Scientific Note

Studying the Genetic Pathogenesis of Atopy and Asthma: Future Directions for Research

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Introduction

Atopy as a group of diseases is increasing in its prevalence worldwide, which is drawing much interest into its pathogenesis. However, it is frustrating that its pathogenesis is not simple or clear, like many other complex diseases like diabetes mellitus or ischemic heart disease. One thing that is simple and clear is that both genetic or inherited traits and environmental exposures play important roles in the phenotypes that we see. What factors of each type, how many are needed and how they interact are the complex questions that will be answered by reviewing the literature in this article.

Most diseases do not follow a simple Mendelian genetic of autosomal, X linked dominant or recessive design (although there is the question of penetrance in the phenotype for the same genotype). So to solve this type of problem one has to have a good understanding of the models and tools used in the studies and the strengths and weaknesses of each study design. This understanding is vital to simplify the complexities that we see in the medical literature nowadays in the immunology and genetics fields.

For example, to understand from where the name 'major histocompatibility complex' genes came from one needs to understand a few deeper points. For the experimental design in inbred strains of mice skin transplantation (which are all identical twins for other mice of the same strain and are homozygous for all genetic loci), it was estimated that there are 50 genes responsible for the graft rejection phenomena. So when the HLA antigens locus was found with its 18 slots for alleles, the name 'major histocompatibility complex' became simple and understood although no minor ones were found later.

This review article walks through the models of experiments that tried to explain genetic pathogenesis of asthma and atopy and the technological tools and statistical models used in them. Some recent studies have been listed using each model.

(J Med J 2011; Vol. 45 (4):355-358)

Received	***Accepted***
May 13, 2009	*September 19, 2011*

1. Segregation Studies

This type of study is a population-based case or proband versus control type of study. One study of this type is the Tasmanian Asthma Survey. [1] Jenkins in 1997 found that asthma is three times more common when a member of the family is affected which is a strong indicator of some genetic basis. On the other hand, using different statistical models for genetic inheritance models, the study concluded that it was unlikely that a single gene is responsible for that and these genes are co-dominantly inherited.

This type of study is large scale and can easily point to a genetic or familial factor, but it requires more resources to be completed. It also fails to propose the genetic basis or specific genes and it is difficult to isolate the environmental factors which can be shared by the same family living together.

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2. Candidate Gene Approach

This type of study depends on suspecting a gene involved in the pathogenesis steps (e.g. IgE or IL-4 cytokine genes or receptors genes). The researcher compares asthmatics versus normal individuals regarding functional polymorphism of that gene. It has the advantage of trying to explain the molecular pathogenesis steps involved in atopy. So far 10 genes have been replicated in more than 10 studies, and another 15 genes have been replicated in 6 to 10 studies. Examples include cytokine genes (IL-13, IL-4, IL-10, and TNFA), cytokine receptor genes (IL-4), HLA genes and the CD14 gene. [2]

This type of research design is more feasible regarding the numbers required in each group and the cost of laboratory work. The cause why some genes fail to be implicated might be due to population differences in the type of polymorphism in them as most mutations might be silent and not functional.

3. Genome Wide Linkage Screens and Associations

Here recent molecular biology advances are used, such as positional cloning by restriction enzymes and markers of the whole genome. Comparing asthmatics versus controls within the same family, linkage between gene segments and the disease can be discovered covering the whole human genome but failing to identify a specific gene using this technique, necessitating further study for the involved gene in the pathogenesis at a later step. So far more than 18 genome wide screens using a variety of intermediate phenotypes have been published. Some segments of the genome were previously suspected such as the study by Moffatt that found the linkage to chromosome 11q was the β chain of the high affinity IgE receptor. [3, 4] Other times, the found segment was not suspected before, such as the study by Raby which concluded that the strongest associations to asthma was with the polymorphism vitamin D receptor gene in females. [5] This study initiated the study of the possible roles of vitamin D intake, supplementation in the diet and sun exposure in the pathogenesis of asthma and so far no conclusive results have been reached yet.

This type of study needs large numbers of samples and can be the initial step in a more needed study looking for the gene involved.

4. Pharmacogenetics

This type of study looks into the differences among individuals regarding responses to treatments by the types of their genetic makeup. One study was published by Malmstrom [6] who looked for variations in responses of asthmatics to oral montelukast and inhaled beclomethasone due to polymorphisms in the genes for leukotriene synthesis and corticosteroids receptors. Although this line of study looks promising, not many studies have been done because of lack of funding. Drug producing companies do not want to report that a large group of people might not respond to their drugs, and because these drug responses are not life threatening, the National Institute of Health in the USA has not given this type of research a big priority or funding.[2] There are fears for unethical practices or discrimination after the discovery of certain genetic factors, and this type of study requires a moderate number of subjects and advanced genetic laboratory testing to be done.

