American Journal of Epidemiology

Vol. 162, No. 4
Printed in U.S.A.
DOI: 10.1093/aje/kwi201

A Network of Investigator Networks in Human Genome Epidemiology

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Received for publication April 20, 2005; accepted for publication May 18, 2005.

The task of identifying genetic determinants for complex, multigenetic diseases is hampered by small studies, publication and reporting biases, and lack of common standards worldwide. The authors propose the creation of a network of networks that include groups of investigators collecting data for human genome epidemiology research. Twenty-three networks of investigators addressing specific diseases or research topics and representing several hundreds of teams have already joined this initiative. For each field, the authors are currently creating a core registry of teams already participating in the respective network. A wider international registry will include all other teams also working in the same field. Independent investigators are invited to join the registries and existing networks and to join forces in creating additional ones as needed. The network of networks aims to register these networks, teams, and investigators; be a resource for information about or connections to the many networks; offer methodological support; promote sound design and standardization of analytical practices; generate inclusive overviews of fields at large; facilitate rapid confirmation of findings; and avoid duplication of effort.

epidemiology; genome; meta-analysis; multicenter studies

The task of understanding the role played by human genetic variation in complex diseases is daunting (1–4). High-throughput genotyping, exploratory statistical analyses in studies with limited sample sizes, publication bias,

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TABLE 1. International network-registries in human genome epidemiology

Field	Network-registry	Type*	No. of teams (no. in thousands)†	Principal contact(s)
Parkinson's disease	Genetic Epidemiology of Parkinson's Disease (GEO-PD) consortium	D (CC>C)	18 (10)	D. M. Maraganore (dmaraganore@mayo.edu)
HIV‡ infection	International Meta-Analysis of HIV Host Genetics	D (C>CC)	30 (7)	T. R. O'Brien (obrient@exchange.nih.gov)
Cardiovascular disease	Fibrinogen Studies Collaboration and Emerging Risk Factors Collaboration (new genetics component being launched)	D (C)	50 (200)	J. Danesh (john.danesh@phpc.cam.ac.uk)
Craniofacial anomalies	Craniofacial anomalies network developed by the International Collaborative Research on Craniofacial Anomalies Project	D (CC)	9 (4)	J. Little (jlittle@uottawa.ca); Internet Web address: www.who.int/genomics/anomalies/cfaproject/en/#mtg
Osteoporosis	Genetic Markers for Osteoporosis (GENOMOS)	D (C>CC)	10 (30)	A. G. Uitterlinden (a.g.uitterlinden@erasmusmc.nl)
Antiphospholipid syndrome	International Meta-analysis of Antiphospholipid Syndrome Genetics	D (CC>C)	9 (4)	J. P. A. Ioannidis (jioannid@cc.uoi.gr)
Child growth and metabolism	Birth Cohorts Consortium	D (C)	24 (55)	M.-R. Jarvelin (m.jarvelin@imperial.ac.uk)
Preterm birth	Preterm Birth International Collaborative (PREBIC)/Preterm Birth and Genetics International Alliances (PREGENIA)	D (C, CC)	10 (20)	S. Dolan (sdolan@marchofdimes.com); Internet Web address: www.prebic.org
Cancer, cardiovascular diseases, diabetes, aging	European Prospective Investigation on Cancer, chronic diseases and nutrition (EPIC)	D, E (C)	521 (120)	E. Riboli (riboli@iarc.fr)
Lymphoma	International Lymphoma Epidemiology Consortium (InterLymph)	D (CC>C)	15 (20)	P. Hartge (ph43v@nih.gov), P. Boffetta (boffetta@iarc.fr)
Lung cancer	International Lung Cancer Consortium (ILCCO)	D (CC>C)	30 (51)	R. Hung (hung@iarc.fr)
Head and neck cancer	International Head and Neck Cancer Consortium (INHANCE)	D (CC)	13 (28)	M. Hashibe (hashibe@iarc.fr)
Melanoma	Melanoma Genetics Consortium (GenoMel)	D (CC)	12 (3)	J. A. Newton Bishop (j.newton-bishop@cancer.org.uk); Internet Web address: www.genomel.org
Pancreatic cancer	Pancreatic Cancer: Genetic Epidemiology (PACGENE) Consortium	D (CC)	10 (5)	G. Petersen (peterg@mayo.edu)
Breast cancer and prostate cancer	Breast and Prostate Cancer and Hormone-Related Variants Cohort Consortium	D (C)	6 (13 + 20)	D. Hunter (dhunter@hsph.harvard.edu)
Brain tumors	Brain Tumor Epidemiology Consortium (BTEC)	D (CC)	22	M. Bondy (mbondy@mdanderson.org), B. Malmer (beatrice.malmer@onkologi.umu.se)
Breast cancer and colon cancer	Breast and Colon Cancer Family Registries	D	10 (34 + 30)	I. L. Andrulis, N. M. Lindor (seminard@mail.nih.gov)
Cancer	Cancer Genetics Network (CGN)/Informatics Technology Group	D (C)	8 (24)	C. Kasten (seminard@mail.nih.gov)
Radiation and breast cancer	Women's, Environmental, Cancer, and Radiation Epidemiology (WECARE) Study Consortium	E (CC)	15 (2)	J. Bernstein (bernstej@mskcc.org)
Environmental carcinogens	International Collaborative Study on Genetic Susceptibility to Environmental Carcinogens (GSEC)	E (CC)	130 (58)	E. Taioli (taioli@policlinico.mi.it); Internet Web address: www.gsec.net
Assisted reproduction	International Pooled Analysis of Children Born after Assisted Procedures (APIKIDS)	E (C)	6 (7)	E. Taioli (taioli@policlinico.mi.it); Internet Web address: www.apikids.org
DNA repair genes and cancer	Web-based meta-analysis on DNA repair and cancer risk	G (CC>C)	5	P. Vineis (p.vineis@imperial.ac.uk); Internet Web address: perseus.isi.it/huge
Other cancer-related networks		D, G (C/CC)		D. Seminara (seminard@mail.nih.gov), D. M. Winn (winnde@mail.nih.gov)
Proposals for other networks	Human Genome Epidemiology Network (HuGE Net)			J. P. A. Ioannidis (jioannid@cc.uoi.gr), M. Khoury (muk1@cdc.gov)

