THE EU FP6 EPIGENCHLAMYDIA CONSORTIUM: CONTRIBUTION OF MOLECULAR EPIDEMIOLOGY AND HOST–PATHOGEN GENOMICS TO UNDERSTANDING CHLAMYDIA TRACHOMATIS-RELATED DISEASE

S.A. Morré¹, S. Ouburg¹, A.S. Peña¹ and A. Brand²

¹Laboratory of Immunogenetics, Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands; ²Department of Social Medicine, School of Public Health and Primary Care (caphri), Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands

CONTENTS

Summary ....................................................................................................................... ............................................ 7
Chlamydia trachomatis infections ................................................................................. 8
Chlamydia twin studies ................................................................................................. 8
The EpiGenChlamydia Consortium ............................................................................. 8
Introduction .................................................................................................................. 8
Meetings organized by the consortium ......................................................................... 9
Deliverables .................................................................................................................. 9
Public Health Genomics European Network and the EGC Consortium ....................... 10
References .................................................................................................................. 12

SUMMARY

Chlamydia trachomatis infections are responsible for the world's leading cause of blindness (trachoma) and its most prevalent sexually transmitted disease, which is strongly associated with pelvic inflammatory disease, ectopic pregnancy and tubal infertility. Twin study-based findings of members of EpiGenChlamydia Consortium estimate that there is a 40% genetic predisposition to C. trachomatis infections. It is likely that the advances in human genomics will help to unravel the genetic predisposition at the gene level and will help to define a genetic fingerprint that can be used as a marker for this predisposition. The information

Correspondence: Servaas A. Morré, PhD, Head, Laboratory of Immunogenetics, Department of Pathology, VU University Medical Center, De Boelelaan 1117, 1081HV, Amsterdam, the Netherlands. E-mail: samorretravel@yahoo.co.uk
Chlamydia trachomatis infection and the development of tools for early detection of a predisposition to Chlamydia infection and its complications. This review summarizes the consortium aims and progress, and future perspectives and directions.

CHLAMYDIA TRACHOMATIS INFECTIONS

Chlamydia trachomatis infection is responsible for the world’s leading cause of blindness (trachoma), and its most prevalent sexually transmitted disease, which is strongly associated with pelvic inflammatory disease, ectopic pregnancy and tubal infertility. Prevalences are increasing worldwide with almost 100 million new infections each year (1).

Striking differences between individuals have been observed in the clinical course of infection with C. trachomatis. In the case of sexually transmitted infection with C. trachomatis the following differences have been observed: i) transmission versus no transmission; ii) symptomatic versus asymptomatic course of infection; iii) persistence versus clearance of infection; and iv) development of late complications (e.g., tubal infertility) versus no development of late complications. However, only a portion of women develop secondary complications after infection (2-5).

Ocular C. trachomatis infection causes inflammatory changes in the conjunctiva, and repeated infections sometimes lead to fibrosis and scarring of the subtarsal conjunctiva. This may cause the upper eyelid margin to turn inwards causing the lashes to rub against the eyeball (trichiasis), which damages the cornea and leads ultimately to blindness. Sadly, it is common in children. It now appears possible that a subgroup of individuals develops more severe and persistent clinical disease in response to infection and is more likely to develop conjunctival scarring and trichiasis in later life.

In general, the differences in the clinical course of infection can be explained by the interaction between the host (host factors) and the pathogen (virulence factors). This is an interaction which will be influenced by environmental factors such as coinfections in poor hygienic and crowded conditions. Although some studies have shown association between C. trachomatis serovars (6-8) and the clinical course of infection (2), and differences in infection vary between serovars (9), no clear single bacterial virulence factor has been identified. If the cellular immune response to C. trachomatis is subject to genetic influences, then the degree and mechanisms of such genetic control may have important implications in understanding the immunopathogenesis of C. trachomatis infection. Deeper knowledge in these areas will lead to therapeutic strategies and vaccine development. This is what is necessary to effectively treat and prevent C. trachomatis infection.

Chlamydia twin studies

In this supplement Bailey et al. (10) describe the most relevant study in the field of Chlamydia immunogenetics. A preliminary report was presented at the Ninth International Symposium on Human Chlamydia Infections in Napa, California, USA in 1998. They have now estimated the relative contribution of host genetics to the total variation in lymphoproliferative responses to C. trachomatis antigen by analyzing these responses in 64 Gambian twin pairs from trachoma-endemic areas. Proliferative responses to serovar A elementary body (EB) antigens were found to be stronger in monozygotic twins than in dizygotic twin pairs. Based on these observations, they calculated a heritability of 0.39, thus suggesting that host genetic factors contribute to almost 40% of the clinical presentation.

