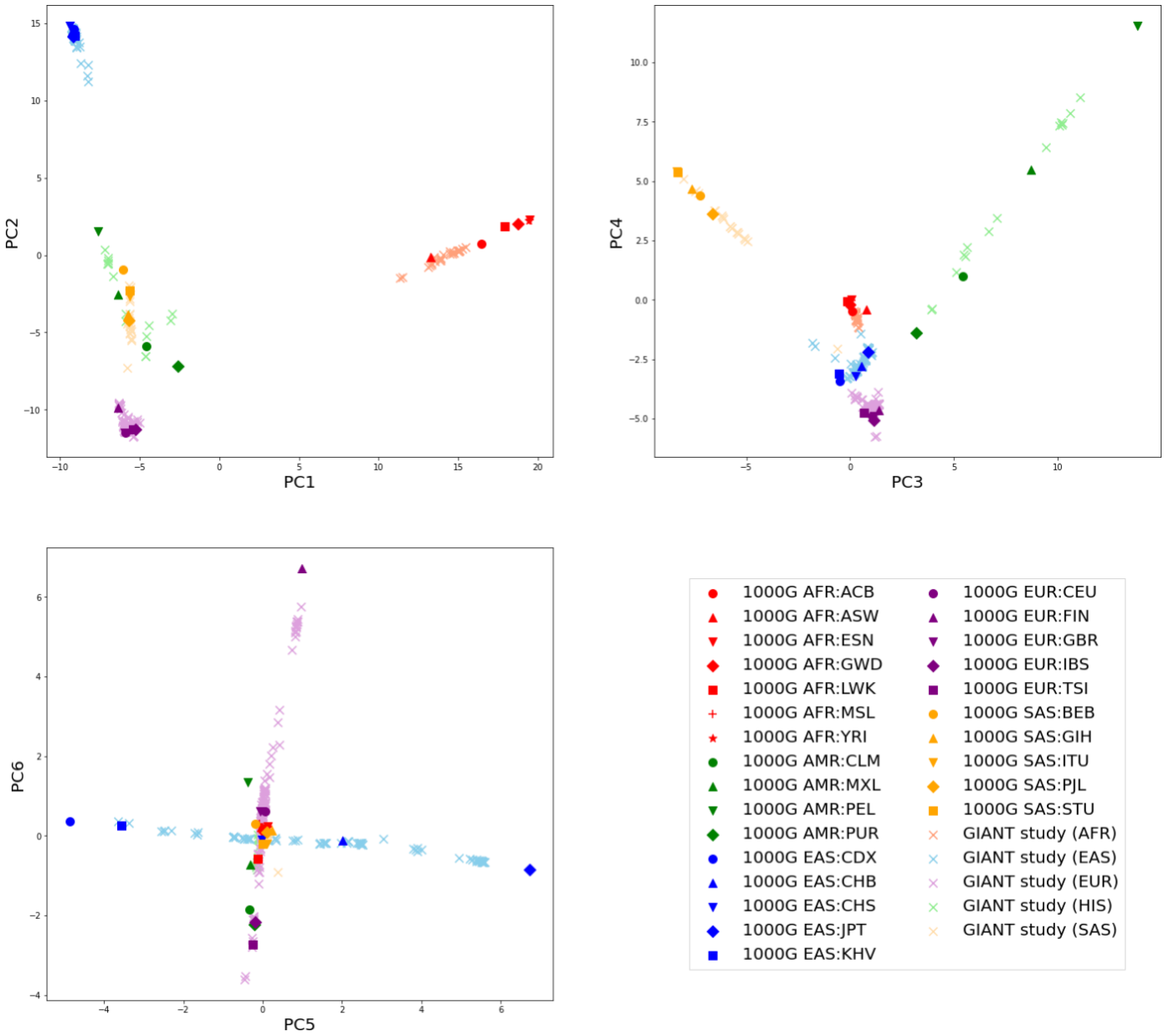
Hospital Ulm, Ulm, Germany, [645]Department of Oncology, University Hospital Centre Zagreb, University of Zagreb, School of Medicine, 10 000 Zagreb, Croatia, [646]Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, D-20246 Hamburg, Germany, [647]Department of Urology, University Hospital Center Zagreb, University of Zagreb School of Medicine, 10 000 Zagreb, Croatia

Understanding Society Scientific Group

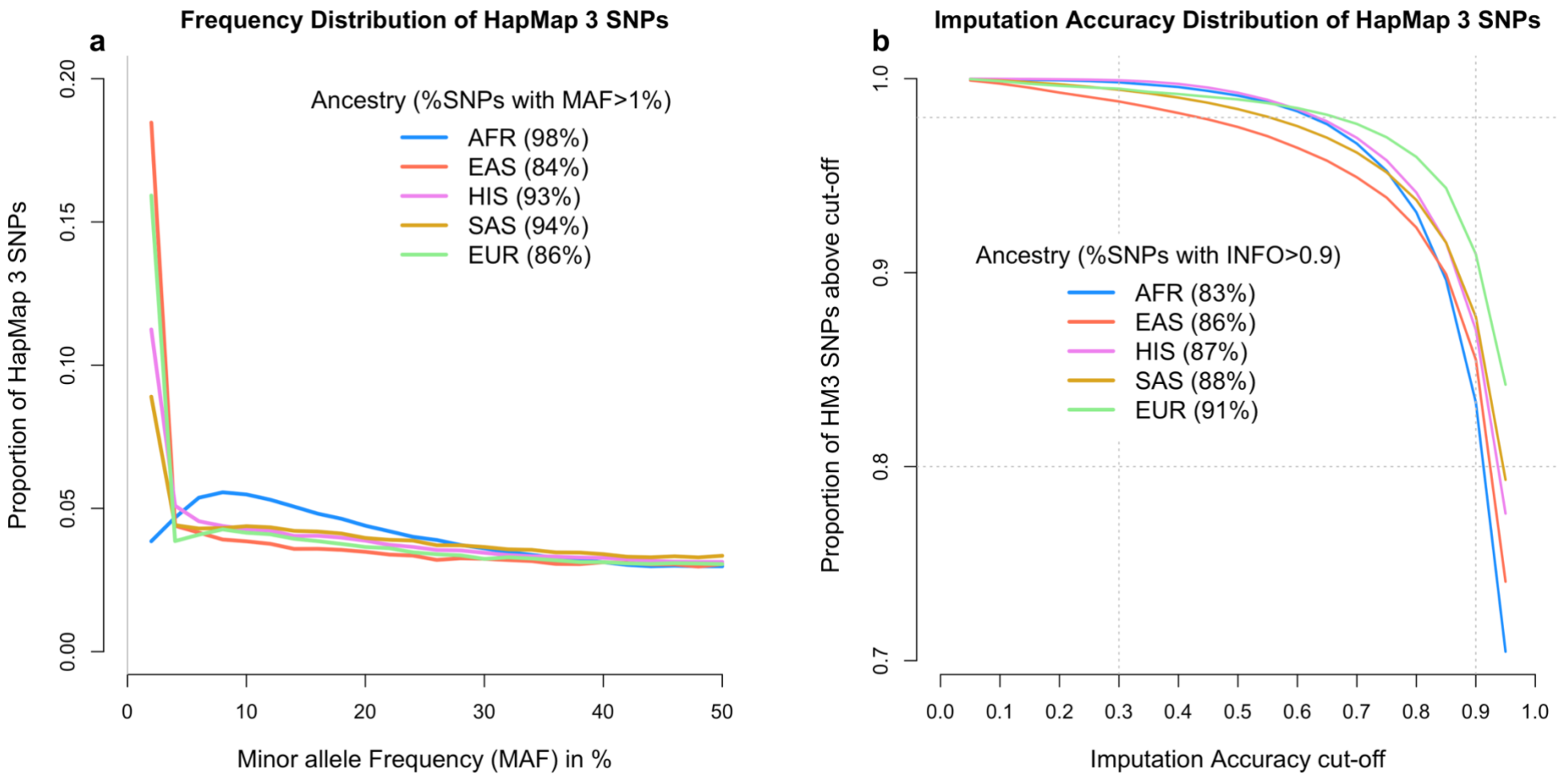
Michaela Benzeval[387], Jonathan Burton[387], Nicholas Buck[387], Annette Jäckle[387], Meena Kumari[387], Heather Laurie[387], Peter Lynn[387], Stephen Pudney[387], Birgitta Rabe[387], Dieter Wolke[648]

[387]Institute for Social and Economic Research, University of Essex, Wivenhoe Park CO4 3SQ, UK, [648]Division of Health Science, Warwick Medical School, University of Warwick, Coventry CV4 7AL, UK

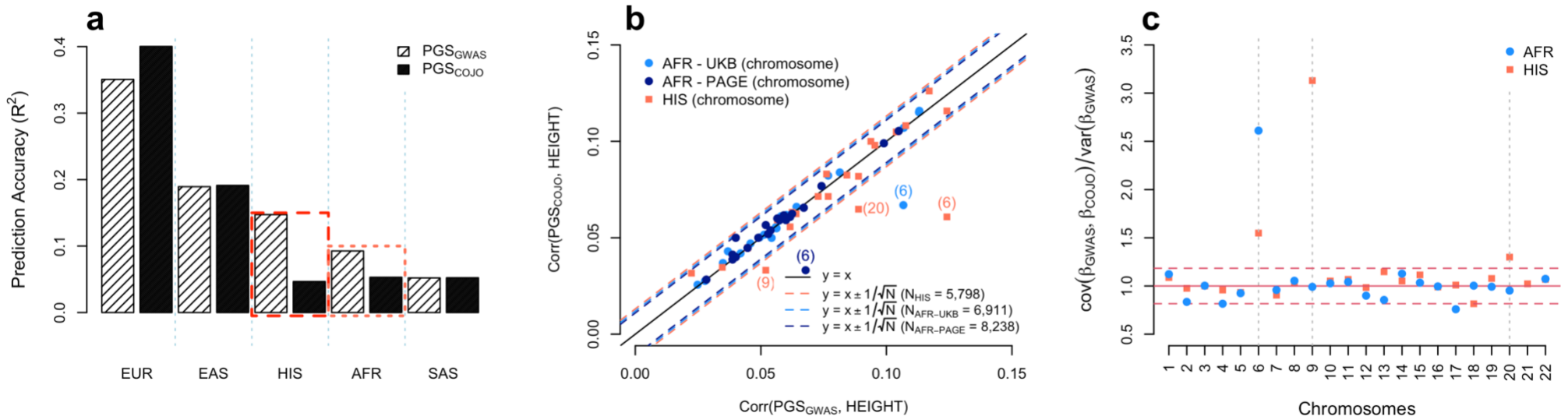
SUPPLEMENTARY FIGURES



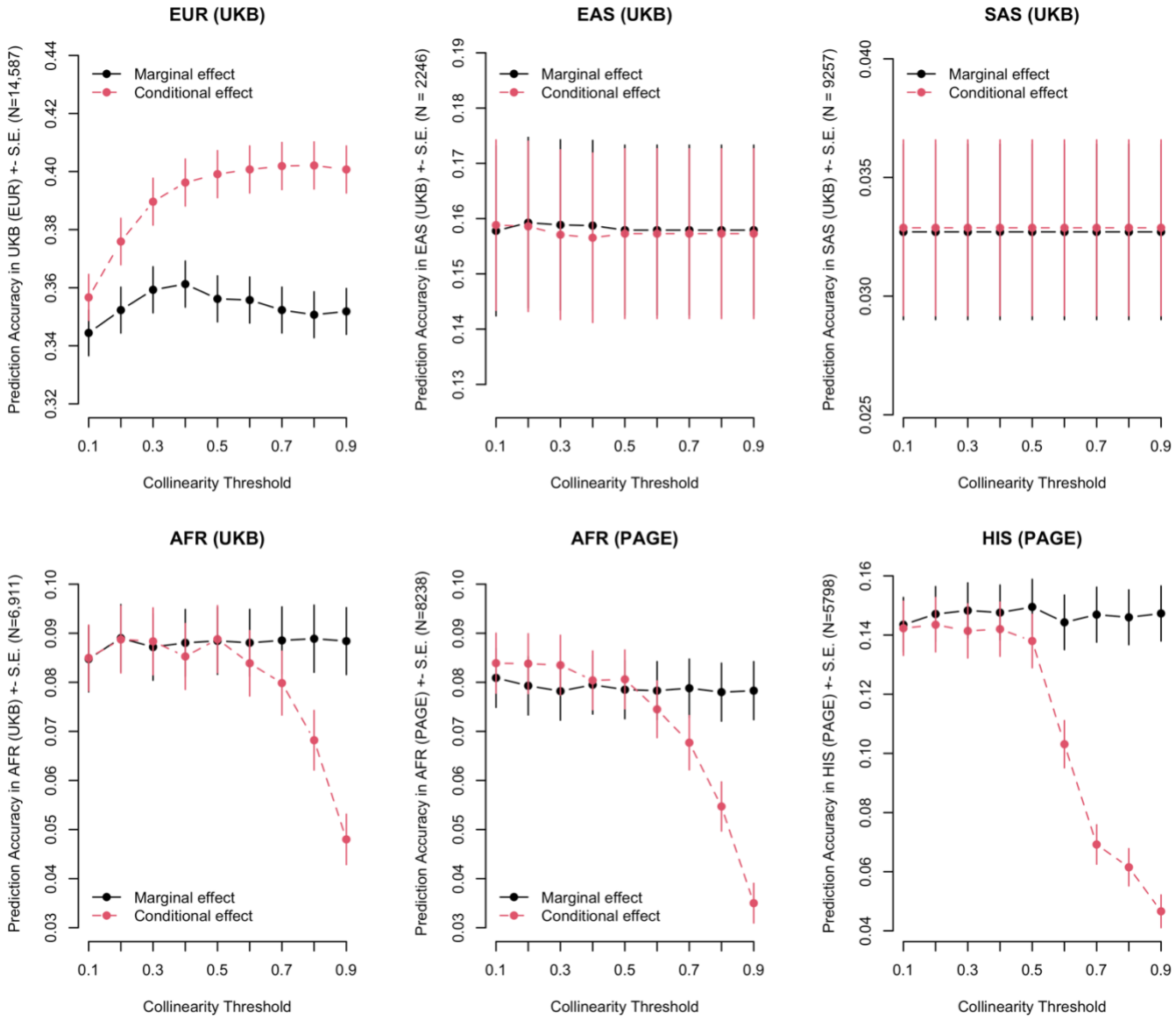
Suppl. Fig. 1. Principal components analysis of contributing studies to the height meta-analysis alongside 26 genetic ancestry groups from the 1000 Genomes Project. Using data from 2,504 samples from the 1000 Genomes Project (1KGP), genotypes for 354,568 HapMap3 SNPs with frequency data from all participating studies were extracted. LD-pruning was subsequently performed using PLINK with a window size of 1Mb, a shift size of 50 variants, and an LD r^2 cut-off of 0.1 (PLINK command: --indep-pairwise 1000 50 0.1). After LD-pruning, 18,125 SNPs remained for subsequent analysis. Allele frequencies for the pruned set of variants were subsequently calculated within each of the 26 1KGP ancestral groups and aligned to the same reference allele. Principal components analysis was subsequently performed by using the 1KGP frequency data to build the model prior to projection of participating studies, having ensured study allele frequencies were also aligned to the same 1KGP reference allele.



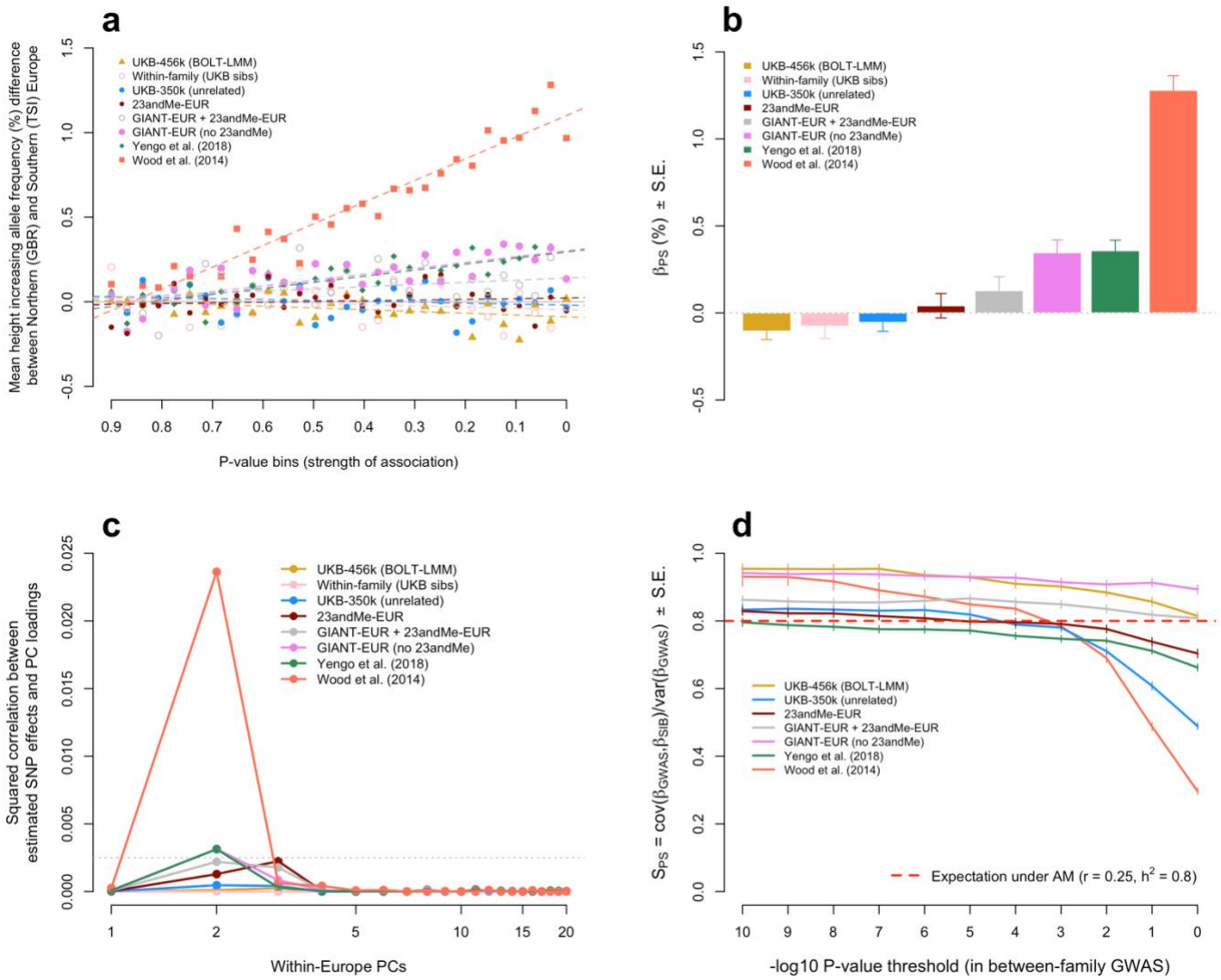
Suppl. Fig. 2. Frequency and imputation accuracy distribution of HapMap 3 SNPs across ancestry groups. **Panel a**. Minor allele frequency (MAF) distribution of HapMap 3 SNPs across 5 ancestries: European (EUR), Hispanic (HIS), African (AFR), East-Asian (EAS) and South-Asian (SAS). **Panel b**. Average (across cohorts) proportion (y-axis) of HapMap 3 SNPs with a imputation accuracy statistic (INFO) above a certain threshold (x-axis). Vertical lines highlight two thresholds (0.3 and 0.9) commonly used to ascertained SNPs on imputation accuracy. Overall, **Panel b** shows that HapMap 3 SNPs are well imputed across all ancestry groups with >98% of SNPs with INFO>0.3 and >80% of SNPs with INFO>0.9.