* D, disease-based network; CC>C, mostly case-control but also cohort studies included; C>CC, mostly cohort but also case-control studies included; C, cohort studies included; CC, case-control studies included; E, exposure-based network; G, gene-based network.

† In determining the number of teams, multicenter teams counted as one team, and the number of investigators may be much larger; numbers in parentheses show the approximate total number of subjects in the compiled databases.

‡ HIV, human immunodeficiency virus.

and selective reporting may generate spurious findings that fail replication (1). Publication bias and selective reporting are well-recognized problems across all domains of epidemiologic and clinical research (5–7). The editors of leading medical journals recently required up-front registration of clinical trials as a prerequisite for eventual publication in their journals (8). However, study registration is difficult to implement in genetic epidemiology: molecular studies often can be carried out rapidly by using established specimen and data collections, and investigators are reluctant to publicly register their hypotheses in advance of publication.

An alternative to study registration is to create inclusive registries of investigators and information about sample and/or data collections in different fields. Whereas individual investigators continue to pursue their chosen lines of research, networks permit broad, consistent, and transparent assessment and replication of novel findings obtained in individual studies (9). These networks can also facilitate prompt publication—with due credit—of ''negative'' results and explore reasons for conflicting findings. Finally, the quality and credibility of research can be enhanced by standardization of clinical, laboratory, and statistical methods used by investigators working on the same research questions.

Several registries and networks addressing specific diseases or research questions are already ongoing (9). It is important to share with the international research community at large the expertise and experiences in creating these networks and to provide a comprehensive registry including information on the existing networks. A network of networks is needed to perform this function across diseases and genes. Doing so is critical, because some biologic pathways can affect the risk of many different diseases, and genetic effects also impact multiple pathways and diseases. Moreover, many issues affecting large-scale collaborations such as publication policies, informed consent, biospecimen processing and management, and creation of informatics infrastructures are common to networks across disciplines. The network of networks should offer methodological support, promote sound design and standardization of practices, and generate up-to-date overviews of each field. This structure will operate without limiting the scientific independence of each network to maximize efficiency and will avoid unhelpful duplication of efforts.

The proposed network-of-networks concept arose at a Human Genome Epidemiology Network–sponsored (10, 11) workshop in Cambridge, United Kingdom, in November 2004 that targeted methodological issues pertaining to the quantitative synthesis of genetic epidemiologic information from diverse studies. The workshop was attended by several scientists involved in existing networks. Within a short time, we have grown to include 23 networks representing several hundreds of teams and thousands of individual investigators (table 1) and have identified many additional networks. Most consortia focus on specific diseases, but others are organized around a common interest in specific genes or environmental risk factors modulated by genes.

We are currently creating and expanding the core registry that lists information on all teams participating in each existing network, as well as wider registries that also list information on all other teams working in the same field worldwide. The wider registries are being compiled based on electronic searches of the published literature in each field, but we also want to identify all investigators interested in working in the specific area. These efforts will generate a comprehensive map of each field and would eventually facilitate creation of a credible synopsis of validated associations of genetic variants with complex disease. We encourage investigators worldwide to communicate with the coordinators of each network (refer to table 1 for contact information) to discuss the possibility of mutually beneficial collaboration. We want to be as inclusive as possible. We also invite other existing networks to join in this initiative, and we encourage investigators who want to create networks in other fields to communicate with us. An October 6–7, 2005, meeting is being planned in Cambridge, United Kingdom, where network representatives will present and share experiences in creating, managing, and maintaining their collaborations. We would also like to have this meeting attended by scientists interested in creating new networks in their fields. Other future meetings and consensus statements will aim at developing ''best practices'' for study designs and standardizing statistical methods for analyzing data from international consortia.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

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