THE EPICEN CHLAMYDIA CONSORTIUM

Introduction

The EpiGenChlamydia Consortium (EGC) has been funded by the European Union (EU) Sixth Framework Programme under the Coordination Actions in functional genomics research for a period of 2.5 years (July 2007–December 2009). The aim of the consortium was to structure transnational research to such a degree that comparative genomics and genetic epidemiology could be performed in large numbers of unrelated individuals. This funding enabled the participation of 20 groups from Europe, Africa and the
United States (see www.EpiGenChlamydia.eu for details). The overall goal of the EGC Consortium is to create the optimal environment to build and prepare a consortium to reliably determine the genetic predisposition to *C. trachomatis* infection in both ocular and sexually transmitted *C. trachomatis* (11). This will allow the development of diagnostic tools that can determine an individual’s predisposition to infection and the risk of developing late complications. Further, it is hoped that the knowledge generated with this effort will contribute to the understanding of the *C. trachomatis*-host interaction in order to facilitate the development of a vaccine and novel tools for the detection and treatment of *C. trachomatis* infections.

The consortium defined six interdependent work packages (Fig. 1): epidemiology (to define suitable cohorts in Europe); genetics and genomics (to define a single nucleotide polymorphism [SNP]-Chip approach, based on the complete host and bacterial genomes available); biobanking and data warehouse (to build a biomedical, ethically acceptable, central sample collection and data management system); research integration (to streamline all European groups working on immunogenetics and Chlamydial infections in general to gain synergy); dissemination (to extend and further validate this consortium); and project management.

**Meetings organized by the consortium**

The kick-off meeting was held on December 12, 2007 and the final meeting will be held November 15–16, 2009. In the interval, two other meetings were organized and submeetings were held during the Sixth Meeting of the European Society of *Chlamydia* Research in Aarhus, Denmark in July 2008, among others. In addition, the Aarhus meeting featured an open session entitled “Immunogenetics of *Chlamydia* Infection”.

**Deliverables**

The EGC Consortium has provided and is in the process of providing reports on its deliverables to the EU, including state-of-the-art reports on the epidemiology of both ocular and sexually transmitted *C. trachomatis* infections (12), bacterial typing (13, 14), SNP genotyping strategies and sample validation. Three deliverables are of major importance for the future success of the consortium and for obtaining new funding: a biobank, consisting of physical and virtual sample collections; a data warehouse in which genotyping data together with clinical and demographic data can be merged and accessed; and finally, development to assure dissemination.

**Biobank**

The partners working on ocular *Chlamydia*-related diseases, coordinated by the London School of Hygiene and tropical medicine by David Mabey and Robin Bailey together with their Gambian partners, have already defined and secured 1,500 case–control pairs (N = 3,000). The scientific coordinator (Servaas Morré), together with Dutch collaborators, has collected more than 4,000 specimens which are currently in use, while 10,000 specimens are available for further studies. The consortium is exploring the possibilities of genetic and epidemiologic *Chlamydia* research using samples from existing biobanks in North European countries. Scandinavian countries are well known for excellent biobanks with large quantities of samples and biological data. The Nordic Biological Specimen Banks is a collaboration of major Scandinavian biological speci-
men banks, including maternity and infectious disease cohorts. The biobank currently contains biological specimens and lifestyle data for more than 4 million residents of Nordic countries. Samples can be linked to medical registries to obtain clinical information, making it one of the largest longitudinal cohorts in the world. Several Scandinavian researchers and clinicians are participants in the EpiGenChlamydia Consortium.

**Data warehouse**

To study larger quantities of clinical, biological and epidemiologic data, proper data management and storage are required. Researchers at the Wellcome Trust Centre for Human Genetics (WTCHG) have developed the MalariaGen database (www.malariagen.net), which unites data from 30 research teams worldwide. The MalariaGen data management system automatically manages the biobank and its data. Part of the research data is automatically checked for quality control and automatically curated. All patient data are completely anonymous and secure. Secure access is available to participating researchers. The WTCHG is a participant in the EGC Consortium. The consortium and the WTCHG have explored the possibilities for using a secure section of the MalariaGen database to store the data generated by the EGC Consortium and part of the data generated by its participants is already available in this data warehouse.

**Dissemination**

The EGC Consortium has organized different sessions at scientific meetings to increase the outreach if its aims and goals. In addition, dissemination at an EU policy level has been achieved through two separate articles in the biweekly *The Parliament Magazine* which is directly distributed to all Members of the European Parliament, senior members of the European Commission, the Council of the European Union and various EU institutions. The first publication was in May 2008 and was presented in a supplement at the Congress of Europe, 60th Anniversary Special, May 23–24, 2008, in the Hague, the Netherlands. The second was very recently presented at the European Health Forum, at the Gastein meeting and published in *The Parliament Magazine* on September 21, 2009.

This *Drugs of Today* supplement, “*An integrated approach to the understanding of Chlamydia infections: 2009 update*”, is the most recent example of the dissemination achieved by the EpiGenChlamydia consortium.

**PUBLIC HEALTH GENOMICS EUROPEAN NETWORK AND THE EGC CONSORTIUM**

The new insights and new pathways to the understanding of *C. trachomatis* disease provided by the EpiGenChlamydia Consortium and currently presented in this supplement will benefit population health. If these evidence-based findings are translated into health policies and practice in a timely and ethically acceptable fashion, the EU should feel proud to have supported the EpiGenChlamydia consortium. We trust that public health genomics (PHG), as the internationally acknowledged umbrella for translating genome-based knowledge and technologies into public health research, health policies and health care on the regional, national, European and international level, will benefit from the goals reached by the ECC Consortium (15).