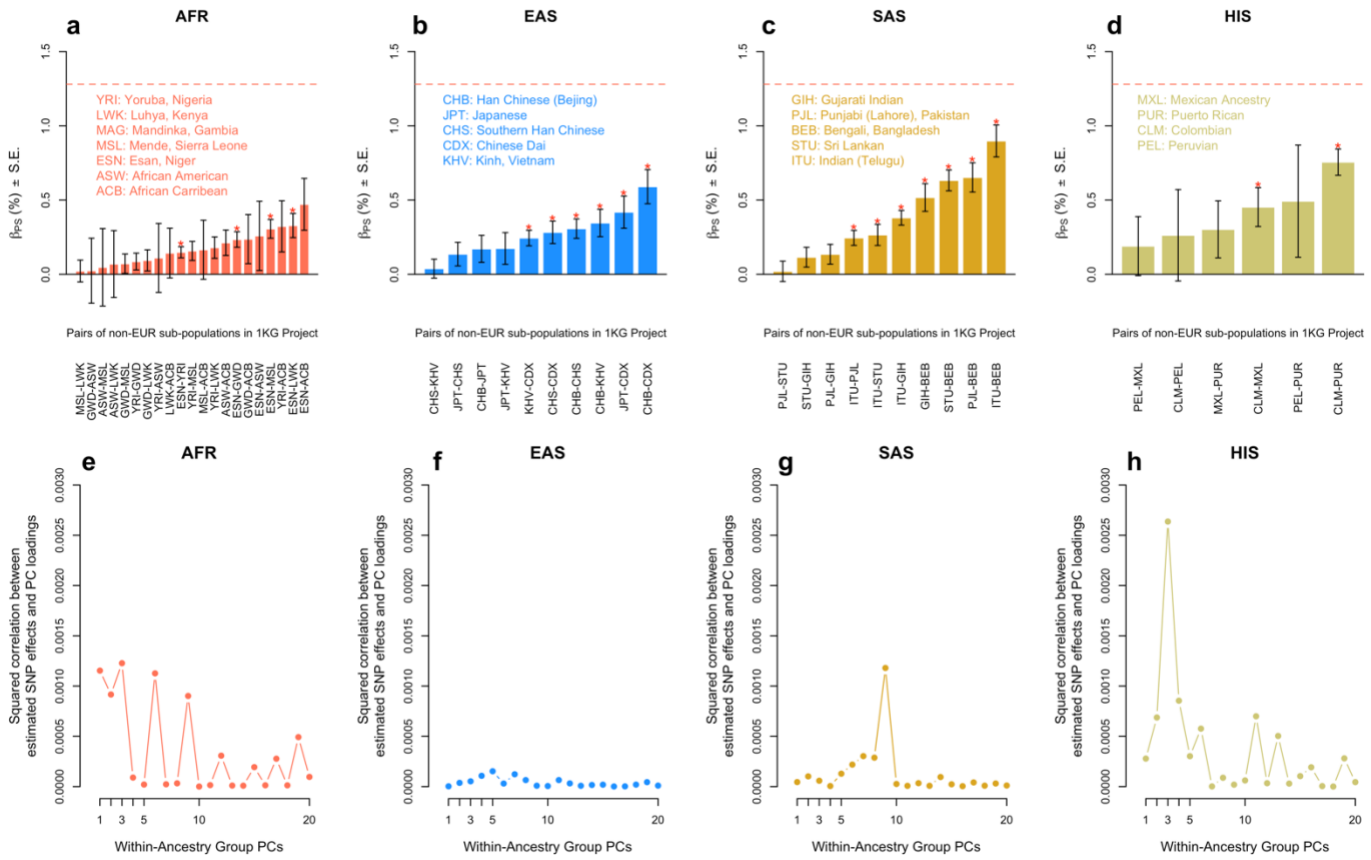
Suppl. Fig. 3. Biases in conditional and joint effect estimates. Panel a: Prediction accuracy (squared correlation R^2) of polygenic scores (PGS) based on genome-wide significant (GWS) SNPs identified in 5 ancestry groups (EUR: European, EAS: East-Asian, HIS: Admixed Hispanic ethnicity, AFR: African (mostly Admixed African American) and SAS: South-Asian). For each set of GWS SNPs, Panel a compares the prediction accuracy obtained when the PGS is calculated from marginal SNP effects (PGS_{GWAS}) versus when the PGS is calculated from joint SNP effects (PGS_{COJO}) estimated with the GCTA-COJO algorithm using default parameters. In ancestry groups, except HIS and AFR, the accuracy of PGS_{COJO} is larger than that of PGS_{GWAS}. **Panel b** contrasts the per-chromosome correlation between PGS_{GWAS} and height (x-axis) with the per-chromosome correlation between PGS_{COJO} and height (y-axis). These correlations were calculated in 2 samples of African ancestry participants from the UK Biobank (UKB, $N_{AFR-UKB}$=6,911) and the PAGE study ($N_{AFR-PAGE}$=8,238) and in 1 sample of Admixed Hispanic individuals also from the PAGE study ($N_{HIS-PAGE}$=5,798). **Panel c** represents for each chromosome (x-axis) the slope from regressing marginal SNP effects on joint SNP effects (y-axis). Regression slopes were estimated for GWS SNPs identified on each chromosome in GWAS meta-analyses in African and Hispanic ancestry groups. These results are further described and discussed in **Suppl. Note 1**.



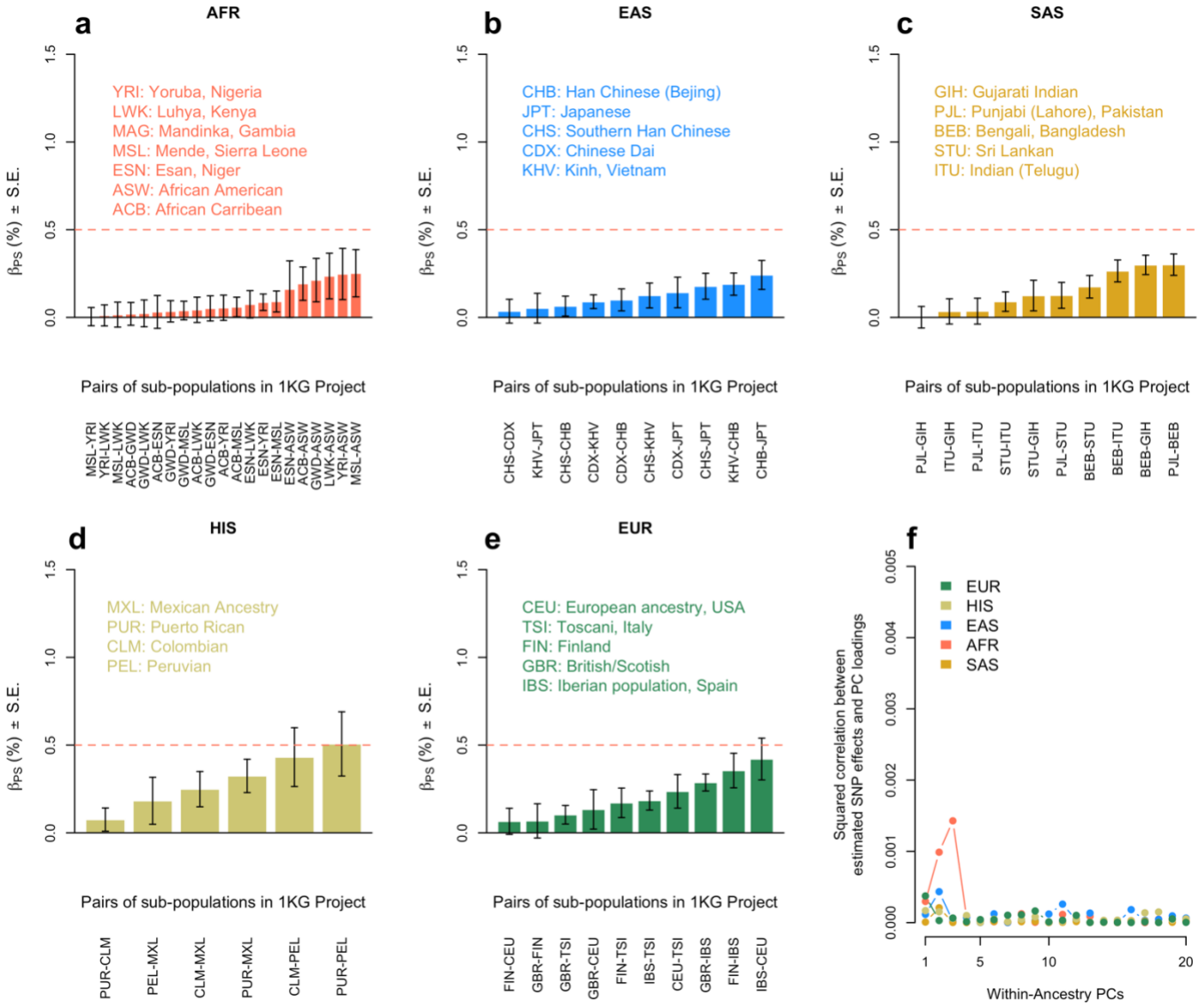
Suppl. Fig. 4. Impact of the collinearity threshold (CT) used in the GCTA-COJO algorithm on prediction accuracy of polygenic scores (PGS) based using estimates joint effects. By default, the GCTA-COJO algorithm implements a stepwise model selection to identify sets of jointly significant SNPs such that the variance of genotypes at any SNP retained in the final model is not explained at more than CT=90% by other SNPs included in the model. We varied the value of the CT between 0.9 (least stringent) and 0.1 (most stringent) and monitored the prediction accuracy of PGS in different samples. Each panel represents CT on the x-axis and the prediction accuracy on the y-axis in a given ancestry group match with the ancestry of GWAS participants. Red dots represent prediction accuracies of PGS calculated from joint effects (PGS_{COJO}) and black that from marginal effects (PGS_{GWAS}). Overall, using stringent CT values tend to degrade the performances of PGS_{COJO} in all ancestry groups (EUR: European, EAS: East-Asian and SAS: South-Asian) except in admixed individuals with African ancestries (AFR) and of Hispanic ethnicity (HIS). These results are further described and discussed in **Suppl. Note 1**.



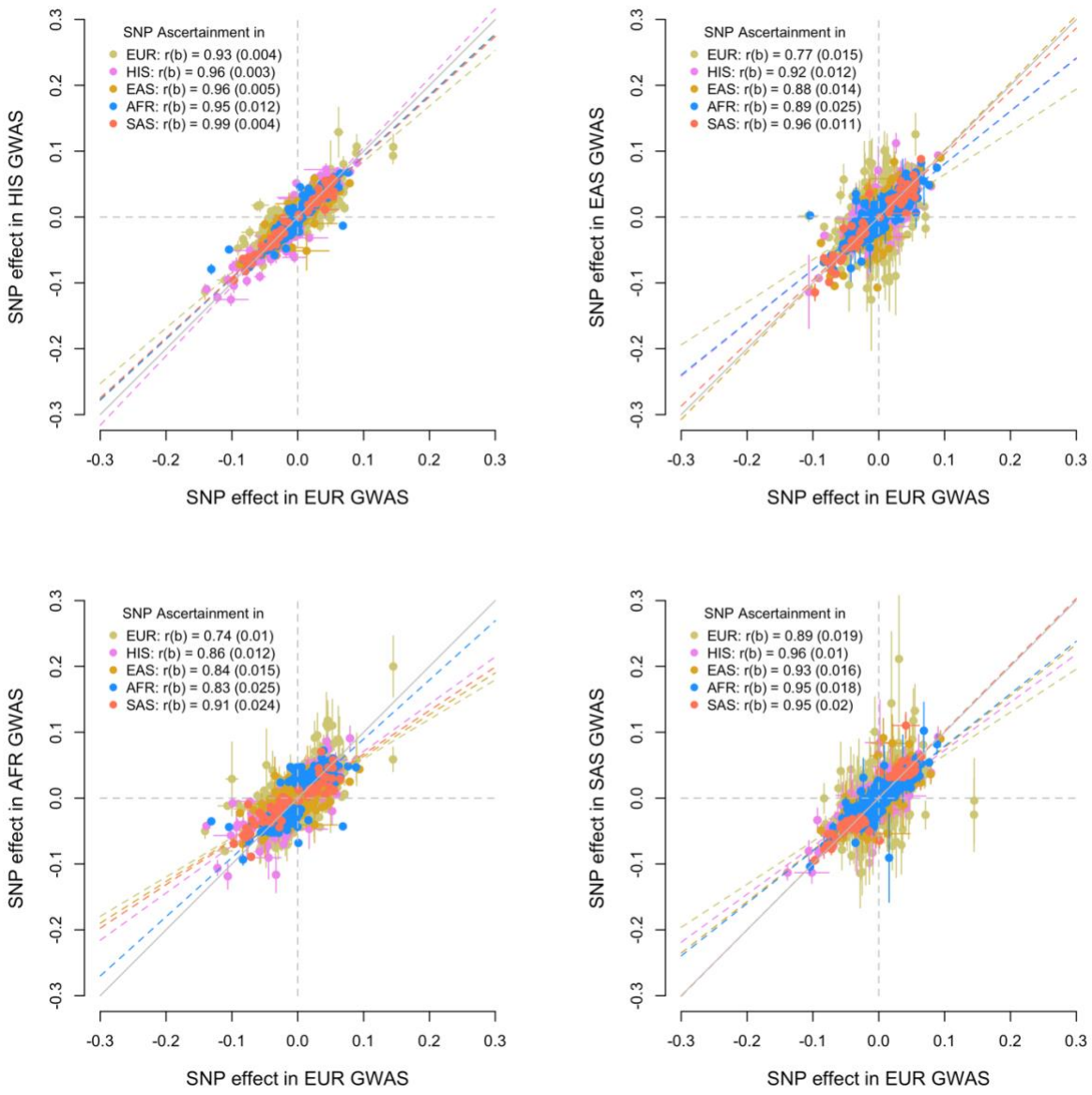
Suppl. Fig. 5. Quantification of confounding due to population stratification (PS) in various European ancestry (EUR) GWAS of height. UKB-456k (BOLT-LMM): GWAS in 456,414 EUR participants of the UKB. UKB-350k (unrelated): GWAS in 348,501 unrelated (i.e. estimated genetic relatedness <0.05) EUR participants of UKB. 23andMe-EUR: GWAS in EUR participants of 23andMe. GIANT-EUR: GWAS meta-analysis of 173 EUR cohorts from the GIANT consortium. Within-family (UKB): Family-based GWAS performed in 17,942 independent EUR sibling pairs from the UKB. **Panel a** represents the relationship between strength of association between 101,360 independent (LD r^2<0.1) HM3 SNPs and height (x-axis: 30 SNP bins) and height-increasing allele frequency differences between the British (GBR) and Tuscan (TSI) samples from the 1,000 Genomes Project (1KGP). A significant slope (β_{PS}) indicates uncorrected PS. **Panel b** shows estimates of β_{PS} for different GWAS and their associated leave-one-SNP-bin-out jackknife standard errors (S.E.). **Panel c** shows the variance in estimated SNP effects from various height GWAS that is explained by SNP loading on genotypic principal components (PC) calculated among 503 EUR samples from the 1KGP. The x-axis in **Panel c** indicates number of vectors of PC loadings including in the regression model (SNP effect regressed on PC loading). **Panel d** shows on the y-axis the slope ($S_{PS} = \mathrm{cov}(\beta_{GWAS}, \beta_{SIB})/\mathrm{var}(\beta_{GWAS})$) from regressing SNP effects estimated in a family-based GWAS (β_{SIB}) onto SNP effects estimated in a standard population-based GWAS (β_{GWAS}). The x-axis in **Panel d** is the -log10 of the p-value threshold used to ascertain SNPs for estimating the regression slope. For each p-value threshold, the effects of ascertained SNPs were corrected for winner's curse (**Methods**). The horizontal red dotted line represented the expected slope under assortative mating (AM) assuming an equilibrium heritability $h^2 = 0.8$ and a spousal correlation $r = 0.25$ (**Suppl. Note 2**).



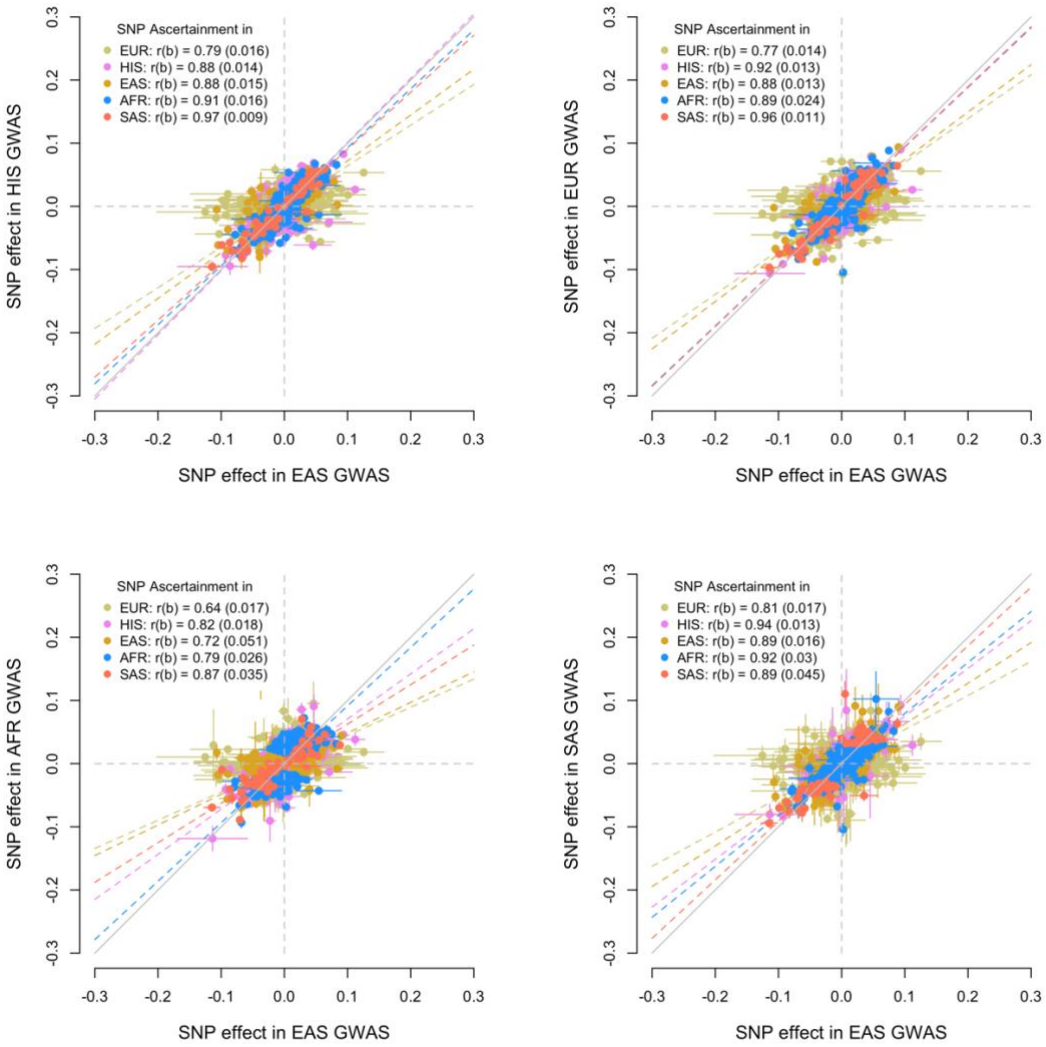
Suppl. Fig. 6. Quantification of confounding due to population stratification (PS) in various non-European ancestry (non-EUR) GWAS of height. Panels **a** and **e**, **b** and **f**, **c** and **g**, **d** and **h** represent quantifications of PS in GWAS conducted in individuals from the African (AFR), East-Asian (EAS), South-Asian (SAS) and Hispanic (HIS) ancestry groups, respectively. The x-axes in all the top panels (**a** – **d**) represent pairs of subpopulations in the 1000 Genomes Project (1KG) within the corresponding ancestry groups. The y-axes in Panels (**a** – **d**) show estimates of β_{PS} (+/- standard errors; S.E.) for SNP effects estimated in the corresponding ancestry group along axes of genetic differentiation between subpopulations indicated on the x-axis. Red dots on top of each bar indicate statistical significance as defined in **Suppl. Note 2** based on different thresholds according to the number of pairs of subpopulation within ancestry groups. The x-axes in all the bottom panels (**e** – **h**) correspond to 20 principal components (PC) calculated in 1KGP samples from the corresponding ancestry group. The y-axes in Panels **e** – **h** show the squared correlations between PC loadings and marginal SNP effects in the corresponding ancestry-specific GWAS meta-analysis. These results are further described and discussed in **Suppl. Note 2**.



