A breath of hope

Researchers are combining their efforts to study the genetic and environmental factors in asthma

Asthma can be a frightening disease. When their airways constrict, asthmatic individuals are left feeling short of breath, wheezing and coughing until they use bronchodilators—usually corticosteroids—to reduce these potentially life-threatening symptoms. The World Health Organization (WHO; Geneva, Switzerland) estimates that this allergic disease affects approximately 300 million people worldwide and killed 255,000 people in 2005 (WHO, 2006). Asthma is the most common chronic disease in childhood; the American Lung Association (New York, NY, USA) estimates that in the USA alone, asthma affects more than 6 million children and adolescents and is the third leading cause of hospitalization among children (ALA, 2006). The WHO foresees that "asthma deaths will increase by almost 20% in the next 10 years if urgent action is not taken" (WHO, 2006), such as strengthening healthcare, and reducing exposure to cigarette smoke and environmental air pollution, particularly for children.

On the scientific side, researchers are now teaming up in networks and focused projects to understand more clearly the heterogeneous phenotypes that underlie asthma. Although the disease is multifactorial and involves both genetic and environmental factors—making it expensive and more difficult to tackle—scientists hope to make significant steps in developing new diagnostic tests and therapies, and possibly in steering environmental and health policies, such as air quality measures.

Given the prevalence of asthma, and estimates that it might affect more than 400 million people by 2025 (Masoli *et al*, 2004), this research seems to be much needed. "Although citing the magnitude of [asthma] increase to be 100 million [individuals] over the next 25 years is maybe overstating a little, it is not outside the realm of possibility," said Kelan Tantisira, an associate physician from Brigham and Women's Hospital and Harvard Medical School (Cambridge, MA, USA). The incidence of asthma is greater still in developed countries, but rising levels of industrialization and traffic in many developing nations might increase their rates of the disease in the near future. Although large-scale studies, such as the Global Initiative for Asthma and the International Study of Asthma and Allergies in Childhood (ISAAC), have reported a decrease in disease incidence in some countries, such as the UK, Australia, Italy and Switzerland (Masoli *et al*, 2004; Asher *et al*, 2006), the "epidemic of allergy will persist in the population for the next 60 years," according to Peter Burney, Chair in Respiratory Epidemiology and Public Health at the National Heart & Lung Institute at Imperial College, London, UK, and a member of the ISAAC research team.

The enormous number of publications on asthma susceptibility genes, biomarkers and polymorphisms indicates that researchers already have a large amount of information about the genetics of asthma; however, as yet, they do not have a clear picture of how these factors interact in the pathology of the disease. According to William Cookson, Chair in Respiratory Genetics at the National Heart & Lung Institute, the number of genetic factors is still disputed and many remain undiscovered. He estimates that there are now approximately 20 candidate asthma susceptibility genes, but believes only four have been definitively identified through positional cloning.

Despite progress in identifying asthma susceptibility genes through positional cloning and family studies, "high-throughput genotyping studies taking environment into consideration are necessary and [are] transforming how asthma genetics are now being done," commented Stephen Holgate, a professor of medicine at the University of Southampton, UK. To this end, under its Sixth Framework Programme, the European Union is funding the Global Allergy and Asthma European Network (GA²LEN) and the multidisciplinary GABRIEL study to unify disparate research institutes and initiatives, create common standards in laboratory sample collection and processing, and discover the genetic and environmental causes of asthma.

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GA²LEN began in 2004 "to provide a platform for research, which adopts the same standards of excellence, and which aims to spread good practices and to foster collaboration within Europe and worldwide", according to their website (www.ga2len.net). Francine Kauffman, a leader in the GA²LEN network from the Department of Epidemiology and Biostatistics at INSERM (France), described the joint research activities as gathering epidemiological and environmental data across different age populations, studying genetics and genomics, and modelling airway sensitivity. In a manner typical of an EU research network, the project integrates resources such as databases, birth cohorts, biobanks, and common protocols and standards to understand the epidemiology, gene–environment interactions and disease mechanisms of asthma.