5. Gene-Environment Interaction

To explain the basis of variations between studies in different populations regarding the effects of certain genetic factors, the environmental exposure has to be studied in relation to the genetic factor as they can have a dramatic confounding factor. For example, to explain the differences between urban and rural rates of allergy, one might look into tobacco smoke or house dust mite antigens which are more in urban environments versus endotoxin from bacteria which is more in certain rural environments. Fageras et al looked into the effects of toll-like receptor 4 (TLR-4) polymorphism and endotoxin exposure in asthmatics. [7] The group found that the polymorphism of the TLR-4 had decreased the interleukin-12 response to lipopolysaccharide and was associated with asthma in a Swedish

population.

This type of study requires a large number of subjects and observations in the study and assumes that the environmental factors stay the same for a prolonged period of time.

6. Gene-Gene Interactions

With improved and cheaper techniques to study genes, more studies are done now to study the effects of gene-gene interactions. Larger numbers of cases and increasing numbers of genes studied at the same time have made it possible to do a statistical model to study these interactions among genes. Howard studied the combined effects of polymorphism of both the interleukin-4 receptor α gene and interleukin-13 which both are already known to be associated with asthma.[8] The study found that each allele alone conferred almost a double increase in the risk of asthma, when both are inherited the risk jumps to five times which was statistically significant.

7. Epigenetics

Epigenetics is the study of inherited expression patterns of genes independent of the DNA changes. They are mediated by enzymatic modifications (such as acetylation, phosphorylation or methylation) of the DNA and histone proteins affecting gene expression. [9] The enzymatic changes affecting the histones structure can become fixed and certain gene expressions that are involved with certain phenotypes such as T h2 type of lymphocytes and then can be maintained in daughter cells and subsequent generations. This is the explanation proposed by Li et al, for their observation that not only maternal smoking patterns are associated with early childhood asthma (odds ratio of 1.5 times) in their offspring[10], but also grand maternal smoking is associated with asthma even more (odds ratio of 2.1 times).

This study design is the most recent and might be most suited to explain the phenomena of complex but common genetic diseases and hopefully newer treatment strategies can be found.

Conclusions

Allergy is another disease with increasing prevalence all over the world and its cost is increasing. Huge efforts are exerted to explain its complex pathogenesis and new models are proposed with more sophisticated techniques for laboratory tests and more powerful statistical models are becoming available. This research should force us to study our population characteristics and the specific genes involved in our parts of the world and hope for different or newer interventions to decrease its rate. This hope covers the studying of effects of proposed changes in the environment such as the effort to decrease olive pollen exposure by removing the trees from the sidewalks of the streets and newer treatments.

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دراسة العوامل الوراثية للاستشراء والربو: التوجهات المستقبلية للبحث

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الملخص

الاستشراء هو مجموعة من الأمراض التي يزداد انتشارها في جميع أنحاء العالم، والذي يستحوذ على اهتمام كبير لمعرفة مسبباته. ومع ذلك، فالعوامل المرضية ليست بسيطة أو واضحة، مثل العديد من الأمراض المعقدة الأخرى كمرض السكري أو نقص تروية القلب. الشيء الوحيد الواضح والبسيط هو أن كلا من الصفات الجينية الموروثة أو التعرض للعوامل البيئية تلعب أدواراً مهمة في الظواهر التي نراها. ما هي العوامل لكل نوع، وكم هي الاحتياجات، وكيف تتفاعل؟ هي الأسئلة المعقدة التي سيتم الرد من خلال مراجعة الأدبيات في هذا المقال.

لا تتبع معظم الأمراض المندلية الوراثية، الجين X ذا التصميم المسيطر أو المتنحي (على الرغم من أن هناك مسألة انتفاذ في النمط الظاهري، النمط الجيني نفسه). بغية حل مشكلة من هذا النوع على المرء أن يكون لديه فهم جيد للنماذج والأدوات المستخدمة في الدراسات ونقاط القوة والضعف في كل تصاميم الدراسة. هذا الفهم هو أمر حيوي لتبسيط التعقيدات التي نراها في الأدبيات الطبية في الوقت الحاضر في مجالات علم المناعة وعلم الوراثة.

على سبيل المثال، من أين جاء اسم " التوافق النسيجي الرئيسي المعقد " للجينات؟ جاء من اسم واحد يحتاج إلى فهم نقاط قليلة أعمق. لتصميم تجريبي لزرع الجلد في السلالات الفطرية من الفئران (والتي هي متماثلة لجميع التوائم الفئران الأخرى من نفس السلالة ومتماثلة لجميع المواضع الوراثية)، وقدرت أن هناك 50 جيناً من الجينات المسؤولة عن ظاهرة رفض الكسب غير المشروع. وعندما تم العثور على مكان مستضدات HLA مع فتحات 18 من أجل الأليلات وأصبح بذلك "التوافق النسيجي الرئيسي المعقد" بسيطاً ومفهوماً على الرغم من عدم العثور على تلك التعديلات في وقت لاحق.

هذا المقال استعراض يمشي من خلال نماذج من التجارب التي حاولت تفسير المرضية الوراثية للربو والأدوات التكنولوجية والنماذج الإحصائية المستخدمة فيها، وقد أدرجت بعض الدراسات التي أجريت مؤخرا باستخدام كل نموذج.