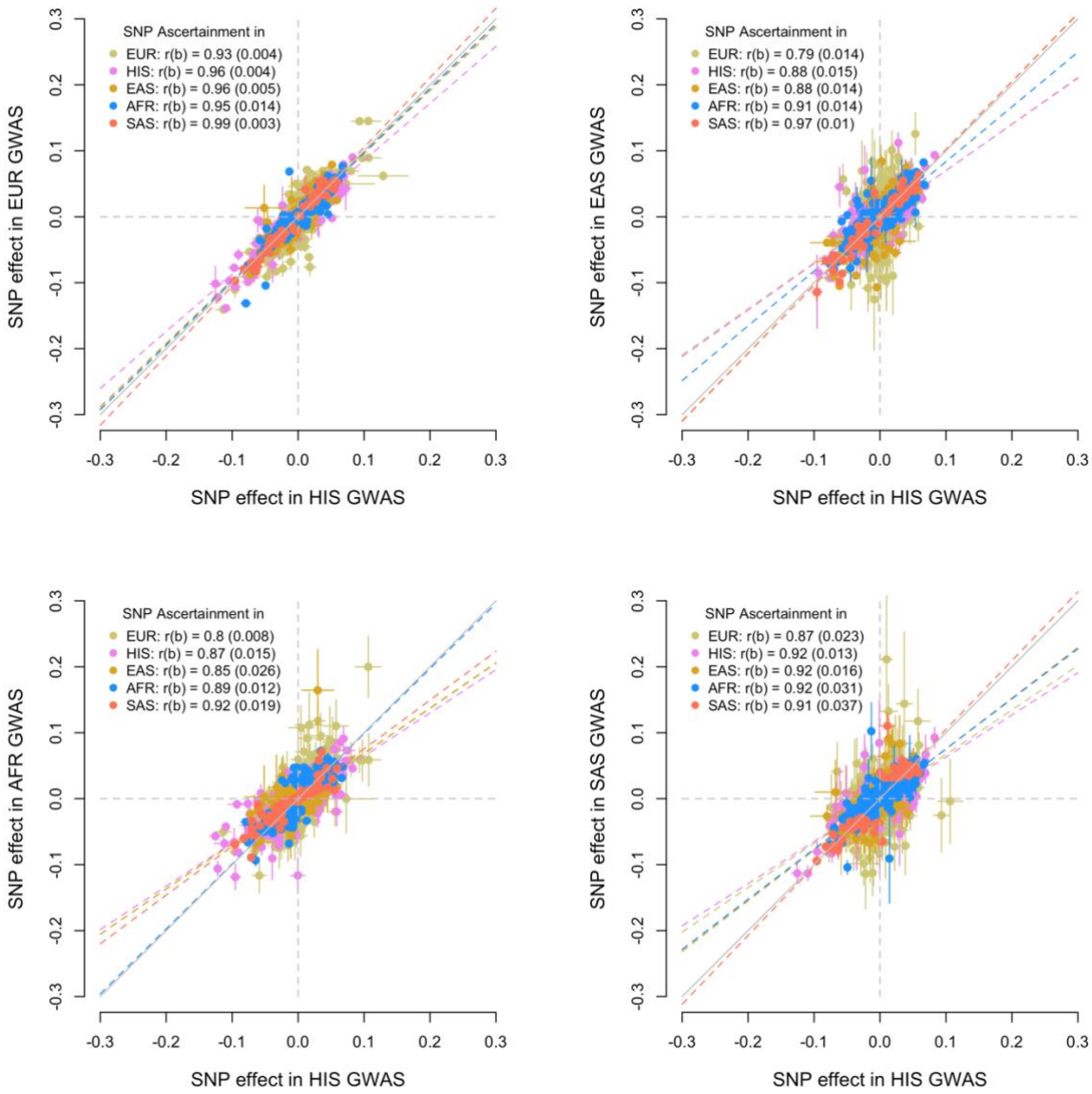
Suppl. Fig. 7. Quantification of confounding due to population stratification (PS) in our cross-ancestry GWAS meta-analysis of height. The x-axis in panels (a – e) shows pairs of subpopulations in the 1000 Genomes Project (1KG) within 5 ancestry groups indicated by the title of the panel (African: AFR, East-Asian: EAS, South-Asian: SAS, HIS: Hispanic, European: EUR). The y-axis in panels (a – e) shows estimates of β_{PS} (+/- standard errors; S.E.) for SNP effects in our cross-ancestry meta-analysis along axes of genetic differentiation between subpopulations indicated on the x-axis. Each dot in **Panel f** represents the squared correlation (y-axis) between SNP effects and loadings of principal components (PC: 1 to 20, indicated on the x-axis) calculated in 5 ancestry groups indicated in the panel legend. These results are further described and discussed in **Suppl. Note 2**.



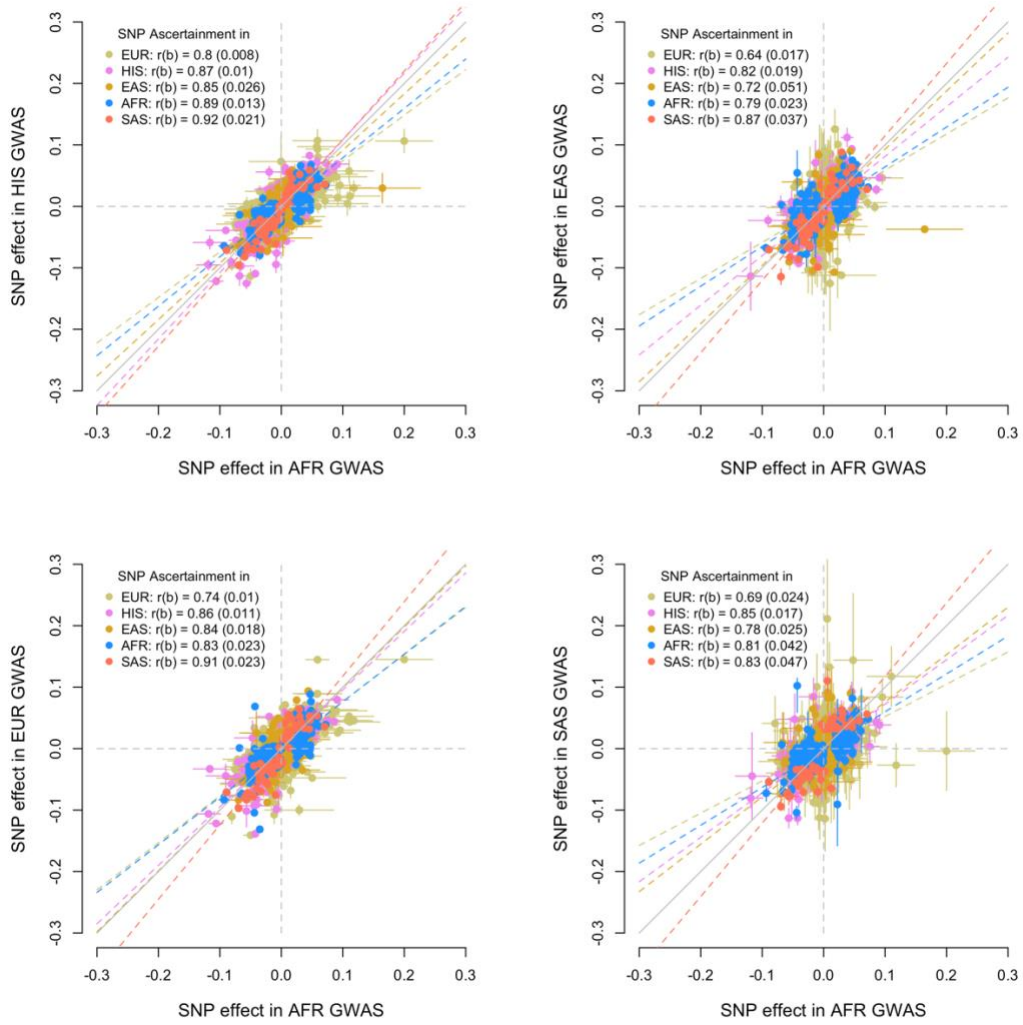
Suppl. Fig. 8. Correlation of marginal SNP effects between European ancestry (EUR, on the x-axis) and non-EUR GWAS (i.e. Hispanic (HIS), African (AFR), East-Asian (EAS) and South-Asian (SAS) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects.



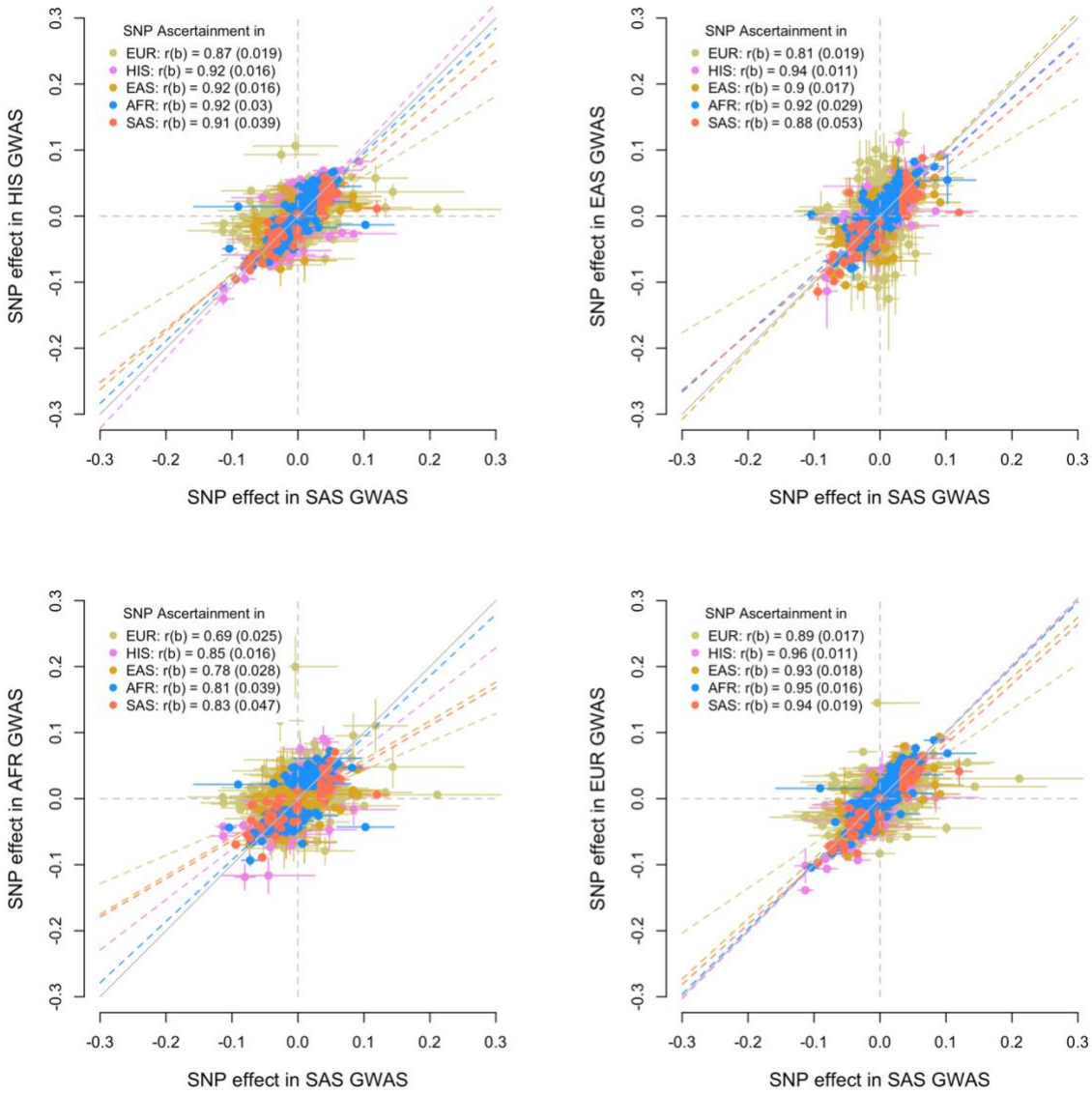
Suppl. Fig. 9. Correlation of marginal SNP effects between East-Asian ancestry (EAS, on the x-axis) and non-EAS GWAS (i.e. Hispanic (HIS), African (AFR), European (EUR) and South-Asian (SAS) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects.



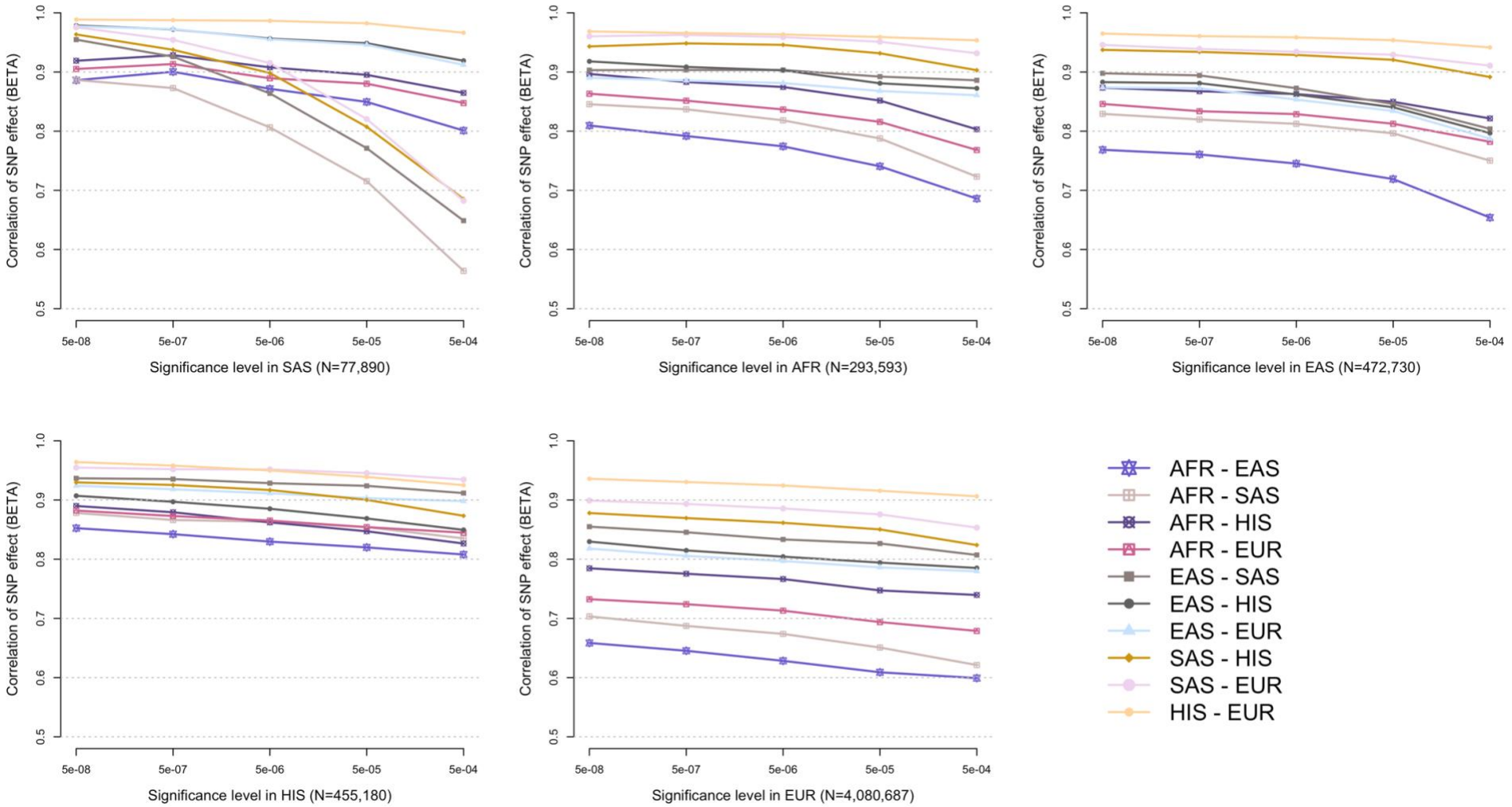
Suppl. Fig. 10. Correlation of marginal SNP effects between Hispanic ethnicity (HIS, on the x-axis) and non-HIS GWAS (i.e. European (EUR), African (AFR), East-Asian (EAS) and South-Asian (SAS) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects.



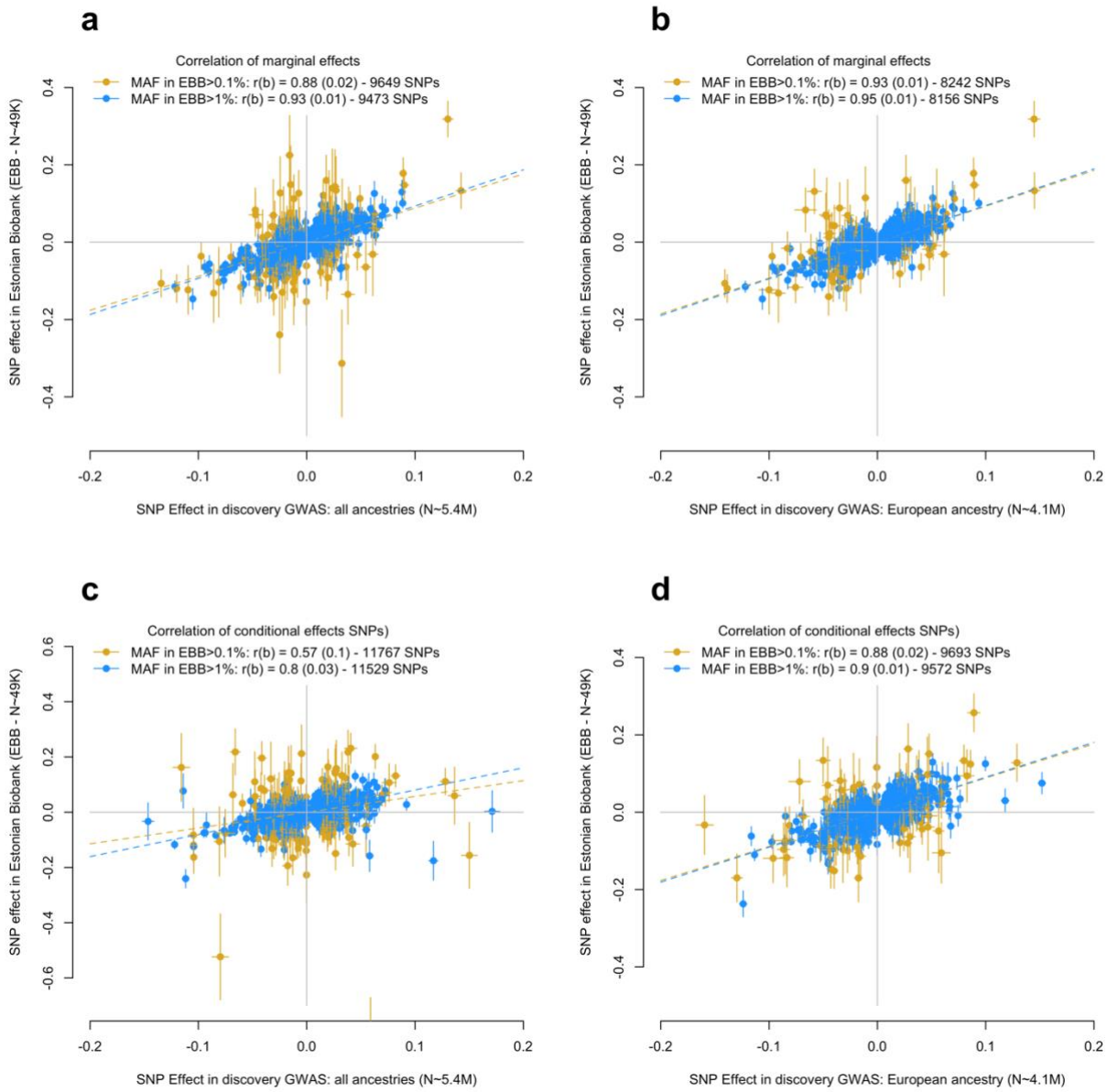
Suppl. Fig. 11. Correlation of marginal SNP effects between African ancestry (AFR, on the x-axis) and non-AFR GWAS (i.e. Hispanic (HIS), European (EUR), East-Asian (EAS) and South-Asian (SAS) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects. Error bars denote standard errors of SNP effects.



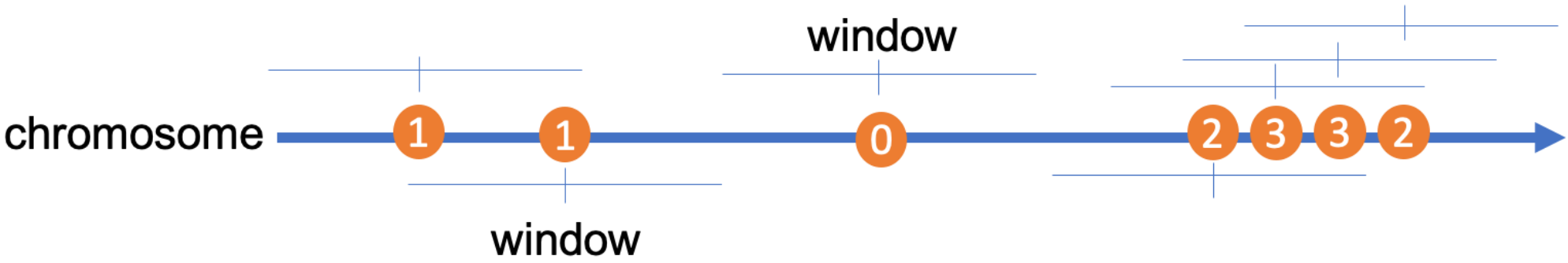
Suppl. Fig. 12. Correlation of marginal SNP effects between South-Asian ancestry (SAS, on the x-axis) and non-SAS GWAS (i.e. Hispanic (HIS), African (AFR), East-Asian (EAS) and European (EUR) on the y-axis). Correlations *r(b)* were corrected for estimation errors as described in the **Methods** section. Each estimate of the correlation of SNP effect is based on SNPs reaching marginal genome-wide significance in any of the 5 ancestries analysed. Standard errors for *r(b)* were obtained using jackknife. Error bars denote standard errors of SNP effects.