The GABRIEL project, which began in March 2006, is a multidisciplinary study led by Imperial College, London, UK, and Munich University, Germany. It combines research across various disciplines such as genetics, immunology and epidemiology to identify genetic and environmentally important factors of asthma, as well as potentially protective factors. A budget of €11 million is allowing researchers to genotype at least 200,000 patients to identify asthma-related gene markers. "Europe is a good place to study asthma genetics and the gene–environment component because different populations have different environments, and cohort studies with questionnaire information, such as ISAAC and ECRHS [European Community Respiratory Health Survey], already exist," explained Ericka von Mutius, a GABRIEL project co-leader from Munich University. Cookson acknowledges that the budget of the project puts it into the category of "big science", but that the decrease in the price of genotyping now makes the project feasible.

GABRIEL has begun genotyping 1,500 asthmatics and 1,500 control patients to investigate approximately 400,000 single nucleotide polymorphisms (SNPs). Once the number of biomarkers is reduced to approximately 1,500, the next step will be to embark on targeted genotyping studies of 40,000 to 50,000 Europeans. However, "even with the number of people we have, it is not enough [to study] everything," commented Cookson; therefore, collaborations with US researchers are expanding the population base. Kathleen Barnes from Johns Hopkins University (Baltimore, MD, USA) has contributed samples from 3,000 African-Americans, and Michael Bracken from the Yale University Center for Perinatal, Pediatric, and Environmental Epidemiology (New Haven, CT, USA) is conducting a survey of children of asthmatic mothers.

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On the side of environmental epidemiology, von Mutius is leading the effort to compare at least 160,000 samples from rural and urban communities in Europe, South America, Siberia and Asia to identify protective factors that could explain why asthma affects more children in cities than in the countryside. "Using the hygiene hypothesis," von Mutius said, "we are testing to see if microbes, such as bacteria or yeast, in rural farming areas serve to protect the populations from asthma." According to Cookson, this study is an interesting comparison of different environments: "Siberia is very cold and clean with various parasites in the water; in Ecuador there are worms and infections in native populations; and Hong Kong could be epidemic [with asthma] if the protective effect was not occurring as people move from the rural to urban environment."

Although the European research networks and projects join previously disparate institutes and organizations, US research efforts—from organizations such as the Environmental Protection Agency (EPA), the National Institute of Environmental Health Sciences (NIEHS) and the National Institutes of Health (NIH)—are relatively independent. More importantly, they do not have the same scale of emphasis on asthma as the European projects. In 1998, the NIEHS initiated the Environmental Genome Project (EGP), although it did not begin with a particular disease in mind: "with 600 genes and at least 30,000 SNPs, [it] is a great resource for gene–environment research," said Gwen Collman, coordinator of the EGP and Chief of NIEHS's Susceptibility and Population Health Branch. Four years later, the EPA published a seven-year asthma research strategy that includes research on susceptibility genes as a basis for risk-management strategies (EPA, 2002).

More recently, the NIH launched the Genes and Environment Initiative (GEI) and the Genetic Association Information Network (GAIN) to determine genetic and environmental causes of common diseases, such as asthma, mental health and diabetes. Although asthma genotyping was not part of the first projects supported as of October 2006, NIEHS Director David Schwartz noted that the funding—approximately US$90 million from both federal and industry sources, such as Pfizer (New York, NY, USA), Abbott (Abbott Park, IL, USA), Affymetrix (Santa Clara, CA, USA) and Perlegen Sciences (Mountain View, CA, USA)—offers new opportunities to drive asthma research forward.

The ultimate aim of these collaborations is the development of new treatments, diagnostics or monitoring devices. In the past 40 years, various asthma drugs have become available that are quite effective for treating intermittent to moderately persistent forms of the disease; however, more are needed. "We are still unable to fully reverse the clinical symptoms and signs of refractory or severe asthma, [which is] a distinct subset of asthma," commented Zuzana Diamant, Director of Respiratory Research at the Centre for Human Drug

Research in Leiden, the Netherlands. "Severe asthmatics represent about 5% of all people affected with asthma … and we don't know if more severe or less severe [asthma] is [the result of] a different mechanism," von Mutius said.