We cannot forget that to date, epidemiologic research and public health practice have been concerned with environmental determinants of health and disease and have paid scant attention to genomic variations within the population as well as between populations. The advances brought about by genomics are changing these perceptions. Many predict that this knowledge will not only enable clinical interventions but also health promotion messages and disease prevention programs to be specifically directed and targeted toward susceptible individuals as well as subgroups of the population, based on their genomic profile and risk stratification. The new technologies will allow researchers to rapidly and comprehensively investigate the whole human genome at the level of individual genes. Furthermore, there will also be a better understanding of the significance of environmental factors, such as chemical agents, nutrition or personal behavior, in relation to the causation not only of diseases like osteoporosis, cardiovascular diseases, cerebrovascular diseases, cancer and diabetes, which accounted for 86% of all deaths and 77% of the disease burden in Europe in 2005. On an international scale, diseases such as those related to *Chlamydia*, which is the most prevalent sexually transmitted infection and leads to tubal infertility as well as being the leading cause of blindness, are bound to benefit from these evidence-based findings are translated into health policies and practice in a timely and ethically acceptable fashion, the EU should feel proud to have supported the EpiGenChlamydia consortium. We trust that public health genomics (PHG), as the internationally acknowledged umbrella for translating genome-based knowledge and technologies into public health research, health policies and health care on the regional, national, European and international level, will benefit from the goals reached by the ECC Consortium (15).

In 2005 the U.S. Institute of Medicine (IOM) defined public health genomics as “an emerging field that assesses the impact of genes and their interaction with behavior, diet and the environment on the population’s health”. In the same year, the international expert group on PHG supported by the Rockefeller Foundation defined PHG as “the
responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health” (Bellagio Statement, 2005; see www.graphint.org for details; Fig. 2).

The task of public health genomics has become a challenge for all health-care systems and has major implications for future research and policy strategies (16). The various stakeholders in public health play a key role in translating the implications of genomics, such as those derived from molecular epidemiology and host–pathogen genomics. This knowledge will not only enable clinical interventions but also the targeting of health promotional messages and disease prevention programs toward susceptible individuals and subgroups of the population based on their genomic profile (personalized health care) (17). So far there has been no systematic integration of genome-based knowledge and technologies into public health research, policy and practice. Thus, the public health agenda demands a vision that reaches beyond the research horizon to achieve an application and a public health impact for these innovations.

The European Centre for Public Health Genomics (ECPHG) is the European center of excellence and a “think tank” in the field of public health genomics operating on national, European and international levels. The coordination of the Public Health Genomics European Network (PHGEN) is one of the current key activities of the ECPHG. PHGEN (www.phgen.eu) is funded by the General Directorate for Health and Consumer Protection (DG SANCO) under the Health Programme of the EU. PHGEN II produced the first edition of the European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies, which assists all member states, applicant countries and European Free Trade Association European–Economic Area countries, and will strongly contribute to the reduction of the disease burden in Europe. It involves key experts such as public health experts, EU lawyers, geneticists, clinicians, ethicists, systems biologists, health technology assessment (HTA) experts, patient groups and competent authorities. Expertise from networks such as the EpiGenChlamydia Consortium, EuroGentest, EUnetHTA and NuGO is provided to assess existing guidelines, identify gaps and set up a coherent, evidence-based framework for quality assurance, provision and use of genome-based information and technologies. PHGEN II is the follow-up to PHGEN I (DG SANCO 2006–2008). Whereas PHGEN I was a “mapping exercise”, PHGEN II systematically builds on
the work of PHGEN I. It uses the concept of “genome-based information and technologies” (Bellagio model) which PHGEN I established as a scientific benchmark in Europe. While protecting human rights, equity in health care and solidarity among citizens, it meets the Lisbon Agenda objectives and values of the Health Strategy. In the long run PHGEN will “serve the European Commission as an ‘early detection unit’ (European observatory on PHC) for horizon scanning, fact finding, and monitoring of the integration of genome-based knowledge and technologies into public health.”

The EpiGenChlamydia Consortium highly contributes to public health and has been chosen by the international network GRaPHint (Genome-based Research and Population Health; www.graphhint.org) as a best practice example for the development of innovative tools for diagnosis and treatment of Host Genetic Determinants of Infectious Diseases (HGDoD) for the benefit of population health.

In close collaboration with the Public Health Agency Canada (PHAC), the Centers for Disease Control and Prevention in the USA (CDC) and the European Centre for Disease Prevention and Control (ECDC), the EpiGenChlamydia Consortium has participated in the planning of a high-level meeting to be held at the end of 2010 in Maastricht, the Netherlands. The main aim of this meeting will be to increase political awareness about the relevance of this topic for public health.

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DISCLOSURE

The authors have nothing to disclose.

REFERENCES