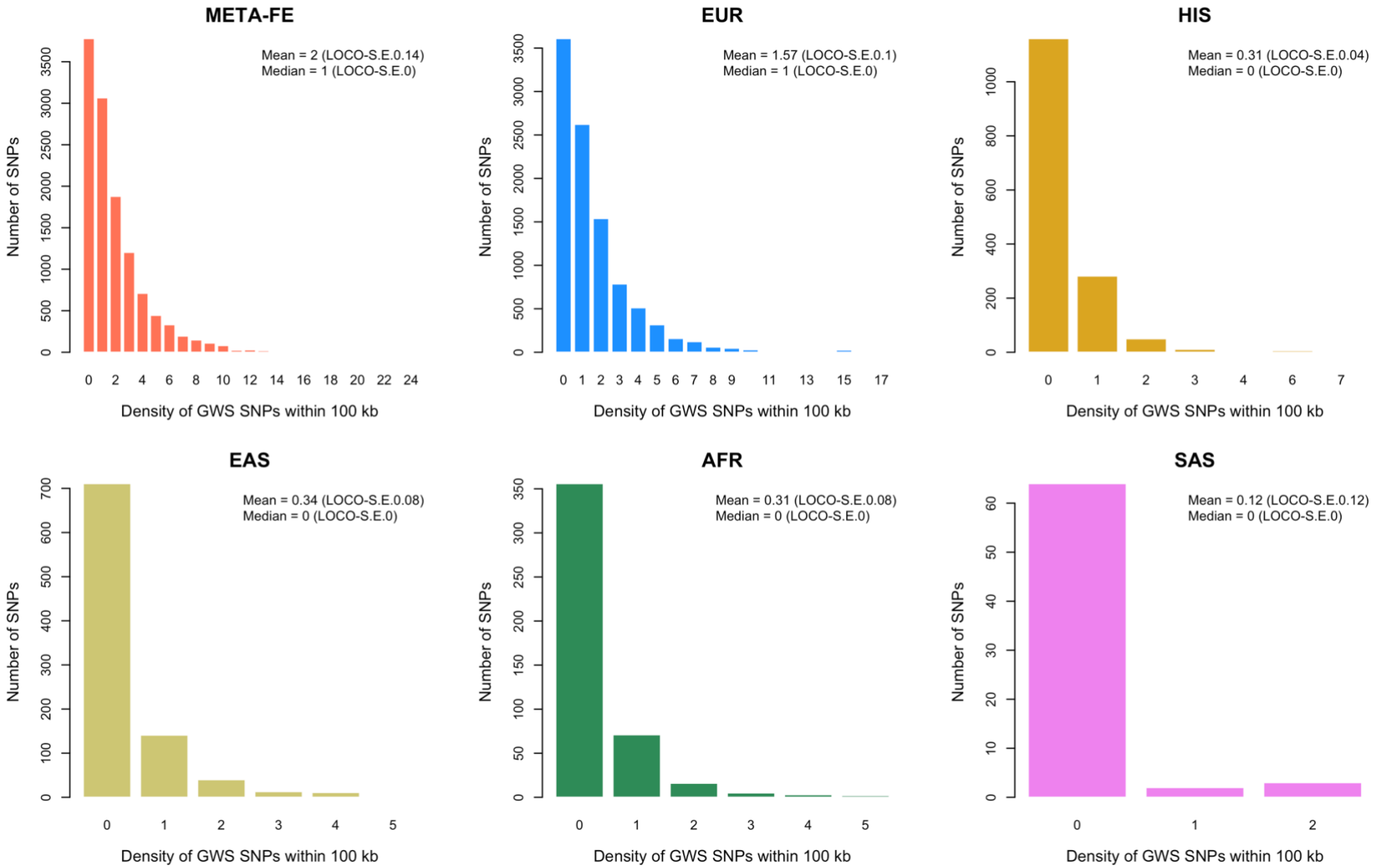
Suppl. Fig. 13. Cross-ancestry correlation of marginal SNP effects ascertained at various significant thresholds. The x-axis in each panel represents significance thresholds used to ascertained SNPs and the y-axis the correlation *r(b)* of estimated marginal effects (**Methods**) across 10 pairs of GWAS performed in 5 ancestry groups (African: AFR, East-Asian: EAS, South-Asian: SAS, HIS: Hispanic, European: EUR). Each panel represents which of the five ancestry-group specific GWAS was used to ascertain SNPs. SNPs were ascertained using GCTA-COJO with a linkage disequilibrium reference set from the corresponding ancestry group. Within each panel, correlations were calculated using the subset of COJO SNPs, which marginal significance also met the significance threshold indicated on the x-axis. Each colour represents a pair of ancestry group.



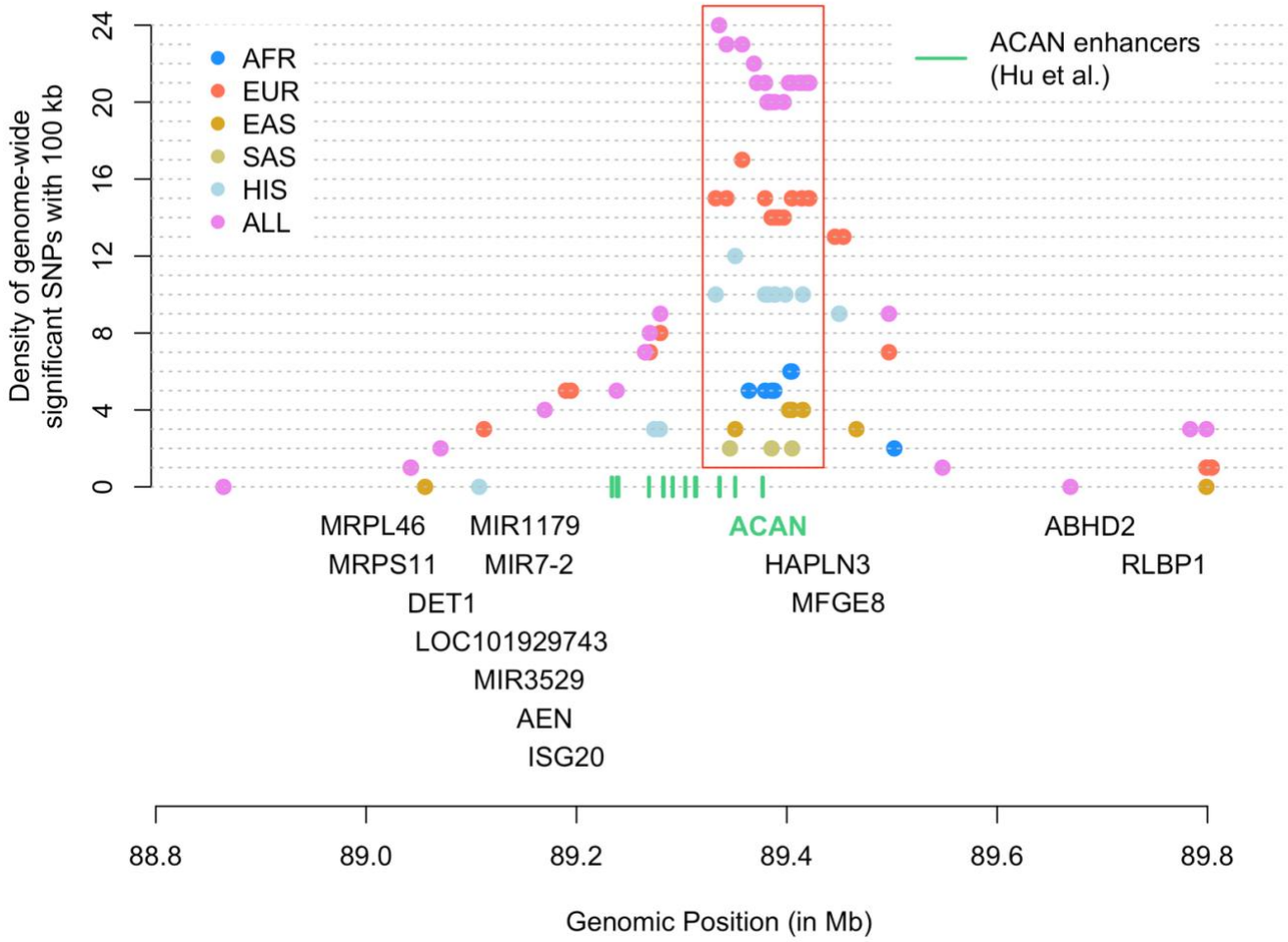
Suppl. Fig. 14. Correlation of marginal and conditional SNPs effects between discovery and replication (Estonian Biobank – EBB) GWAS. Panels a and **b** show correlations of marginal SNP effects for a subset of jointly associated SNPs (identified using the GCTA-COJO methods; **Methods**), which marginal effects also reach genome-wide significance. **Panels c** and **d** represent joint effect re-estimated using approximate conditional analyses (implemented in the GCTA software). Genotypes of ~350,000 unrelated participants of the UK Biobank were used as linkage disequilibrium (LD) reference.



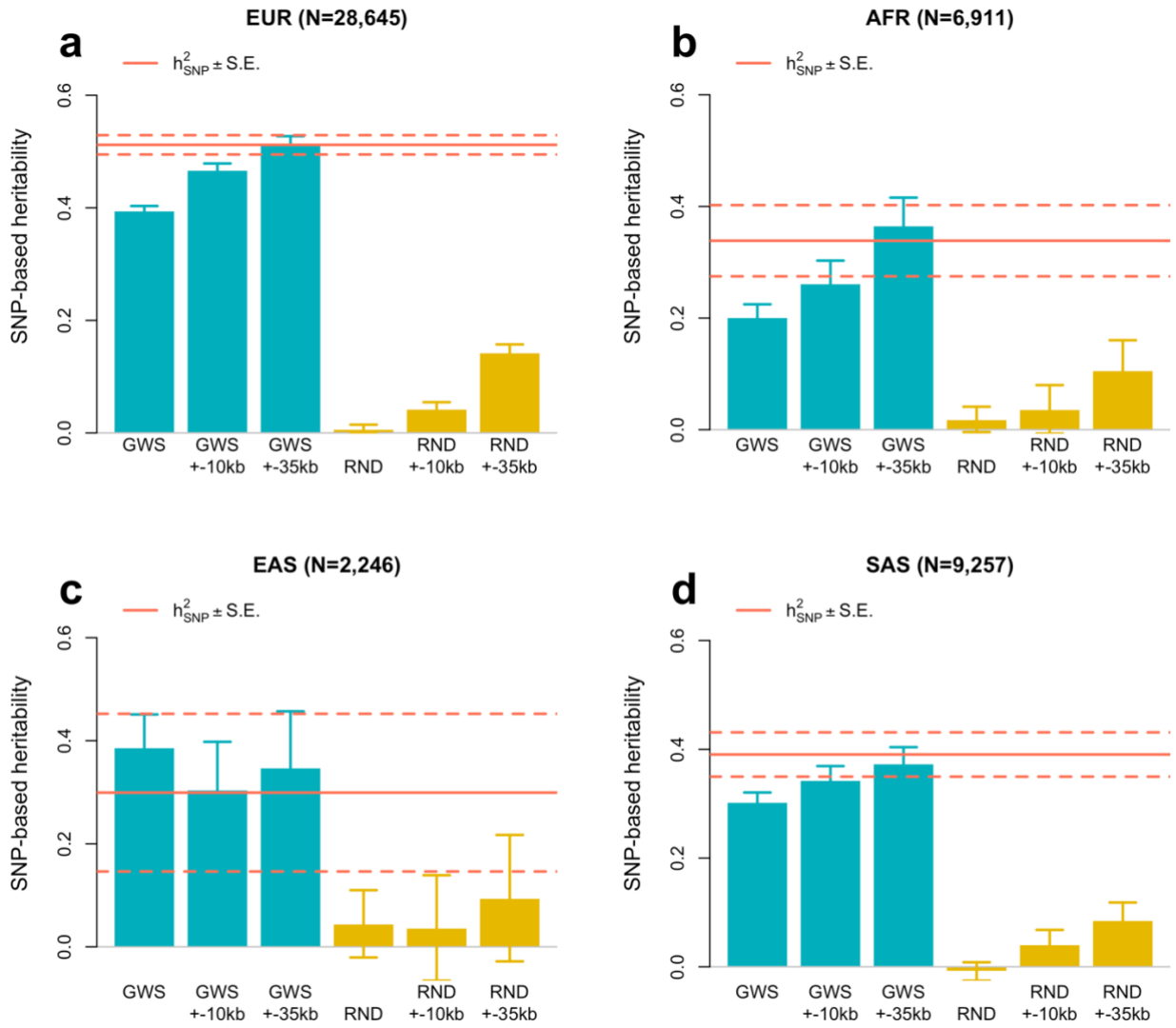
Suppl. Fig. 15. Schematic representation of the measure of signal density. The horizontal arrow represents a chromosome and each circle a specific association. For each association, the density is defined as the number of other independent associations within a certain window. In the example above, the window around the first SNP contains 1 SNP, so its density is 1. Similarly, the density at the third SNP (from the left) is 0 because the window around it does not contain any other association.



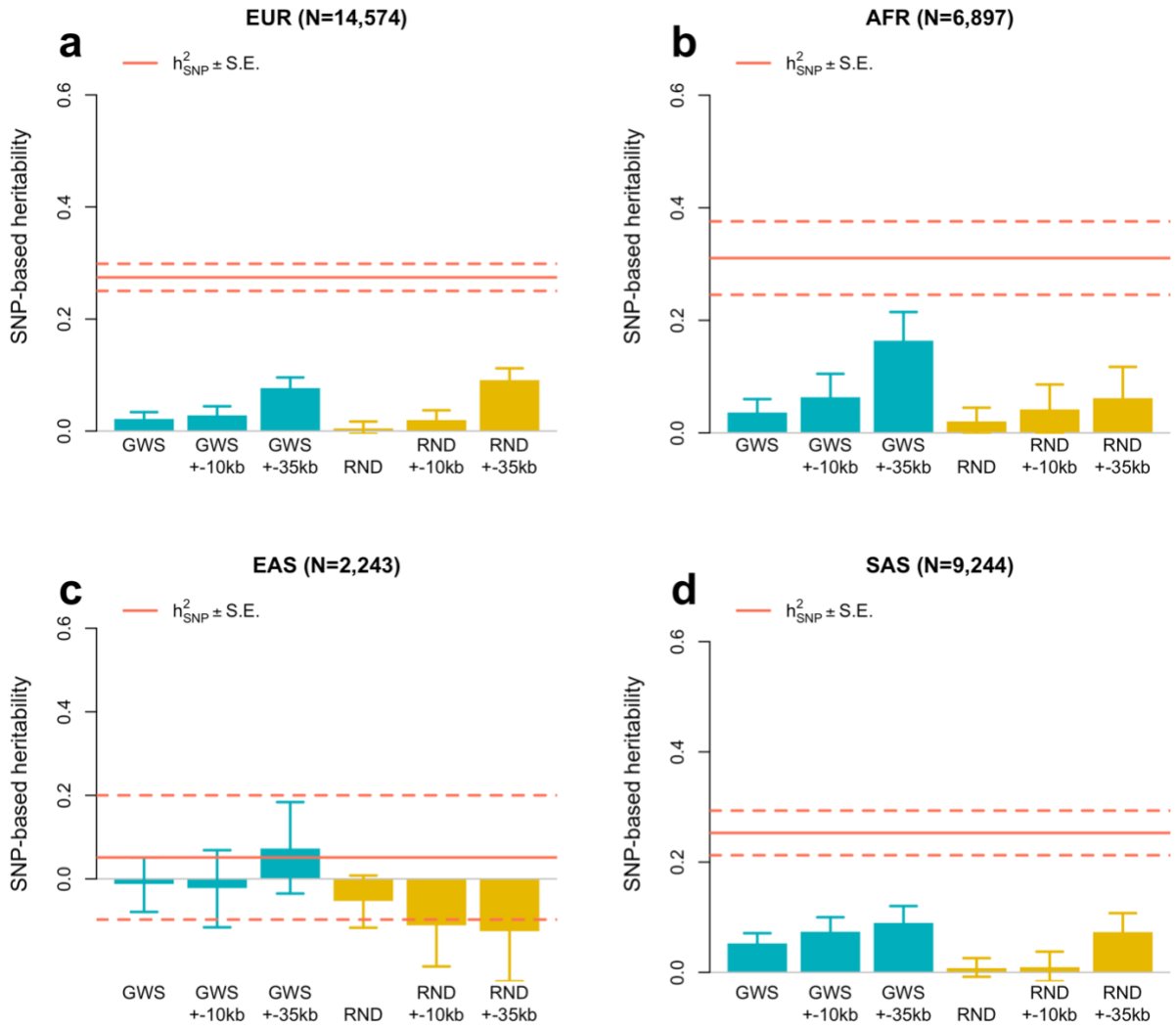
Suppl. Fig. 16. Distribution of signal density. Signal density (x-axes) is defined for each height-associated SNP as the number of other associations detected within 100 kb based on the META$_{FE}$ and ancestries group specific meta-analyses. Y-axes represent the number of height-associated SNPs with a signal density indicated on the x-axis.



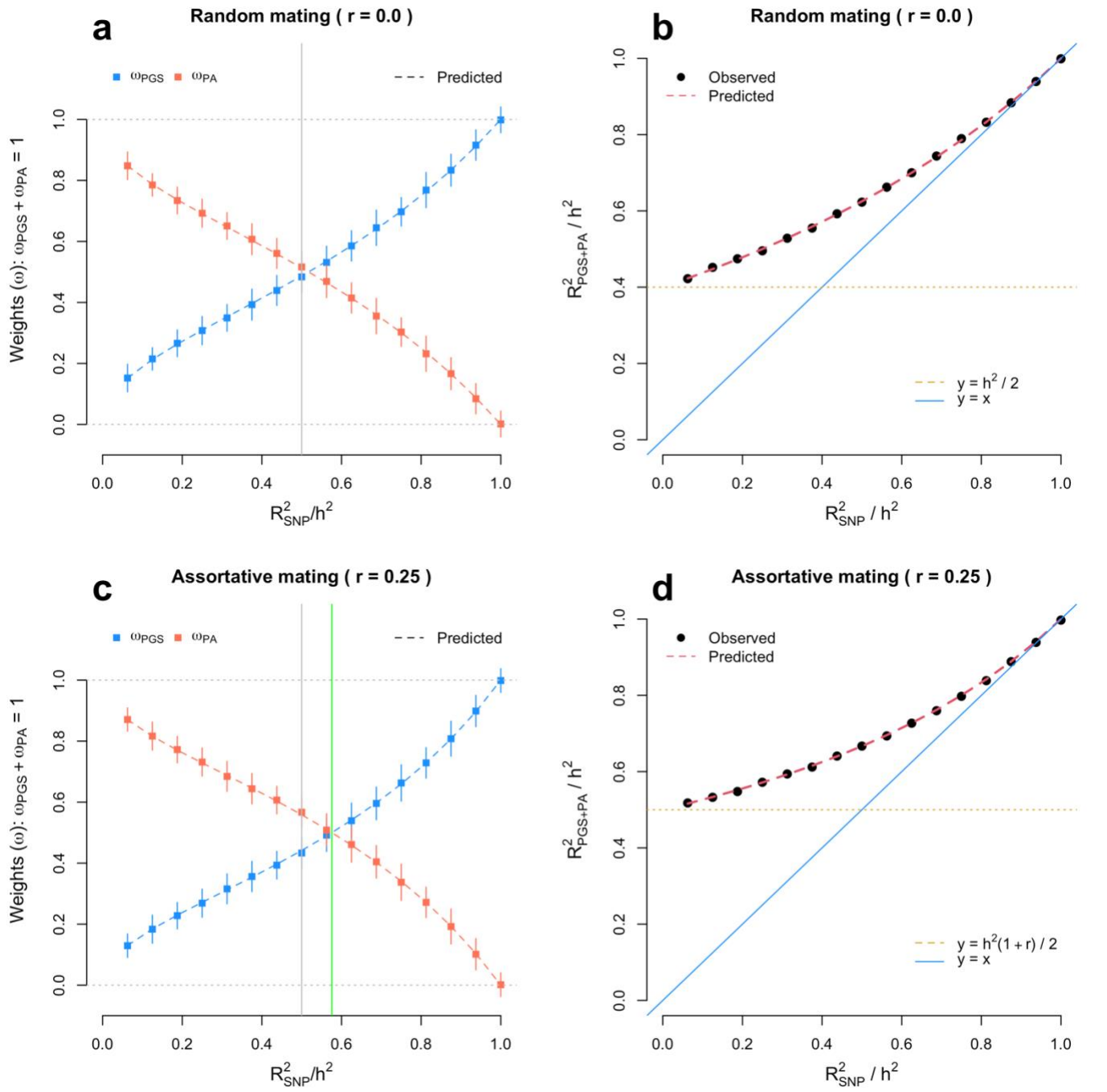
Suppl. Fig. 17. Independent signal density at the *ACAN* gene locus across ancestries. Independent associations were identified from GWAS performed in 5 ancestries (African: AFR; European: EUR; East-Asian: EAS; South-Asian: SAS and Hispanic: HIS) as well as from the meta-analysis of all ancestries (ALL). Genomic segments with a signal density >1 are found in each ancestry group.