Given the potential market for asthma drugs—hundreds of millions of patients—it comes as no surprise that pharmaceutical and biotech companies are not only interested in the results from these US and EU projects, but also actively engaged in the research. Patrice Milos, the Director of Molecular Profiling at Pfizer and a collaborator in GAIN, explained that, "[Asthma] research is exciting because there is a big unmet medical need in the trial and error process of seeing how patients respond to therapies, [such as] different types of bronchodilators, and thus helping better diagnose the patient." She added that "[a]lthough Pfizer is not in the respiratory disease market now, it is part of our discovery programme."

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Indeed, some of the most promising research comes from pharmaceutical companies working independently from these large EU or US research programmes. Cephalon (Frazer, PA, USA) and deCODE (Reykjavik, Iceland) saw positive results from their phase IIa trial of CEP-1347, a non-corticoidal, anti-inflammatory bronchodilator that could circumvent the side effects of corticosteroid drugs. The work was based on deCODE's observation that variants of the MAP3K9 kinase gene are risk factors for asthma; CEP-1347 targets the pathway in which MAP3K9 acts.

Smaller companies are also making progress, thanks to larger collaborative networks. As part of the GABRIEL consortium, Surface Therapeutics (Abingdon, UK) is developing biopharmaceuticals against inflammatory respiratory diseases using targets discovered by GABRIEL. GeneOS (Helsinki, Finland) has begun developing a diagnostic assay based on the G-protein-related receptor for asthma susceptibility (*GPRA*) gene and cohorts of patients. GeneOS will also investigate new markers when they are discovered by GABRIEL, according to Tarja Laitinen, the company's Chief Scientific Officer. And EMC Microcollections (Munich, Germany), which focuses on combinatorial chemistry, is working to develop agonists of the Toll-like receptor 2 (*TLR2*) gene, which has been implicated in the protective effects against asthma observed in Austrian and German farming communities.

Another possible application of asthma research is the development of devices to monitor the environment of a susceptible individual in order to warn of risk factors that might trigger an asthma attack. As part of GEI, a call for research proposals for such personal environmental sensors was issued in September 2006. Possible exposure biomarkers could include proteins and DNA from relevant physiological pathways, such as inflammation. As David Shaughnessy, programme administrator for the NIEHS Susceptibility and Population Health Branch, explained, "It might be possible to create a biomarker signature for an endotoxin or air pollutant using transcriptional RNA gene expression arrays."

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However, despite these efforts to unravel the genetic and environmental details behind asthma, a promising outcome is by no means definite. According to Cookson, asthma is "in the same boat as multiple sclerosis, diabetes or schizophrenia in terms of […] trying to understand [multifactorial] genetics." However, he noted, "asthma [research] has a made a lot of progress in the last few years and the genetic effect in asthma is stronger than in autoimmune diseases, such as multiple sclerosis or inflammatory bowel disease." Cookson emphasized, "We want answers in four years and will have some answers in four years" about genotypes, phenotypes and gene–environment data, although "new methods for treatment will take more time, perhaps ten years." According to Tantisira, for example, asthma pharmacogenetics research is still in its infancy.

In contrast to the slow pace of developing new therapies and diagnostics, preventive measures in environmental and public health policy can be implemented much faster. Schwartz pointed to carbon monoxide recommendations (EPA, 2000) made under the US Clean Air Act as a precedent for using genetics in environmental policy: these were based on the greater sensitivity of people with sickle-cell disease, which has a higher incidence in African-Americans. According to Alison Cullen from the School of Public Health at the University of Washington (Seattle, WA, USA), "[asthma genetics research] is a good opportunity to apply genomics to environmental policy because the Clean Air Act mandates that subpopulations of people must be protected regardless of cost." But, she also cautioned against jumping to conclusions. "There is now new information about asthma genetics coming out every week and it will take a while to understand."

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