Largest genetic study of asthma points towards better treatments

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An international study looking at DNA from over 26,000 people has identified several genetic variants that substantially increase susceptibility to asthma in the population. The findings, published in the *New England Journal of Medicine*, will help scientists to focus their efforts to develop better therapies for the illness.

The study, which was co-ordinated by researchers from Imperial College London, was performed by the GABRIEL consortium, a collaboration of 164 scientists from 19 countries in Europe, along with other groups in the UK, Canada and Australia. It analysed DNA samples from 10,000 children and adults with asthma and 16,000 non-asthmatics.

The researchers performed more than half a million genetic tests on each subject, covering all the genes in the human genome. The study pinpointed seven locations on the genome where differences in the genetic code were associated with asthma.

One in seven children in the UK suffers from asthma. When the airway is irritated in a person with asthma, the airway narrows and the lining becomes inflamed, causing difficulty breathing. The causes of the disease are poorly understood, but genetic and environmental factors are thought to play roughly equal roles.

Today's research has a number of potential implications, according to the study team. It suggests that allergies are probably a consequence of asthma, rather than a cause of the disease. It also suggests that genetic

testing would not help predict who is likely to develop the disease.

The new variants linked to asthma were found in more than a third of children with asthma in the study. The gene with the strongest effect on children did not affect adults, and adult-onset asthma was more weakly linked to other genetic differences, suggesting that it may differ biologically from childhood-onset asthma.

Childhood asthma, which affects boys more than girls and can persist throughout life, is often linked to allergies, and it has been assumed that these can trigger the condition. However, the study found that genes controlling the levels of antibodies that cause allergies had little effect on the presence of asthma, suggesting that allergies are more likely to be a consequence of asthma than a cause.

Professor Miriam Moffatt, Professor of Human Genetics at Imperial College London and one of the study's leaders, said: "As a result of genetic studies we now know that allergies may develop as a result of defects of the lining of the airways in asthma. This does not mean that allergies are not important, but it does mean that concentrating therapies only on allergy will not effectively treat the whole disease."

Some of the genes identified are involved in signalling pathways that tell the immune system when the lining of the airways has been damaged. Other genes appear to control how quickly the airways heal after they have been injured. Identifying these genes should help direct research into new treatments for asthma, the researchers suggest.

"Asthma is a complex disease in which many different parts of the immune system can become activated," said Professor William Cookson, Director of Respiratory Sciences at Imperial College London, who co-ordinated the study. "One of the problems with asthma research has been choosing where to intervene in the disease pathways. Our study now

highlights targets for effective asthma therapies, and suggests that therapies against these targets will be of use to large numbers of asthmatics in the population. "

Professor David Strachan, Professor of Epidemiology at St Georges, University of London, who also co-authored the study, said: "Asthma has often been considered a single disease, but our genetic findings suggest that childhood-onset asthma may differ biologically from asthma that is acquired in adult life. The GABRIEL consortium is now investigating whether the causes of asthma differ between people with and without these newly discovered genetic variants."

The study also found that the genes associated with asthma did not have strong enough effects to be useful for predicting early in life which children might eventually develop the disease. This indicates that environmental factors are also very important in causing asthma to develop. The GABRIEL consortium is working to identify environmental exposures that could protect against the illness.

The study was primarily funded by the European Commission, the French Ministry for Higher Education and Research, the charity Asthma UK and the Wellcome Trust.

Although large multi-national collaborations are becoming the norm with the study of many complex genetic diseases, the GABRIEL study is unique in that nearly all of the 15 billion genetic tests were performed in a single institution, the Centre National de Genotypage near Paris.

Professor Mark Lathrop, the Director of the CEA-CNG and the Scientific Director of the Fondation Jean Dausset-Centre d'Etude du Polymorphisme Humain (CEPH), pointed out the crucial role of an integrated large-scale infrastructure like CEA-CNG which has the capacity to perform all the steps from receiving the biological samples,

to high throughput genotyping, quality control and data analysis. The Fondation Jean Dausset - CEPH was also a major player in this study.

Professor Miriam Moffatt said: "It has been enormously gratifying to work with such a group of dedicated scientists from so many countries. This genetic study has taken five years from planning until completion, but it builds on many earlier years of work in which all the 26,000 volunteers were recruited and studied in great detail. The study would not have been possible without the contribution of all of the GABRIEL members."

Professor Ivo Gut, former Deputy Director of the CEA-CNG and now Director of the Centro Nacional de Análisis Genómico in Barcelona, said: "These results constitute a huge leap forward in the understanding of asthma that will lead to major advances in the treatment and quality of life of people suffering from the disease. It has been an immense effort to get this far but is well worth it. The generous support from the funding agencies, the kind donation of DNA by the research subjects and the huge personal dedication of the collaborators of the Gabriel consortium, have made this study possible."

Professor Florence Demenais, Director of the Genetic Variation and Human Diseases laboratory in Paris (UMR-946 Inserm-Université Paris Diderot, Fondation Jean Dausset), who led the statistical analysis that combined all of the data, said: "Large scale genetic studies, such as this one, provide a powerful tool to decipher the genetic mechanisms underlying asthma and to unravel different types of disease that make up the asthma syndrome."

Professor Erika von Mutius at the University of Munich and co-coordinator of GABRIEL said: "The puzzle now is to work out what is causing the damage to the airway lining in asthma. The GABRIEL study has also been busy looking for clues as to the environmental causes of

asthma, particularly by dissecting the strong protective effects of living on a farm. In the next year we will be combining the results from the genetic and environmental wings of the GABRIEL study, and we are greatly looking forward to what we may find."

More information: M.F. Moffatt et al. "A large-scale, consortium-based genome-wide association study of asthma" *New England Journal of Medicine*, 2010.

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