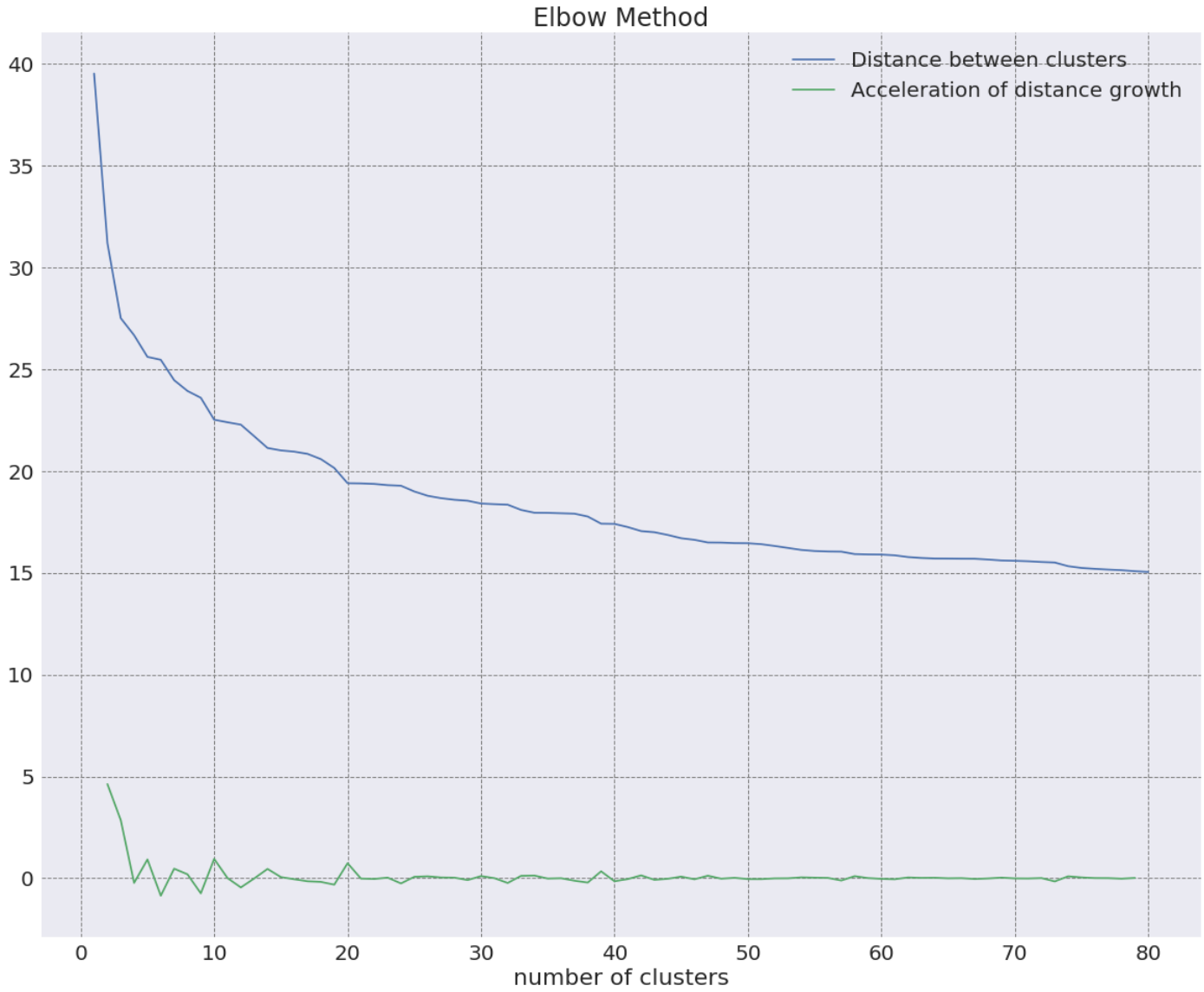
Suppl. Fig. 18. Variance of height explained by SNPs in genome-wide significant (GWS) loci defined with various window sizes. Stratified SNP-based heritability (h^2_{SNP}) estimates were obtained for three partitions of the genome: (1) GWS SNPs alone vs. all other HapMap 3 (HM3) SNPs; (2) GWS SNPs +/- all HM3 SNPs within 10 kb vs. all other HM3 SNPs and (3) GWS SNPs +/- all HM3 SNPs within 35 kb vs. all other HM3 SNPs. Analyses were performed in samples of four different ancestries: European (EUR: meta-analysis of UK Biobank (UKB); N=14,587 + Lifelines data; N=14,058), African (AFR: UKB), East-Asian (EAS: UKB) and South-Asian (SAS: UKB). Estimates from stratified analyses were compared with SNP-based heritability estimates obtained from analysing all SNPs jointly (horizontal red bar; dotted lines represented standard errors). Analyses were repeated using a random set of 12,111 SNPs (and redefining loci relative to those), which minor allele frequency and linkage disequilibrium distribution matched that of GWS SNPs (RND: gold bars).



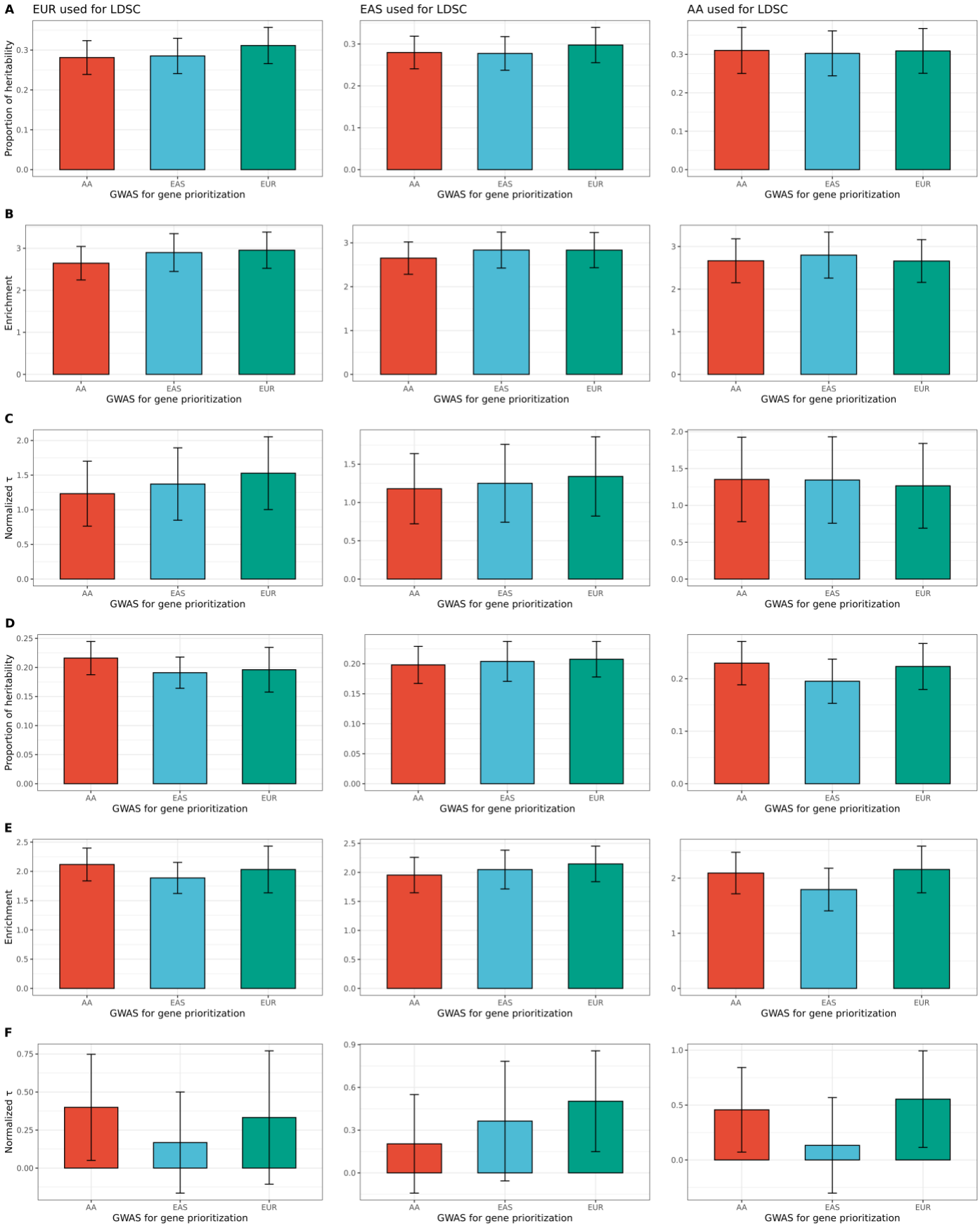
Suppl. Fig. 19. Variance of body mass index (BMI) explained by height-associated genome-wide significant (GWS) loci defined with various window sizes. Stratified SNP-based heritability (h^2_{SNP}) estimates were obtained for three partitions of the genome: (1) GWS SNPs alone vs. all other HapMap 3 (HM3) SNPs; (2) GWS SNPs +/- all HM3 SNPs within 10 kb vs. all other HM3 SNPs and (3) GWS SNPs +/- all HM3 SNPs within 35 kb vs. all other HM3 SNPs. Analyses were performed in UK Biobank samples of four different ancestries: European (EUR), African (AFR), East-Asian (EAS) and South-Asian (SAS). Estimates from stratified analyses were compared with SNP-based heritability estimates obtained from analysing all SNPs jointly (horizontal red bar; dotted lines represented standard errors). Analyses were repeated using a random set of 12,111 SNPs (and redefining loci relative to those), which minor allele frequency and linkage disequilibrium distribution matched that of GWS SNPs (RND: gold bars).



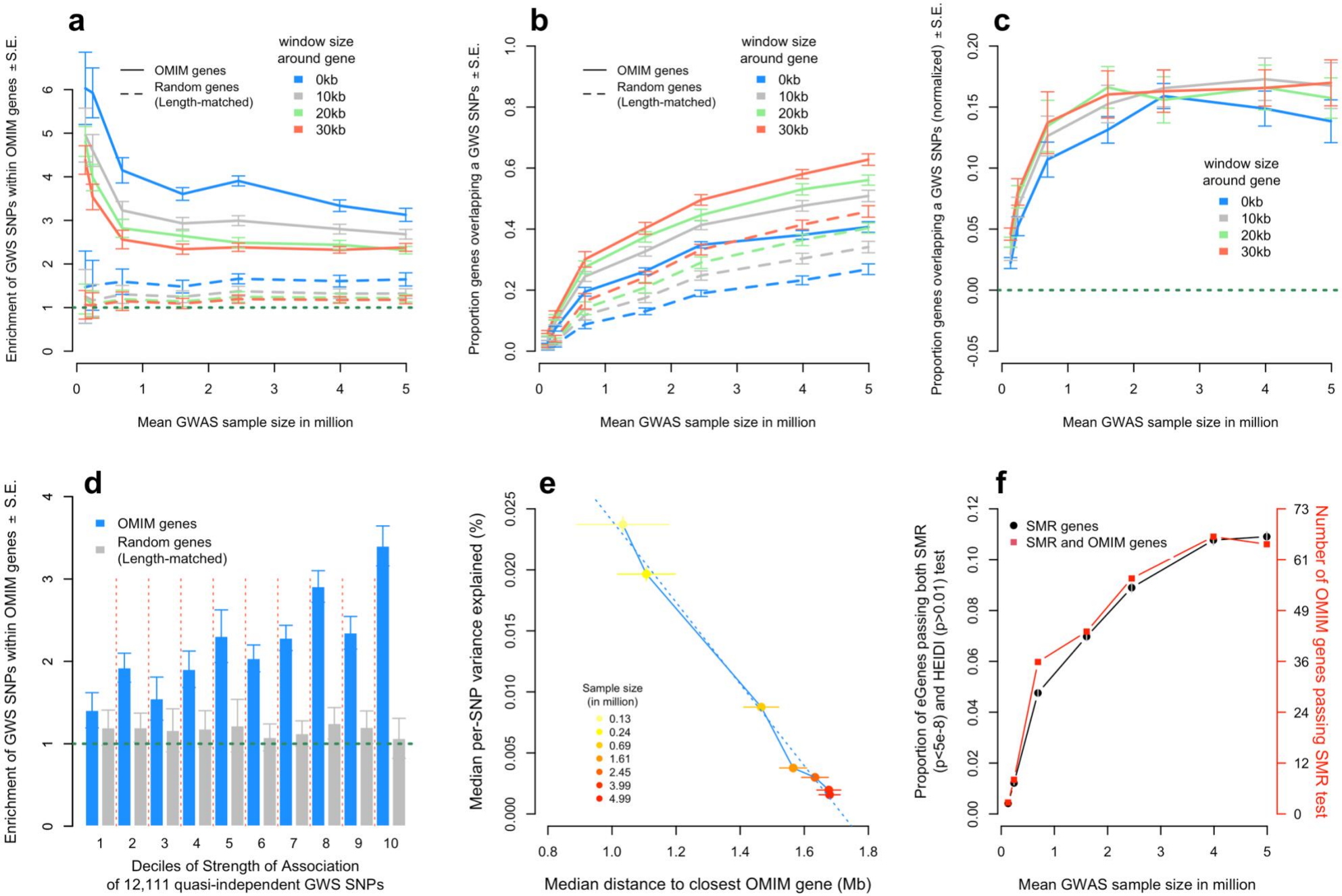
Suppl. Fig. 20. Optimal weighting of PGS and parental information in simulated data. We simulated a population of N=2,000 individuals and a trait controlled by M=1,000 causal variants. For simplicity, we assumed that a variable proportion of causal SNPs is used to calculate the PGS, and that SNP effects are estimated with negligible errors. We show below in Equation (3.11) how this proportion is chosen to achieve the desired prediction accuracy. We considered two scenarios: (i) random mating, i.e. r=0 (**Panels a** and **b**) and assortative mating (for 20 generations) based on a spousal phenotypic correlation r=0.25 (**Panels c** and **d**). In all simulations, we assumed a heritability $h^2 = 0.8$ and varied the expected prediction accuracy (R^2_{SNP}) between 0.05 and 0.8. The notation R^2_{SNP} is general and applies to any PGS based on independent SNPs, not just genome-wide significant as described in the main text. For each simulated population, we compared our predictions from Equation (S3.1) and (S3.2) with estimated regression coefficients obtained from regressing y on $\hat{y}$ and $\bar{y}_p$. The vertical green bar in panel **c**, denotes the threshold above which PGS information outweighs parental information. The vertical grey bar in panels **a** and **c** denotes the threshold when $R^2_{SNP} = h^2/2$. This threshold is predicted using Equation (S3.4). We also compared our variance explained by fitting both predictors with our predicted expectation from Equation (S3.3). Each dot is generated using 100 replicates. Overall, we found a perfect consistency between our theoretical and simulation results, which provides an empirical validation of these predictions.



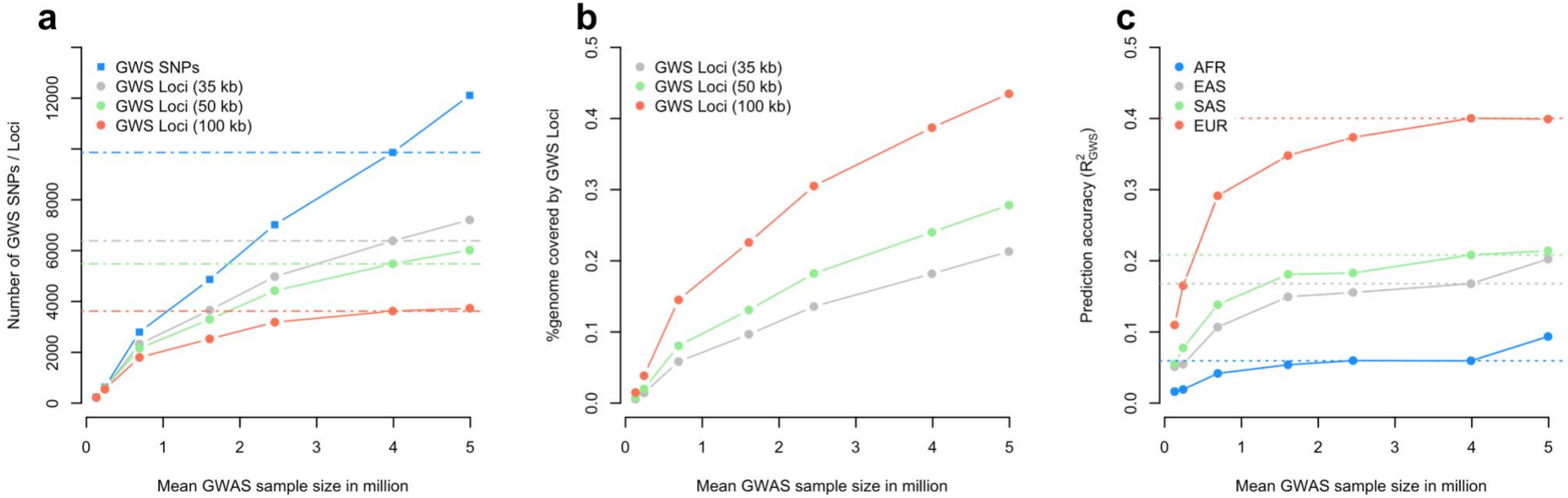
Suppl. Fig. 21. Selection of the number of gene set clusters using the "Elbow method". Gene sets were hierarchically clustered at different sizes and the distance between each cluster evaluated. 20 clusters was chosen as an appropriate number of gene set clusters to evaluate for enrichment.



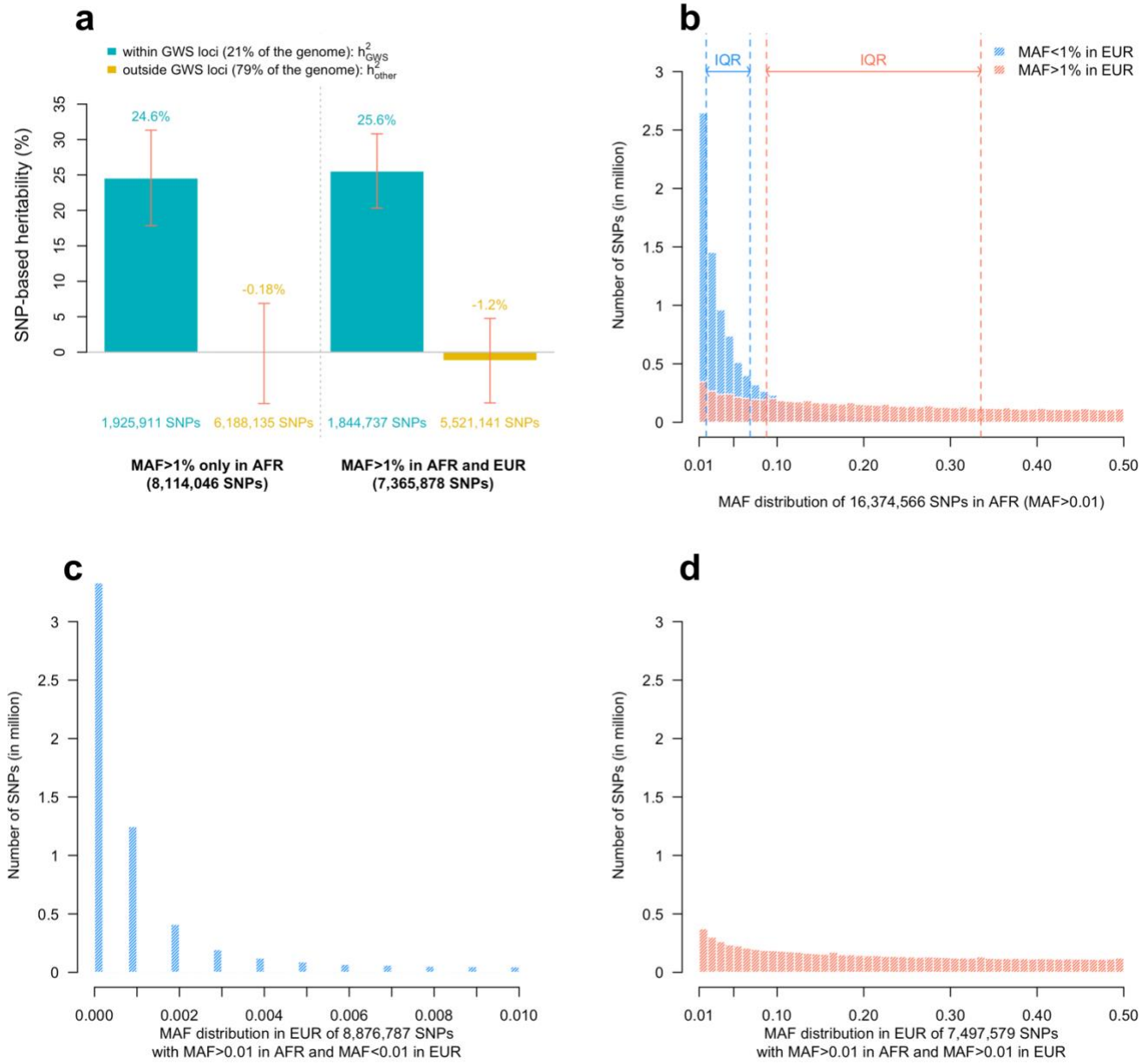
Suppl. Fig. 22. Proportional heritability (h^2) explained, enrichment, and normalized τ estimates for MAGMA (panels A-C) and DEPICT (panels D-F). The error bars represent the 95% confidence interval, calculated as estimate +/- 1.96*standard error. The labels for each subpanel indicate the ancestry represented in the GWAS used for LDSC, and the x-axis labels indicate the ancestry represented in the "discovery" GWAS used to prioritize the genes. EUR: European ancestry; AA: African-Americans of admixed European and African ancestries; EAS: East Asian ancestry. Analyses underlying this figure are further described in **Suppl. Note 5**.


a
Enrichment of GWS SNPs within OMIM genes ± S.E.
OMIM genes
Random genes
(Length-matched)
window size
around gene
0kb
10kb
20kb
30kb
Mean GWAS sample size in million
b
Proportion genes overlapping a GWS SNPs ± S.E.
OMIM genes
Random genes
(Length-matched)
window size
around gene
0kb
10kb
20kb
30kb
Mean GWAS sample size in million
c
Proportion genes overlapping a GWS SNPs (normalized) ± S.E.
window size
around gene
0kb
10kb
20kb
30kb
Mean GWAS sample size in million
d
Enrichment of GWS SNPs within OMIM genes ± S.E.
OMIM genes
Random genes
(Length-matched)
Deciles of Strength of Association
of 12,111 quasi-independent GWS SNPs
e
Median per-SNP variance explained (%)
Sample size
(in million)
0.13
0.24
0.69
1.61
2.45
3.99
4.99
Median distance to closest OMIM gene (Mb)
f
Proportion of eGenes passing both SMR
(p<5e-8) and HEIDI (p>0.01) test
SMR genes
SMR and OMIM genes
Number of OMIM genes passing SMR test
Mean GWAS sample size in million

Suppl. Fig. 23. Gene-level saturation of GWAS discoveries as a function of sample size. Increase in sample size from ~4 million to ~5 million is achieved by including ~1 million participants of non-European ancestry. **Panel a** shows the enrichment of genome-wide significant (GWS) SNPs identified from an approximate conditional and joint (COJO) analysis within 462 genes associated with skeletal growth disorders from the Online Mendelian Inheritance in Man (OMIM) database (y-axis) as a function of GWAS sample size (x-axis). Standard Error (S.E.) were calculated as the standard deviation of enrichment statistics (odds ratio in the 2x2 contingency table contrasting for each gene: "is the gene an OMIM gene" vs. "does the gene contain a GWS SNP") across 1,000 randomly sampled sets of 462 non-OMIM genes length-matched with OMIM genes. The average enrichment calculated across the 1,000 random gene sets is represented with dotted lines. Presence of a GWS SNP within a gene was assessed relative to gene start and stop position, considering flanking regions within 0 kb, 10 kb, 20 kb and 30 kb. **Panel b** shows the proportion of OMIM overlapping genes with at least one GWS SNPs (y-axis). As in **Panel a**, dotted lines represents the null distribution from 1,000 random sets of genes length-matched with OMIM genes. Standard errors (S.E.) were calculated as the standard deviation of the proportion observed across the 1,000 draws from the null distribution. **Panel c** represents the proportion of OMIM genes near GWS SNPs after subtracting the mean of the null distribution at each sample size. **Panel d** represents the enrichment of OMIM genes as a function of the strength of association of 12,111 independent GWS SNPs identified in our largest GWAS (N~5.4M). GWS SNPs were grouped into 10 decile groups of ~1,211 SNPs. Enrichment near OMIM genes is stronger of SNPs explaining a larger proportion of height variance (top decile). **Panel e** shows the median per-SNP variance explained (y-axis) as a function of the median distance to the closest OMIM gene. Large GWAS tend to identify variants with smaller effect sizes and further away from OMIM genes. **Panels f** shows the number of genes prioritised using Summary-data based Mendelian Randomization (SMR; $P<5\times10^{-8}$), which expression may act a mediator of the effects of SNP on height. SMR analyses were based on expression quantitative trait loci (eQTL) identified in the GTEx and eQTLgen studies (**Methods**). The z-axis (in red) shows the number of OMIM genes overlapping with SMR genes identified from analysing GWAS with various sample sizes (x-axis).



Suppl. Fig. 24. Variant-level saturation of GWAS discoveries as a function of sample size. Increase in sample size from ~4 million to ~5 million is achieved by including ~1 million participants of non-European ancestry. **Panel a** shows number of independent genome-wide significant (GWS) SNPs and loci identified at various GWAS sample sizes (Details about down-sampled GWAS are given in Table 2). GWS loci were defined using various window sizes including 35kb, 50kb and 100 kb. **Panel b** shows the percentage of the genome covered by GWS loci. Coverage was calculated as the cumulative length of GWS loci in Mb divided 3,039 Mb, the estimated length of the human genome. **Panel c** shows the prediction accuracy (R^2_{GWS}) of various polygenic scores on GWS SNPs identified at various sample sizes. In **Panels a** and **c**, dotted lines represent y-axis values for our largest European ancestry GWAS (N~4 million).



Suppl. Fig. 25. Partitioned SNP-based heritability of height in African ancestry individuals. Panels a represent partitioned SNP-based heritability estimates from a sample of 6,911 unrelated African ancestry (AFR) individuals from the UK Biobank, independent of our discovery GWAS. This analysis focuses on 16,374,566 SNPs with a minor allele frequency (MAF)>1% in AFR. These SNPs were further stratified according to their MAF in European ancestry (EUR) populations: 7,365,878 SNPs with MAF>1% in EUR (47%) vs. 8,114,046 SNPs with MAF<1% in EUR (53%) and their position within vs. outside genome-wide significant (GWS) loci. **Panel b** shows the MAF distribution of the 16M SNPs in AFR and panels (c – d) the distribution of these SNPs in EUR. The SNP-based heritability contributed by SNPs within GWS loci is denoted h^2_{GWS}, while that contributed by SNPs outside these loci is denoted h^2_{other}. These results are further discussed in **Suppl. Note 6**.

SUPPLEMENTARY NOTES

Supplementary Note 1: Sensitivity Analyses of COJO results

Long range LD in admixed populations can bias estimation of approximate conditional SNP effects

We compared the prediction accuracy of polygenic scores (PGS) based on genome-wide significant (GWS) SNPs identified in each ancestry groups. For each set of ancestry-specific GWS SNPs we calculated a PGS using either marginal SNP effects (hereafter denoted PGS_{GWAS}) or conditional effects (hereafter denoted PGS_{COJO}) approximated using GCTA-COJO (Methods). Given that COJO is designed to detect secondary signals, i.e. explaining additional trait variance, we expect the prediction accuracy of PGS_{COJO} to be similar, if not outperform, that of PGS_{GWAS}.

Consistently, we found that PGS_{COJO} yields a higher accuracy than PGS_{GWAS} in most cases except in HIS and AFR (**Suppl. Fig. 3a**). We further investigated that observation and found that the poor performances of PGS_{COJO} relative to PGS_{GWAS} in HIS and AFR were driven by specific chromosomes such chromosome 6, 9 and 20 (**Suppl. Fig. 3b**), where estimated conditional effects were abnormally large (**Suppl. Fig. 3c**).

We hypothesized that these unexpected observations could be explained by estimation errors during the stepwise model selection procedure, e.g., because of collinearity between SNPs included in the model. Note that GCTA sets a default threshold of 0.9 for collinearity between SNPs, which means that the variance of genotypes at a given SNP included in the model cannot be explained at >90% by all other SNPs included in the model. To explore the impact of this parameter on our observations we performed a sensitivity analysis by varying the collinearity threshold between 0.1 and 0.9.

We found that using a more stringent collinearity threshold reduces the prediction accuracy of PGS_{COJO} in EUR and EAS (accuracy in SAS remained unchanged) but produces an opposite effect in AFR and HIS (**Suppl. Fig. 4**). More specifically, setting the collinearity threshold below 0.5 restored the prediction accuracy of PGS_{COJO} up to a level comparable to that of PGS_{GWAS}. Therefore, our sensitivity analyses suggest that stringent collinearity thresholds are preferable when applying COJO to GWAS from admixed ancestry groups such as HIS and AFR.

Consequently, the COJO results presented in the main text are based upon a collinearity threshold of 0.1 for HIS and AFR and the default threshold of 0.9 for all other COJO analyses. We chose 0.1 because it produces the most parsimonious model (i.e. fewer number of associations) without impacting prediction accuracy.

Impact of ancestry composition of LD reference panel on COJO results

We re-analysed summary statistics from our cross-ancestry GWAS meta-analysis using two LD reference sets. First, we randomly selected 37,900 EUR, 4,400 EAS, 4,250 HIS, 2,750 AFR and 700 SAS individuals (i.e. 50000 individuals in total) to form a LD reference set with ancestries proportions matching that in our cross-ancestry meta-analysis. The second set contained 50,000 individuals with EUR ancestries. We restricted analyses with both LD reference sets to 882,755 HM3 SNPs, which passed quality control (Hardy-Weinberg Equilibrium test, missingness and imputation quality) in all five ancestry groups.

We found that COJO based on the multi-ancestry LD panel only detected 3,635 (3380 using a collinearity-threshold of 0.1) independent associations vs. 11,001 associations using the EUR LD reference. The latter number is smaller than the 12,111 reported in the main text but consistent with a ~10-15% smaller number of HM3 SNPs used as input. We also repeated analyses using the 37,900 EUR individuals as LD reference and found that COJO detects 11,065 SNPs, indicating that using this multi-ancestry LD panel leads to underestimation by COJO of the number of associations. This

conclusion is supported by the fact that a PGS based on 11,001 COJO SNPs detected using a EUR LD panel explains a significantly larger amount of height variance than that of a PGS based on only 3,380 COJO SNPs detected with a multi-ancestry panel (EUR: 38.2% vs 26.4%; SAS: 20.3% vs 13.4%; EAS: 19.5% vs 13.3% and AFR: 9.0% vs 5.0%). Moreover, we ran another COJO analysis of our cross-ancestry GWAS using LD information from 10,636 AFR individuals (i.e. same LD panel for our AFR GWAS meta-analysis). Note that 242,891 / 882,755 (i.e. 27.5%) SNPs were filtered out by GCTA prior to analysis because of expected large differences in allele frequencies between our cross-ancestry GWAS including >75% of EUR individuals and the AFR LD panel (by default GCTA exclude SNPs with an absolute frequency difference is >0.1). Nevertheless, we detected 5,701 quasi-independent joint associations (i.e. more associations than using a mix-ancestry panel), explaining 24.6%, 13.2%, 10.9% and 3.5% of height variance in EUR, SAS, EAS and AFR individuals respectively. The latter predictive performances are lower to that obtained with a PGS from 3,380 COJO SNPs.

Altogether, these results demonstrate that COJO with a composite LD reference panel does not improve and likely hinders the detection of associations in our cross-ancestry GWAS meta-analysis. We emphasize that extending the COJO methodology for analysing multi-ancestry GWAS is an independent research question, which goes beyond the scope of our study.

Supplementary Note 2: Investigation of population stratification in large GWAS of height

Assessment of population stratification in European ancestries GWAS

Recent studies[9,10] have shown evidence of significant confounding in estimated SNP effects induced by uncorrected population stratification (PS) in summary statistics from the Wood et al. (2014)[20] study. Importantly, Wood et al. (2014) also reported residual PS mostly affecting estimated effects of SNPs weakly associated with height (Figure 2a-c in ref.[20]). To ensure increased robustness and reliability of our findings, we perform here a series of analyses to quantify confounding effects of residual PS in all GWAS results reported in this study.

LD score regression analysis of European ancestries GWAS

First, we performed a LD score regression (LDSC) analysis[16] of our GWAS meta-analysis of EUR participants (N=4,080,687). We assessed the degree of PS using the attenuation ratio statistic (R_{LDSC}), which provides a quantification of PS that is independent of sample size. The estimated R_{LDSC} is ~3.8% (S.E. 0.8%), suggesting that most of the inflation of association test statistic is explained by polygenicity and not PS. In comparison, GWAS of height without any adjustment for population stratification produce values of R_{LDSC} ~10-13%.[67] Our estimated R_{LDSC} is slightly smaller than that from LDSC analyses of previously published GWAS of height (Wood et al. (2014): 4.3% (S.E. 1.3%); Yengo et al. (2018)[3] 4.0% (S.E. 1.2%)), which suggests a reduced effect of residual PS on our results. Note that the estimated R_{LDSC} shown here are obtained from analysing imputed GWAS summary statistics from Wood et al. (2014) and Yengo et al. (2018) (**Supplementary Methods**), which have a better coverage of HM3 SNPs; and thus explaining the difference with the ~6.0% (S.E. 1.0%) reported in Yengo et al. (2018). However, as a measure of PS, R_{LDSC} is not strictly comparable across studies. In fact, the expectation of R_{LDSC} (across repeated GWAS) not only depends on how much trait variance is explained by PS, but also on the degree of genetic differentiation between cohorts (F_{ST}) and the trait heritability within each cohort.[16] The last two factors can vary from one GWAS meta-analysis to another as a function of cohort composition. In summary, these LDSC analyses suggest that uncorrected PS only marginally affects SNP effects from our large GWAS of height in EUR participants.

Assessment of allele frequencies for height increasing alleles across the North-South axis of Europe reveals attenuated correlation relative to previous studies

As an alternative to R_{LDSC}, we next quantified PS in our GWAS using the correlation between strength of association (p-value) and height-increasing allele frequency differences between Great Britain (GBR sample in the 1000 Genomes Project – 1KGP) and the Italian Tuscan population (TSI sample in 1KGP). This statistic was previously introduced by Sohail and colleagues[10] to reveal biases in SNP effect estimates from the Wood et al. study, that were induced by uncorrected PS along the North-South gradient of Europe. More precisely, the strategy implemented by Sohail et al. consists in grouping SNPs based on strength of association, then regress the mean height-increasing allele frequency differences between GBR and TSI for each SNP bin onto the mean p-value of the corresponding bin. The slope of that linear regression (β_{PS}) measures the degree of PS. We estimated β_{PS} using 101,360 near independent HM3 SNPs with MAF>1% and calculated standard errors using a bootstrap strategy based on 1,000 independent draws.

As previously reported, we found a significant β_{PS} of ~1.28% (S.E. 0.08%; $P = 2.3 \times 10^{-61}$) using summary statistics of the Wood et al. (2014) study but no significant β_{PS} from within-family GWAS in 17,942 independent UKB siblings pairs (β_{PS}=-0.08%, S.E. = 0.07%; P=0.27). We show in **Suppl. Fig. 5a-b** estimates of β_{PS} from GWAS summary statistics of Yengo et al. (2018), EUR participants of 23andMe (23andME-EUR), all EUR participants of the UKB (UKB-456k; GWAS using BOLT-LMM), unrelated EUR participants of the UKB (UKB-350k; GWAS using PLINK), the meta-analysis EUR participants from multiple cohorts of the GIANT consortium (GIANT-EUR; N~1.6M); and the meta-analysis of GIANT-EUR and 23andMe-EUR. Overall, we find that β_{PS} decreases with sample size, consistent with an increased signal-to-noise ratio. In particular, β_{PS} is ~0.13% (P=0.1) in our largest GWAS meta-analysis of N~4.1M

EUR participants, which demonstrates a better correction of PS than previously published EUR GWAS of height.

Furthermore, we assessed the squared correlation between estimated effects at these 101,360 independent HM3 SNPs and SNP loadings from 20 principal components (PCs) calculated in 503 EUR samples from 1KGP. Across SNPs, we found that SNP loadings on PC2 explain most of the variance in estimated SNP effects (**Suppl. Fig. 5c**). This observation is not surprising given that PC2 is the PC that correlates the most with the North-South axis of Europe, and therefore explains the consistency with our results based on β_{PS}. However, <0.3% of the variance of SNP effects estimated in our largest GWAS is explained by SNP loadings, which is much lower than ~2.3% obtained when analysing SNP effects from Wood et al. (2014).

Comparison of estimated SNP effects between GWAS meta-analyses and family-based GWAS

Finally, we directly compared SNP effects from our GWAS (β_{GWAS}) with that of a within-family GWAS in 17,942 independent UKB siblings pairs (β_{SIB}). We used $S_{PS} = \mathrm{cov}(\beta_{GWAS}, \beta_{SIB})/\mathrm{var}(\beta_{GWAS})$ as our metric of interest in this comparison, where both $\mathrm{cov}(\beta_{GWAS}, \beta_{SIB})$ and $\mathrm{var}(\beta_{GWAS})$ are calculated across SNPs. When SNP effects are estimated using ordinary least-squares (OLS) regression, the expectation of S_{PS} in the absence of PS is $E[S_{PS}] = 1$. Therefore, a significant deviation of S_{PS} below 1, may indicate confounding due to residual PS. However, the statistical properties of S_{PS} based on SNP effects estimated using linear mixed models (LMM) (or meta-analyses of OLS and LMM estimates) are not well characterised, which may affect our interpretation below.

We found that estimates of S_{PS} based on SNPs strongly associated with height are much closer to 1 than when all SNPs are used, i.e. regardless of strength of association (P<1; **Suppl. Fig. 5d**). We observed the lowest value of S_{PS}~0.29 (S.E. 0.01) when using effects of all 101,360 SNPs estimated in the Wood et al. study. In comparison, estimated SNP effects from our largest EUR GWAS yields an S_{PS}>0.8 regardless of strength of association, yet still significantly lower than 1 ($P < 7 \times 10^{-30}$).

Lee et al.[68] previously showed that assortative mating (AM) on height can produce values of $S_{PS} < 1$. Under the assumption that the population has reached an equilibrium after many generations of AM with a constant spousal correlation (r), they showed that

$$E[S_{PS}] = 1 - rh^2, \quad (1.1)$$

where h^2 is the full narrow-sense heritability in the current generation (at equilibrium). We note here an error in the Supplementary Notes of Lee et al. (2018), who used in their derivations the heritability in the base population undergoing random mating (h_0^2) instead of the equilibrium heritability, h^2. In practice, differences between $h_0^2 = (h^2 - rh^4)/(1 - rh^4)$ and h^2 are small. Therefore, using one or the other heritability has a limited impact on the expected value of S_{PS}. Using Equation (1.1) and assuming an equilibrium heritability, $h^2 = 0.8$ and a spousal correlation, $r = 0.25$, we expect S_{PS} to be $\sim 1 - 0.8 \times 0.25 = 0.8$, which is consistent with our observations (**Suppl. Fig. 5d**).

Altogether, these analyses show that estimated SNP effects from our EUR GWAS are inflated by ~10-20% relative to that from a family-based GWAS and that this inflation is not larger than expected because of phenotypic AM on height.

Assessment of population stratification in non-European ancestries GWAS

We extended the previous analyses performed in EUR to quantify the impact of residual PS in GWAS of height performed in the four other ancestry groups, i.e. HIS, SAS, EAS and AFR.

LD score regression analysis of non-European ancestries GWAS

We performed LD score regression analyses using LD scores estimated from the same ancestry-matched samples as in our COJO analyses (i.e. 10,636 AFR samples, 5,875 EAS samples, 9,448 SAS

samples and 4,883 HIS samples). LD scores were calculated from imputed HapMap3 SNPs using the LDSC software (version 1.0.1) with a window size of 1 cM.

The R_{LDSC} statistic was 6.7% (S.E. 2.2%) in AFR, 9.5% (S.E. 1.4%) in HIS, 11.1% (S.E. 1.7%) in EAS, and 25.6% (S.E. 3.7%) in SAS. Previous studies have shown that longer range LD in admixed populations as compared to non-admixed populations can bias estimates from LD score regression.[8] Therefore, we repeated our analyses in AFR and HIS using 20 PCs adjusted LD scores based on a 20 cM window, as recommended by Luo et al. (2021).[8] The R_{LDSC} statistic decreased from 6.7% (S.E. 2.2%) to 0.9% (S.E. 1.9%) in AFR and from 9.5% (S.E. 1.4%) to 7.5% (S.E. 1.7%) in HIS. Importantly, using PC adjusted LD scores based on a 20cM window did not change estimates of R_{LDSC} in SAS (25.6%; S.E. 3.7% vs. 25.9%; S.E. 3.7%) nor in EAS (11.1%; S.E. 1.7% vs. 11.1%; S.E. 1.7%).

It is noteworthy that values of R_{LDSC} above 20%* as observed in our SAS GWAS may also reflect strong LD differences between GWAS participants and samples used to estimate LD scores. We applied the DENTIST method (Detecting Errors iN analyses of summary staTISTics) to distinguish these two potential explanations. In brief, DENTIST compares the observed distribution of Z-scores from GWAS to an expected distribution based on a reference LD matrix. Deviations from that expected distribution reflect errors in the GWAS summary statistics or inconsistencies in LD patterns. DENTIST detected 213 outlier SNPs in the SAS GWAS ($P<5 \times 10^{-8}$) relative to LD patterns from 9,448 unrelated SAS from the UKB. However, excluding these 213 outliers SNPs did not substantially affect the value of the R_{LDSC} statistic (26.2%; S.E. 3.6%).

Altogether, these LD score regression analyses suggest the presence of residual PS that might potentially confound estimates of SNP effects in our HIS, EAS and SAS GWAS.

Correlation between for height-increasing alleles frequencies and genetic differentiation within four ancestry groups

Next, we estimated β_{PS} for each non-EUR GWAS meta-analysis along various axes of within-continent genetic differentiation defined by pairs of 1KGP subpopulations. For example, we estimated β_{PS} in our AFR GWAS meta-analysis along an axis that differentiates Yoruba populations in Nigeria (West Africa) from Luhya populations in Kenya (East Africa), as well as in our EAS GWAS meta-analysis along an axis that differentiates Japanese populations from Han Chinese populations. We used ancestry-specific significance thresholds calculated as 0.05 divided by the number of pairs of subpopulations within the corresponding 1KGP ancestry group. More specifically, we considered 7 subpopulations in AFR (21 pairs), 5 subpopulations in EAS (10 pairs), 5 subpopulations in SAS (10 pairs) and 4 subpopulations in HIS (6 pairs).

We found significant β_{PS} in each non-EUR GWAS meta-analysis (**Suppl. Fig. 6a-d**). The largest magnitude of β_{PS} was observed in the SAS GWAS meta-analysis along the India-Bangladesh axis (β_{PS}=0.89%, S.E. 0.11%, P=6.2×10^{-17}, **Suppl. Fig. 6c**) and the second largest in the HIS GWAS meta-analysis along the Colombia-Puerto Rico axis (β_{PS}=0.75%, S.E. 0.08%, P=1.2×10^{-17}, **Suppl. Fig. 6d**). Importantly, estimated β_{PS} in non-EUR are significantly lower than 1.28% observed in the Wood et al. (2014) study.

Finally, we assessed the squared correlation between SNP effects estimated in each non-EUR GWAS meta-analysis and SNP loadings of 20 PCs calculated in corresponding superpopulations from 1KGP (**Suppl. Fig. 6e-h**). Overall, all squared correlations were smaller than 0.3% as observed with our largest EUR GWAS (N=4M), where PS was better controlled (**Suppl. Fig. 5c**).

*a rule-of-thumb recommended by the authors of the LDSC software.

In conclusion, we detected a small amount residual PS in all non-EUR GWAS meta-analyses, in particular in SAS (smallest sample size).

Effect of residual population stratification on cross-ancestry GWAS meta-analysis

In this final section, we focus on SNP effects from our cross-ancestry GWAS meta-analysis (referred to as $META_{FE}$ in the main text). Using these estimated SNP effects, we quantified β_{PS} along multiple axes of within-continent genetic differentiation and also the squared correlations between SNP effects and within-ancestry PC loadings and SNP effects (as in the previous section). Overall, β_{PS} remain below 0.5% across all pairs of 1KGP subpopulations (**Suppl. Fig. 7a-e**), and the squared correlation between SNP effects and PC loadings was also smaller than 0.15% (**Suppl. Fig. 7f**).

In summary, the various analyses shown here demonstrate that residual PS has a minimal confounding effect on estimated SNP effects from our cross-ancestry GWAS meta-analysis.

Supplementary Note 3: Distinguishing loss of tagging from multiplicity of causal variants at the *ACAN* locus

We observed the largest density of independent associations around rs4932198, where 24 other GWS SNPs were detected within less than 100 kb on each side (**Fig. 2**; **Suppl. Fig. 17**). We hereafter refer to the set of these 25 GWS SNPs as *ACAN* GWAS signals. A large density of signals may reflect the presence of multiple causal variants or the presence of poorly tagged causal variants with large effects at this locus. To disentangle these two possible explanations, we first used statistically phased haplotypes from 346,959 unrelated UKB participants of EUR and tested their association with height. We analysed 14,117 haplotypes covering a 100 kb long genomic region at this locus (hg19 genomic coordinates: chr15:89,307,521-89,407,521) and that were present in at least 5 UKB participants. We tested the association between each haplotype and height but could not identify a single haplotype with a large enough effect that can explain the majority of signals at this locus (**Extended Data Fig. 5**). In fact, *ACAN* GWAS signals cumulatively explain ~0.3% of height variance, while the two most associated haplotypes ($P<10^{-7}$) jointly only explain 0.01% of height variance.

Next, we used genotypes at this locus from 291,683 unrelated EUR participants of the UKB to simulate a trait controlled by a single rare biallelic variant (MAF<1%) explaining between η^2=0.5% and 5% of variance, then performed a GCTA-COJO analysis to estimate the density of independent signals. Previous studies have shown that large discrepancies in sample size between discovery GWAS and LD reference may contribute to inflate the number of independent associations detected with GCTA-COJO.[69] Therefore, to mimic that effect we used a random subset of 10,000 unrelated EUR participants of the UKB as LD reference, i.e. ~$1/30^{th}$ of the discovery sample. On average over 100 simulation replicates for each value of η^2, we observed a signal density lower than 2.3 associations per 100kb (**Extended Data Fig. 5**). The largest density of 10 associations per 100 kb was observed only when the simulated causal variant explains 5% of trait variance (i.e. β between ~2 and ~43 trait SD/allele), which is an extreme and unrealistic scenario. In contrast, even when the simulated causal variant explains 0.5% of trait variance, which in this case corresponds to a median allelic effect of ~1.4 SD/allele (~10cm, so very large) across simulations, we found that signal density never exceeded 7 associations per 100 kb. Altogether, the results of our haplotype- and simulation-based analyses suggest that a multiplicity of independent causal variants is the most likely explanation of our observations, although signal density is not a standard estimator of the number of causal variants.

Finally, we sought to quantify how much the presence of a recently identified[21,70] height-associated variable-number-of-tandem-repeat (VNTR) polymorphism in *ACAN* may contribute to the observed density of GWS SNPs. Therefore, we regressed VNTR length imputed in UKB participants[28] onto allele counts at *ACAN* GWAS signals and found that these 25 SNPs explain ~73%, ~47%, ~42% and ~40% of VNTR length variation in SAS (N=9,219), EUR (N=414,429), AFR (N=7,543) and EAS (N=1,496) respectively (**Extended Data Fig. 5e**). Consistent with partial tagging of VNTR length variation, *ACAN* GWAS signals explain ~0.24% ($R^2_{VNTR} = 0.21\%$ vs. $R^2_{VNTR+25\ SNPs} = 0.45\%$; $P=8.7 \times 10^{-55}$) additional height variance in EUR over what is explained by VNTR length variation alone (**Extended Data Fig. 5f**). In summary, these complementary analyses suggest that a large density of independent GWS SNPs near *ACAN* is partially explained by the presence of a VNTR at this locus and also by additional causal variants not yet identified.

Supplementary Note 4: Optimal weighting of PGS and parental information to maximize prediction accuracy in the presence of assortative mating

Overview of theory, simulations and application to real data from the UK Biobank

For a given individual, we denote y their phenotype, y_m and y_f the phenotypes of their mother and father respectively, $\bar{y}_p = (y_m + y_f)/2$ the average of their parents' phenotypes and $\hat{y}$ their own PGS. We consider combined predictor that is a linear combination of $\hat{y}$ and $\bar{y}_p$. Under the assumption that the resemblance between relatives is solely due to genetic factors, our main result is that the optimal weighting $\alpha_{PGS}\hat{y} + \alpha_{PA}\bar{y}_p$ is given by

$$(S3.1)\quad \alpha_{PGS} = \frac{R_{\hat{y},y}[1 - h^2(1 + r)/2]}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

and

$$(S3.2)\quad \alpha_{PA} = \frac{h^2 - R^2_{\hat{y},y}}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

where h^2 denotes the heritability of the trait in the current population, r the correlation between spouses phenotypes in the population, and $R^2_{\hat{y},y} = \mathrm{corr}(\hat{y}, y)^2$, the prediction accuracy of the PGS. The expected accuracy ($R^2_{\hat{y}+\bar{y}_p}$) of the combined predictor using these optimal weights, is given by

$$(S3.3)\quad R^2_{\hat{y}+\bar{y}_p} = \frac{R^2_{\hat{y},y} + \left(\frac{h^2}{2}\right)(1 + r)\left[h^2 - 2R^2_{\hat{y},y}\right]}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

Suppl. Fig. 20 shows the results of simulations performed to verify the results from Equations (S3.1-S3.3). These simulations use an arbitrary number of SNPs included in the PGS and are not designed to match the number of SNPs used in various PGS analyses presented in the main text. Nevertheless, our conclusions are general and applicable to our empirical data under the assumption that each SNP in the PGS contributes about the same amount of genetic variance. We define the regression weights as $\omega_{PGS} = \alpha_{PGS}/(\alpha_{PGS} + \alpha_{PA})$ and $\omega_{PA} = \alpha_{PA}/(\alpha_{PGS} + \alpha_{PA})$. Therefore, values of ω_{PGS} such that $\omega_{PGS} > 0.5$ imply that the PGS has a stronger weight that the parental average.

Under assortative mating, **Suppl. Fig. 20** shows that ω_{PA} remains above 0.5 even when the PGS explains 50% of h^2. We show below that $\omega_{PGS} = \omega_{PA}$ if

$$(S3.4)\quad R_{\hat{y},y} = \frac{-[1 - h^2(1 + r)/2] + \sqrt{[1 - h^2(1 + r)/2]^2 + 4h^2}}{2}$$

For example, with $r = 0.25$ and $h^2 = 0.8$, Equation (S3.4) predicts an equal contribution of the PGS and parental information if $R^2_{\hat{y},y} \approx 0.46$.

Next, we estimated α_{PGS}, α_{PA} and $R^2_{\hat{y}+\bar{y}_p}$ in 981 trios from the UK Biobank (**Methods**). For this analysis, we used a PGS based on 12,111 GWS SNPs identified in our largest GWAS meta-analysis. We found $\hat{\alpha}_{PGS}$~0.375 (S.E. = 0.025) and $\hat{\alpha}_{PA}$~0.634 (S.E. = 0.034). The variance explained by fitting both predictors is $\hat{R}^2_{\hat{y}+\bar{y}_p}$ = 0.542 (S.E. = 0.032), which is larger than the accuracy of each single predictor ($R^2_{\hat{y}}$ = 0.38, S.E. 0.031; and $R^2_{\bar{y}_p}$ = 0.439, S.E. 0.032). Next, we estimated the spousal correlation $\hat{r}$ = 0.233 (S.E. = 0.031) and the heritability $\hat{h}^2$ = 0.894 (S.E. = 0.032) using mid-parent regression. Besides, the prediction accuracy of the PGS is $\hat{R}^2_{\hat{y},y}$~0.4. Therefore, from these estimates of r, h^2 and $R^2_{\hat{y},y}$

we predict using Equations (S3.1-S3.3) that $\alpha_{PGS} = 0.377$, $\alpha_{PA} = 0.656$ and $R^2_{\hat{y}+\bar{y}_p} = 0.599$. These three predictions are not statistically distinct from estimated values, which further validates our model.

Proof of theoretical results

The linear combination (y_{Opt}) of $\hat{y}$ and $\bar{y}_p$ that maximises prediction of y is derived from multivariate linear regression theory:

(3.1) $y_{Opt} = \alpha_{PGS}\hat{y} + \alpha_{PA}\bar{y}_p$

where

$$(3.2)\ \alpha_{PGS} = \frac{var(\bar{y}_p)cov(\hat{y},y) - cov(\hat{y},\bar{y}_p)cov(\bar{y}_p,y)}{var(\bar{y}_p)var(\hat{y}) - cov(\hat{y},\bar{y}_p)^2} = \frac{var(\bar{y}_p)var(\hat{y})}{var(\bar{y}_p)var(\hat{y})} \times \frac{cov(\hat{y},y)/var(\hat{y}) - \frac{cov(\hat{y},\bar{y}_p)cov(\bar{y}_p,y)}{var(\bar{y}_p)var(\hat{y})}}{1 - [cov(\hat{y},\bar{y}_p)^2]/[var(\bar{y}_p)var(\hat{y})]}$$

and

$$(3.3)\ \alpha_{PA} = \frac{var(\hat{y})cov(\bar{y}_p,y) - cov(\hat{y},\bar{y}_p)cov(\hat{y},y)}{var(\bar{y}_p)var(\hat{y}) - cov(\hat{y},\bar{y}_p)^2} = \frac{var(\bar{y}_p)var(\hat{y})}{var(\bar{y}_p)var(\hat{y})} \times \frac{cov(\bar{y}_p,y)/var(\bar{y}_p) - \frac{cov(\hat{y},\bar{y}_p)cov(\hat{y},y)}{var(\bar{y}_p)var(\hat{y})}}{1 - [cov(\hat{y},\bar{y}_p)^2]/[var(\bar{y}_p)var(\hat{y})]}$$

Without loss of generality, we assume that y and $\hat{y}$ are both centred (i.e. $E[y] = E[\hat{y}] = 0$) and scaled (i.e. $var[y] = var[\hat{y}] = 1$). Assuming that $var[y] = 1$ implies that $var[\bar{y}_p] = (1 + r)/2$, where r denotes the phenotypic correlation between mates in the population.

We also denote $R_{\hat{y},y} = corr(\hat{y},y) = cov(\hat{y},y)$, $R_{\bar{y}_p,y} = corr(\bar{y}_p,y)$ and $R_{\hat{y},\bar{y}_p} = corr(\bar{y}_p,y)$. Therefore, Equations (3.2) and (3.3) simplify as

$$(3.2')\ \alpha_{PGS} = \frac{cov(\hat{y},y)/var(\hat{y}) - \frac{cov(\hat{y},\bar{y}_p)}{\sqrt{var(\bar{y}_p)var(\hat{y})}} \times \frac{cov(\bar{y}_p,y)}{\sqrt{var(\bar{y}_p)var(y)}} \times \sqrt{\frac{var(y)}{var(\hat{y})}}}{1 - R^2_{\hat{y},\bar{y}_p}} = \frac{R_{\hat{y},y} - R_{\hat{y},\bar{y}_p}R_{\bar{y}_p,y}}{1 - R^2_{\hat{y},\bar{y}_p}}$$

and

$$(3.3')\ \alpha_{PA} = \frac{\frac{cov(\bar{y}_p,y)}{\sqrt{var(\bar{y}_p)var(y)}} \times \sqrt{\frac{var(y)}{var(\bar{y}_p)}} - \frac{cov(\hat{y},\bar{y}_p)}{\sqrt{var(\bar{y}_p)var(\hat{y})}} \times \frac{cov(\hat{y},y)}{\sqrt{var(\hat{y})var(y)}} \times \sqrt{\frac{var(y)}{var(\bar{y}_p)}}}{1 - R^2_{\hat{y},\bar{y}_p}}$$

$$= \sqrt{\frac{2}{1+r}}\left(\frac{R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p}R_{\hat{y},y}}{1 - R^2_{\hat{y},\bar{y}_p}}\right)$$

and further as

$$(3.2'')\ \alpha_{PGS} = \frac{R_{\hat{y},y} - R_{\hat{y},\bar{y}_p}R_{\bar{y}_p,y}}{1 - R^2_{\hat{y},\bar{y}_p}}$$

and

$$(3.3'')\ \alpha_{PA} = \sqrt{\frac{2}{1+r}}\left(\frac{R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p}R_{\hat{y},y}}{1 - R^2_{\hat{y},\bar{y}_p}}\right)$$

Equations (3.2'') and (3.3'') are expressed in function of $R_{\hat{y},y}$, $R_{\bar{y}_p,y}$, $R_{\hat{y},\bar{y}_p}$ and r.

We assume that $R_{\hat{y},y}$ is known, e.g., from quantifying the accuracy of the PGS in some validation sample. If we denote h^2 as heritability in the current population (which could be undergoing assortative mating, i.e. $r \neq 0$) and assume no shared environmental effects between parents and offspring then

$$(3.4) \quad h^2 = \text{cov}(\bar{y}_p, y)/\text{var}(\bar{y}_p) \Longrightarrow R_{\bar{y}_p,y} = h^2\sqrt{\frac{1+r}{2}}$$

Finally, denote $\hat{y}_p$ as the average PGS of parents. We can express $\bar{y}_p$ as a function of $\hat{y}_p$ as follows

$$(3.5) \quad \bar{y}_p = \frac{\text{cov}(\bar{y}_p, \hat{y}_p)}{\text{var}(\hat{y}_p)}\hat{y}_p + \varepsilon_p$$

where ε_p is a residual term with mean 0 and such that $\text{cov}(\varepsilon_p, \hat{y}_p) = 0$. Given that both phenotypes and PGS are centred, $\text{cov}(\bar{y}_p, \hat{y}_p)$ can be expressed as

$$\text{cov}(\bar{y}_p, \hat{y}_p) = \frac{1}{4}E\left[y_m\hat{y}_m + y_f\hat{y}_f + y_f\hat{y}_m + y_m\hat{y}_f\right] = \frac{1}{2}E\left[R_{\hat{y},y} + E[y_f\hat{y}_m|y_m]\right] = R_{\hat{y},y}(1+r)/2$$

Using a similar reasoning, we can show that $\text{var}(\hat{y}_p) = (1 + rR^2_{\hat{y},y})/2$. Therefore, Equation (3.5) can be rewritten as

$$(3.5') \quad \bar{y}_p = R_{\hat{y},y}\left(\frac{1+r}{1 + rR^2_{\hat{y},y}}\right)\hat{y}_p + \varepsilon_p$$

Besides, we can also write

$$(3.6) \quad \hat{y} = \hat{y}_p + \varepsilon_m,$$

where ε_m (Mendelian segregation) is independent of $\hat{y}_p$. Combining Equations (3.5') and (3.6) leads to

$$(3.7) \quad \text{cov}(\bar{y}_p, \hat{y}) = R_{\hat{y},y}\left(\frac{1+r}{1 + rR^2_{\hat{y},y}}\right)\text{cov}(\hat{y}_p, \hat{y}) + \text{cov}(\hat{y}, \varepsilon_p) = R_{\hat{y},y}\left(\frac{1+r}{1 + rR^2_{\hat{y},y}}\right)\text{var}(\hat{y}_p) + \text{cov}(\varepsilon_m, \varepsilon_p)$$

which, assuming $\text{cov}(\varepsilon_m, \varepsilon_p) = 0$, implies that $\text{cov}(\bar{y}_p, \hat{y}) = R_{\hat{y},y}\left(\frac{1+r}{1 + rR^2_{\hat{y},y}}\right)\text{var}(\hat{y}_p) = R_{\hat{y},y}(1+r)/2$.

Therefore,

$$(3.8) \quad R_{\hat{y},\bar{y}_p} = \text{corr}(\bar{y}_p, \hat{y}) = \frac{R_{\hat{y},y}(1 + r)}{\sqrt{2(1+r)}}.$$

It follows that

$$R^2_{\hat{y},\bar{y}_p} = \frac{R^2_{\hat{y},y}(1 + r)^2}{2(1+r)} = R^2_{\hat{y},y}(1+r)/2 \Leftrightarrow \frac{1}{1 - R^2_{\hat{y},\bar{y}_p}} = \frac{1}{1 - R^2_{\hat{y},y}(1+r)/2}$$

We now express below α_{PGS} and α_{PA} as a function of h^2, $R_{\hat{y},y}$, and r.

We first recall that $\alpha_{PGS} = \frac{R_{\hat{y},y} - R_{\hat{y},\bar{y}_p} R_{\bar{y}_p,y}}{1 - R^2_{\hat{y},\bar{y}_p}}$

$$R_{\hat{y},\bar{y}_p} R_{\bar{y}_p,y} = \frac{R_{\hat{y},y}(1 + r)}{\sqrt{2(1+r)}} \times h^2 \sqrt{\frac{1+r}{2}} = R_{\hat{y},y} h^2 (1 + r)/2.$$

$$R_{\hat{y},y} - R_{\hat{y},\bar{y}_p} R_{\bar{y}_p,y} = R_{\hat{y},y}[1 - h^2(1 + r)/2].$$

To calculate $\alpha_{PA} = \sqrt{\frac{2}{1+r}} \left(\frac{R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p} R_{\hat{y},y}}{1 - R^2_{\hat{y},\bar{y}_p}} \right)$

$$\sqrt{\frac{2}{1+r}} \left(R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p} R_{\hat{y},y} \right) = \sqrt{\frac{2}{1+r}} \left[h^2 \sqrt{\frac{1+r}{2}} - \frac{R^2_{\hat{y},y}(1 + r)}{\sqrt{2(1+r)}} \right] = h^2 - \frac{R^2_{\hat{y},y}(1 + r)}{1+r} = h^2 - R^2_{\hat{y},y}$$

Finally,

$$(3.2''') \quad \alpha_{PGS} = \frac{R_{\hat{y},y} - R_{\hat{y},\bar{y}_p} R_{\bar{y}_p,y}}{1 - R^2_{\hat{y},\bar{y}_p}} = \frac{R_{\hat{y},y}[1 - h^2(1 + r)/2]}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

and

$$(3.3''') \quad \alpha_{PA} = \sqrt{\frac{2}{1+r}} \left(\frac{R_{\bar{y}_p,y} - R_{\hat{y},\bar{y}_p} R_{\hat{y},y}}{1 - R^2_{\hat{y},\bar{y}_p}} \right) = \frac{h^2 - R^2_{\hat{y},y}}{1 - R^2_{\hat{y},y}(1 + r)/2}$$

Special case: $r = 0$

$$\alpha_{PGS} = \frac{R_{\hat{y},y}[1 - h^2/2]}{1 - R^2_{\hat{y},y}/2} \quad \text{and } \alpha_{PA} = \frac{h^2 - R^2_{\hat{y},y}}{1 - R^2_{\hat{y},y}/2}$$

The relative contribution of $\hat{y}$ and $\bar{y}_p$, defined above as $\omega_{PGS} = \alpha_{PGS}/(\alpha_{PGS} + \alpha_{PA})$ and $\omega_{PA} = \alpha_{PA}/(\alpha_{PGS} + \alpha_{PA})$ can be expressed as

$$\omega_{PGS} = \frac{R_{\hat{y},y}[1 - h^2(1 + r)/2]}{R_{\hat{y},y}[1 - h^2(1 + r)/2] + h^2 - R^2_{\hat{y},y}} \quad \text{and } \omega_{PA} = \frac{h^2 - R^2_{\hat{y},y}}{R_{\hat{y},y}[1 - h^2(1 + r)/2] + h^2 - R^2_{\hat{y},y}}$$

These two relative contributions are equal when $\omega_{PA} = \omega_{PGS} = 1/2$, i.e. when

$$2h^2 - 2R^2_{\hat{y},y} = R_{\hat{y},y}[1 - h^2(1 + r)/2] + h^2 - R^2_{\hat{y},y} \Leftrightarrow R^2_{\hat{y},y} + R_{\hat{y},y}[1 - h^2(1 + r)/2] - h^2$$

or equivalently, when

$$R_{\hat{y},y} = \frac{-[1 - h^2(1 + r)/2] + \sqrt{[1 - h^2(1 + r)/2]^2 + 4h^2}}{2}$$

This therefore proves Equation (S3.4).

Prediction accuracy from a linear regression model fitting both PGS and parental average

The expected prediction accuracy ($R^2_{\hat{y}+\bar{y}_p}$) from combining PGS and parental information can be expressed as

$$R^2_{\hat{y}+\bar{y}_p} = \alpha_{PGS}\mathrm{cov}(\hat{y},y) + \alpha_{PA}\mathrm{cov}(\bar{y}_p,y) = \frac{R^2_{\hat{y},y}\left[1-h^2(1+r)/2\right]+h^2(h^2-R^2_{\hat{y},y})(1+r)/2}{1-R^2_{\hat{y},y}(1+r)/2}$$

which can be simplified as

$$(3.9)\quad R^2_{\hat{y}+\bar{y}_p} = \frac{R^2_{\hat{y},y}+\left(\frac{h^2}{2}\right)(1+r)\left[h^2-2R^2_{\hat{y},y}\right]}{1-R^2_{\hat{y},y}(1+r)/2}$$

Prediction accuracy and proportion of causal variants captured

We assume that the trait of interest in underlain by M independent causal SNPs and that m ($m \leq M$) of them are included in a PGS. Moreover, we assume that the population has been undergoing assortative mating for multiple generations, until an equilibrium is reached. We derive below how large m needs to be for the prediction accuracy of the derived PGS, in the equilibrium population, to equal $R^2_{\hat{y},y}$.

We denote $\rho = rh^2$, $f_0 = m/M$, $\gamma = \rho/(1-\rho)$, $\alpha = \gamma/(2M)$ the expected correlation between trait-increasing alleles induced by assortative mating, and $\sigma^2_{g,0}$ and $\sigma^2_{g,eq}$ the genetic variances in a randomly and assortatively mating populations, respectively.

In the equilibrium population, the variance of the PGS can be expressed as

(Int. 3.1) $\mathrm{var}(\hat{y}) \approx \sigma^2_{g,0} f_0(1+\gamma f_0)$, and the covariance between y and $\hat{y}$ as

(Int. 3.2) $\mathrm{cov}(\hat{y},y) \approx \sigma^2_{g,0} f_0(1+\gamma)$.

Equations (Int. 3.1) and (Int. 3.2) are proven below.

Therefore,

$$(3.10)\quad R^2_{\hat{y},y} = \frac{\mathrm{cov}(\hat{y},y)^2}{\mathrm{var}(\hat{y})\mathrm{var}(y)} \approx \sigma^2_{g,0} f_0 \frac{(1+\gamma)^2}{1+\gamma f_0}$$

We divide the previous equation by $\sigma^2_{g,eq}$ and define $\phi_{eq} = R^2_{\hat{y},y}/\sigma^2_{g,eq}$. Therefore, Equation (3.10) implies that

$$(3.11)\quad (1+\gamma f_0)\phi_{eq} \approx \left(\frac{\sigma^2_{g,0}}{\sigma^2_{g,eq}}\right) f_0(1+\gamma)^2 = f_0(1-\rho)(1+\gamma)^2 \Leftrightarrow f_0 \approx \frac{\phi_{eq}}{(1-\rho)(1+\gamma)^2 - \gamma\phi_{eq}}$$

where $\phi_{eq} = R^2_{\hat{y},y}/\sigma^2_{g,eq}$. Note that $\sigma^2_{g,eq}/\sigma^2_{g,0}$ is the inflation in genetic variance due to assortative mating, which is predicted in theory to equal $1/(1-\rho)$.

Using a similar reasoning, Yengo et al.[71] (Eq. 1.20 in their Supplementary Note) derived the relationship between f_0 and the proportion $f_{eq} = h^2_{SNP}/h^2$ of equilibrium heritability explained by the m SNPs included in the PGS as:

$$(3.12)\quad f_0 = \frac{1-\rho}{2\rho}\left[\sqrt{\left(1+\frac{4f_{eq}\rho}{(1-\rho)^2}\right)}-1\right] \underset{|\rho|\ll 1}{\approx} f_{eq}/(1-\rho).$$

Proof of Equation (Int. 3.1) and (Int. 3.2)

We assume an infinitesimal model, where each causal SNP explains the same amount of trait variance. For simplicity, we assume the squared effect size of each causal SNP to equal $b^2 = \sigma^2_{g,0}/M$; and that SNP

effects are estimated with negligible errors so that they could be assumed to be equal to their true value. Finally, we assume that the m first SNPs are included in the PGS.

Under these assumptions, the PGS (i.e. $\hat{y}$) can be written as

$$\hat{y} = \left(\frac{\sigma^2_{g,0}}{M}\right)\sum_{j=1}^{m} z_j$$

where $(z_j - 2p_j)/\sqrt{2p_j(1-p_j)}$ is the centred and scaled count of trait-increasing allele at SNP j and p_j the trait-increasing allele frequency at that same SNP. By definition, we have that $\mathrm{var}(z_j) = 1 + \alpha$, and that $\mathrm{cov}(z_j, z_k) = 2\alpha$. It follows that

$$\mathrm{var}(\hat{y}) = \frac{\sigma^2_{g,0}}{M}[m(1+\alpha) + m(m-1)2\alpha] = \sigma^2_{g,0}\left(\frac{m}{M}\right)[1 + (2m-1)\alpha] = \sigma^2_{g,0} f_0\left[1 + \left(f_0 - \frac{1}{2M}\right)(2M\alpha)\right]$$

For large values of M, this simplifies as $\mathrm{var}(\hat{y}) \approx \sigma^2_{g,0} f_0(1 + \gamma f_0)$.

Similarly, we can write $\mathrm{cov}(\hat{y}, y)$ as $\mathrm{cov}(\hat{y}, y) = \frac{\sigma^2_{g,0}}{M}[m(1+\alpha) + m(M-1)2\alpha] \approx \sigma^2_{g,0} f_0(1+\gamma)$.

Supplementary Note 5: Saturation of GWAS signals within pathways and gene sets

Overview and main results

We assessed the enrichment of broad categories of biological pathways for different GWAS sample sizes, using two different gene set enrichment methods, DEPICT[42] and MAGMA.[43] Specifically, we evaluated the prioritization of 14,462 gene sets, hierarchically clustered into 20 groups of related gene sets based on gene set membership (see Methods below, **Suppl. Fig. 21**, **Suppl. Table 13**). We observed an enrichment of OMIM genes in clusters 1, 2, 5, 6, 11, 16, and 17 (Bonferroni $P < 0.05$ vs. random genes (**Extended Data Fig. 8**, **Suppl. Table 14**). At all sample sizes tested (range N=130,010 to N=5,314,291), similar sets of the clusters consistently showed significant enrichments in DEPICT (clusters 2, 5, 11, 16, and 17) and MAGMA-prioritized gene sets (clusters 5, 11, 16, and 17; **Suppl. Fig. 21**). Thus, the broad patterns of gene set enrichment are apparent even at moderate sample sizes and remain quite stable as sample sizes increase.

In contrast with clusters of gene sets, individual genes may require larger sample sizes or multiple ancestries to be implicated by GWAS. To address these questions, we assessed the fraction of OMIM genes that contain an approximately independent genome-wide significant signal (identified with COJO) across the range of GWAS sample sizes. As sample size increases and the number of independent signals increases, the percent of the 462 OMIM genes overlapping a signal also increases (**Suppl. Fig. 23b**); however, after subtracting the null background from randomly sampled sets of 462 genes, the percentage above background of OMIM genes that overlap GWAS signal plateaus at a sample size of ~2.5 M (**Suppl. Fig. 23c**). In comparing the trans-ancestry meta-analysis with the largest European-ancestry-only GWAS with, we did not observe a noticeable increase in overlapping OMIM genes above background.

We also sought to examine more directly whether the height GWAS results implicate highly similar biology across different continental ancestries. We used MAGMA and DEPICT to prioritize genes based on GWAS results for EUR, EAS, and AA ancestries. We then compared the enrichment of heritability with stratified LD score regression (LDSC)[39,40] for each set of prioritized genes, evaluated either in the same ancestry or in the other two ancestries. Genes prioritized in one ancestry by both MAGMA and DEPICT showed comparable enrichment of heritability when evaluated either in that ancestry or in the other two ancestries (**Suppl. Fig. 22**, **Suppl. Table 15**), strongly confirming the shared biology implicated by GWAS results from different ancestries.

Methods

Evaluation of gene set enrichment analysis (GSEA) methods across sample sizes.

For GWAS summary statistics from multiple sample sizes (**Tables 1 - 2**) two GSEA approaches were applied (DEPICT and MAGMA). DEPICT release 173 was used; the top 1000 SNPs pruned by p-value from each set of summary statistics were used as input for each sample. MAGMA version v1.07b was used; SNPs were annotated with genes within 100kb, and genes were removed if the missingness of their pathway membership was over 0.2.

To evaluate the ability of GSEA methods to identify groups of gene sets at different sample sizes, 14,462 gene sets, each consisting of Z-scores for 19,987 genes (gene sets selected and gene membership Z-scores calculated in ref.[42]), were hierarchically clustered into 20 clusters as follows. Pairwise distances between gene sets were defined as the Euclidean distance between the gene sets' Z-scores and the elbow method was used to choose the number of clusters, evaluating average distances between cluster centroids as the number of clusters is varied (**Suppl. Fig. 21**). For DEPICT and MAGMA, enrichment of prioritization in each cluster was defined as the number of prioritized gene sets in each cluster divided by the size of each cluster; a gene set was considered prioritized if it was in the top 10% of gene sets as prioritized by the GSEA method. Enrichment of OMIM genes in each gene set was defined as the number of OMIM genes in each gene set divided by the size of each gene set divided by the proportion of all genes in OMIM, and then enrichment of OMIM genes in each cluster was defined as the average of the

enrichment of OMIM genes in each gene set in that cluster. Genes were defined to be "in a gene set" if the gene's gene-set Z-score is > 1.96, as described previously.[72] Null distributions for each cluster were generated by randomly selected prioritized gene sets (for DEPICT and MAGMA) or prioritized genes to evaluate enrichment significance.

To evaluate saturation of height-associated gene identification, the percentage of OMIM genes overlapping independent COJO signals was calculated. "Overlapping" was defined as having at least one COJO SNP within the gene body, as defined with the plink version 1.9 hg19 gene list (URL: https://www.cog-genomics.org/static/bin/plink/glist-hg19). A null distribution was calculated by drawing an equivalent number of random genes (binned by size into 20 bins, same number of genes per bin) to match OMIM genes, and calculating the percent of the random genes near a COJO SNP.

Benchmarking of gene prioritization across different ancestries

We applied DEPICT and MAGMA to prioritize genes on height GWAS of European, African-American and East Asian ancestry, resulting in three sets of prioritized genes for each method. To allow for a fair comparison, we used subsets of the available cohorts to create three equally sized GWAS (N~100,000). For MAGMA, we converted gene set prioritizations to gene prioritizations as described previously.[72] For both DEPICT and MAGMA, we then used Benchmarker[72] to evaluate the performance of these three sets of genes in each of the three different ancestries, resulting in three within-ancestry and six cross-ancestry scenarios.

The Benchmarker method is based on a leave-one-chromosome-out approach where one chromosome is withheld, and GWAS results for the remaining 21 chromosomes are used to prioritize genes on the withheld chromosome, iterating across each withheld chromosome. For each of the discovery GWAS ancestries, we selected the top 10% of the prioritized genes on each left out chromosome, resulting in 1,893 prioritized genes. We subsequently annotated SNPs within 50kb of the prioritized genes to generate a LD score annotation for these SNPs using LDSC.[16] Lastly, we applied stratified LDSC[39] (S-LDSC) to compare the three annotation sets to the full GWAS results for each of the three ancestries to determine whether the performance of genes prioritized and then evaluated across the same ancestry would be more enriched for heritability compared with those prioritized and evaluated in different ancestries. Reference panels were based on the 1000 Genomes Phase 3 reference panels[5] for LD score estimation, matching the reference panel ancestry with the GWAS results for that same ancestry. In addition, a category of SNPs that locate within 50kb of any gene in the prioritization method and a set of 53 annotations of known genomic importance were included in the S-LDSC as conditional covariates. The analysis was based on 1,217,311 HapMap3 SNPs. The results of the S-LDSC is summarized using proportional h^2_{SNP} (proportion of heritability explained by the annotation), the regression coefficient (average per-SNP contribution of the annotation to heritability), and enrichment in heritability (h^2 divided by the proportion of SNPs in the annotation). To assess the performance difference between two annotations, we calculated p-values based on standard errors from the different estimates.

Supplementary Note 6: Enrichment of SNP-based heritability from low-frequency variants within loci containing common SNPs associated with height

In this note, we quantify the enrichment of SNP-based heritability due to low-frequency SNPs (MAF<1%) in genomic loci containing common SNPs (MAF>1%) associated with height.

Heritability enrichment from low-frequency variants in European ancestry participants

We first analysed imputed SNPs (INFO>0.3) from 3 samples of unrelated European ancestry (EUR) individuals independent from our discovery GWAS. This analysis included 44,312 participants from the Estonian Biobank (EBB), 14,587 participants of the UK Biobank (UKB) and 14,058 participants from the Lifelines Biobank (LLB), so that the total sample size is N=72,957. We partitioned SNP-heritability estimates in each of the 3 samples, then meta-analysed the results using an inverse-variance weighting scheme. The number of SNPs with MAF>0.1% was 13,040,176 in UKB (incl. 8,547,170 SNPs with MAF>1%), 11,492,146 in LLB (incl. 7,659,695 SNPs with MAF>1%) and 13,695,032 in EBB (incl. 8,620,105 SNPs with MAF>1%). We stratified SNPs into 4 classes: (1) 0.1%<MAF<1% within genome-wide significant loci (GWS), (2) 0.1%<MAF<1% outside GWS loci, (3) MAF>1% within GWS loci and (4) MAF>1% outside GWS loci. Then, we calculated genetic relationship matrices (GRM) for each group of SNPs using GCTA and estimated SNP-based heritability from fitting these 4 GRMs jointly.

Extended Data Fig. 10 shows estimates of SNP-based heritability for each group of SNPs and each sample, as well as the meta-analysis of these estimates across the 3 EUR samples. We found consistent patterns across these samples and, therefore, hereafter focus on meta-analysed estimates. Approximately 88% (i.e. 5.7/(5.7 + 0.78)) of the SNP-based heritability of height explained by variants with 0.1%<MAF<1% is due to SNPs located within our 7,209 height-associated loci. Importantly, these analyses only implicate a fraction (approximately 4/5th, Wainschtein et al.[50]) of low-frequency variants with an imputation accuracy score >0.3, which limits generalisability to all low-frequency and rare variants. Nevertheless, these results suggest that rarer variants associated with height are likely be detected in (or near) the 7209 loci identified in this study.

Height-associated rare variants in European ancestries but common in African ancestries are enriched within GWS loci

Next, we analysed 16,374,566 SNPs with MAF>1% in African ancestries (AFR; N=661) individuals from the 1000 Genomes Project (1KG). We stratified these SNPs in two classes defined by their MAF in EUR individuals from 1KG (N=504). The first class contained 7,365,878 SNPs with a MAF>1% in EUR (47% of which had a MAF<0.1% in EUR; **Suppl. Fig. 25**), and the second one 8,114,046 SNPs with a MAF<1% in the same EUR individuals. We then quantified the enrichment of SNP-based heritability within GWS loci for both classes of variants in 6,911 AFR individuals from the UKB.

Overall, we found similar enrichments of SNP-based heritability within GWS loci for both classes of variants (**Suppl. Fig. 25a**). Therefore, assuming that causal variants for height are shared across ancestries, these results suggest that rare variants in EUR that are associated with height (at least those common enough in AFR) are also likely to be detected within these 7,209 genomic regions. Note that this class of rare variants in EUR could, in principle, be detected with large GWAS of height in AFR.

Conclusions

In summary, we performed two orthogonal analyses, with results suggest that rare variants associated with height in EUR are enriched within our GWS loci. Additional analyses using whole-genome sequence data in large samples are required to confirm these findings as well larger GWAS of height in non-EUR populations.

SUPPLEMENTARY REFERENCES

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