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Genes in their environment: how can we read the riddles?

Andrew Bush*

Once upon a time, as all the best children’s stories begin, a lot of clever geneticists began a huge hunt for the “asthma gene.” At first they thought they had found it, but then more and more of the hunters found different “asthma genes,” and sometimes some gene hunters could not find the gene that previous hunters thought was the key one. Life became more and more confusing, and the root causes, which should have been thought of right from the start, have only recently begun to be identified. These include that there are many types of asthma, not likely all to have the same background, and thus careful clinical phenotyping is essential; that genes do not operate in isolation, but in their environment (which includes other genes around them), and this may modify their effects, and even completely reverse them. Also, statistical dangers lie in wait for those who merely collect DNA, feed it all into a good computer and turn the handle; and detailed attention to methodology is needed. The purpose of this editorial is to place the nice study of de Faria et al.1 into the context of current issues for genetic association studies.

A recent review2 identified more than 30 genes which have been shown to be associated with some aspect of asthma, and the association has been replicated in at least five studies. In broad terms, these fall into one of four groups: genes relating to innate immunity and immunoregulation; genes associated with TH2 cell differentiation and effector functions; genes associated with epithelial biology and mucosal immunity; and genes associated with lung function, airway remodeling and disease severity. These classes of genes find echoes in our knowledge of the basic immunobiology of asthma. However, the bag is by no means empty; there are now three members of a class of unknown function, encoding transmembrane proteins located in the endoplasmic reticulum, which are implicated in asthma, the latest being ORMDL3.3

A number of important methodological issues were discussed which shed light on why so many studies have been conflicting. Linkage studies may implicate a particular locus, for example 5q31-33, but the locus may contain potentially a large number of relevant genes,4 and premature conclusions that a particular gene, and not one of its near neighbors, is important must be avoided. It is important to check the validity of the methods used for genotyping, preferably with validation by a second method; and also to check the association in at least one other population.5,6 However, it should be noted that if the results do not appear to be important in a second population, this does not mean that the first study is invalid; it should instead provoke a careful look for differences between the studies, which may give important insights into novel gene-environment interactions.

Genes are relatively easy to study, but they exist not in a vacuum but in a complex environment, which the investigator ignores at his peril. Studies in mice have shown that gene-environment interactions may explain more phenotypic variance than either genetic or environmental effects considered separately.7 There are many facets to these interactions. Unsurprisingly, the effect of environmental smoke

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exposure is greater in children with null polymorphisms in glu- 
thathione S transferases, which are important antioxidant 
defense genes. A large number of relatively simple interac-
tions like this have been described. However, the phenom-
enon of phenotypic plasticity complicates the picture, whereby 
the effects of a gene may be opposite in different environ-
ments. CD14 is a molecule intimately bound up with the 
response to lipopolysaccharide, and is thus an obvious can-
didate as an “asthma gene.” However, a meta-analysis 
reported that the CD14 C-159T polymorphism was not asso-
ciated with asthma or asthma severity. When the relation-
ships were studied in more detail, with focused hypotheses, 
the CD 14/-260 C/T polymorphism in the CD 14 promoter was 
associated with higher levels of both total and specific IgE to 
aeroallergens in children in regular contact with domestic 
pets, but the opposite relationship, not explained by endoto-
oxin levels, in children in contact with stable animals. 
Finally, the effects of poverty must not be forgotten; in cys-
tic fibrosis, the most powerful modifying influence on mortality was 
not genetic, but the wealth of the family. It is better to be 
rich and ill than poor and ill in many contexts.

There are important interactions within the cell nucleus 
as well. Polymorphisms in transcription factors may affect 
gene expression, in an organ specific manner; Polymor-
phisms in a sequence of genes, each independently of little 
functional consequence, may synergize to magnify the effect 
on the risk of a particular phenotype.

Another prerequisite for genetic studies is careful pheno-
typing of the subjects, and careful selection of controls. 
Although doctor-diagnosed asthma, bronchial responsive-
ness and atopy overlap, they are not the same thing, and have 
different genetic associations. Asthma is a term that has in 
the past served a useful purpose in ensuring that children 
 wheezing with viral colds were not given antibiotics. How-
ever, it may have outlived its usefulness therapeutically, 
because it may lead to the uncritical and unnecessary pre-
scription of inhaled corticosteroids; and the term “asthma” 
certainly has in the context of genetic studies, unless it leads 
inexorably to the question “what sort of asthma.” Preschool 
 wheezing phenotypes offer a good example, and even here 
there is a need for more clarity. Preschool wheeze has been 
described as transient (present age 0-3 years, not age 3-6 
years), persistent (present throughout the first 6 years of life) 
and late-onset (not present age 0-3 years, present age 3-6 
years). These phenotypes are only of any use retrospec-
tively, since at age 2, although various indices have been found 
to predict remission of symptoms, none is much use pre-
dicting persistence. They are also an oversimplification albeit 
one that has clarified our thinking. Recently, more sophisti-
cated mathematical analysis suggests that a more detailed 
breakdown of wheeze patterns is required.

These epidemiological phenotypes are sometimes uncriti-
cally confused with clinical ones; the patterns of intermittent 
(viral) wheeze and multi-trigger wheeze can be distinguished 
with a good clinical history, and are sometimes thought to be 
the same as transient and persistent wheeze respectively, but 
this has never been shown. It would be naive to believe that 
the nonatopic child who wheezes albeit severely three times 
a year with viral infection has the same underlying genetic 
makeup as a child with eczema, who wheezes every day.

Even in the school years, there are important interna-
tional differences. In the western world, atopic asthma is the 
commonest phenotype, and, although nonatopic asthma 
exists in the school-age child, it is sufficiently unusual to 
prompt a careful review of the diagnosis. However, a recent 
paper from Porto Alegre has shown clearly that this pheno-
type is much commoner (around 50%), and associated with 
early severe bronchiolitis. This valuable paper underscores 
the need to be critical about differences between populations 
apparently suffering from the same disease but in different 
countries.

There are further complicating factors. Genes may be 
operative only in a specific time window. Epidemiological 
and pathological data have suggested that the first three years of life are crucial in determining long-term lung function, and that developmental processes may interact with genes at only specific time points. The inflammatory cellular phenotype of asthma may change 
over time. The role of epigenetic modifications in the expres-
sion of crucial genes is little explored and may well be impor-
tant. The complexities of how genes and the environment 
(inter both) interact to produce the multifaceted asthma phenotypes are far from being understood.

Where do the findings of de Faria et al. fit into this com-
plex picture? They have nicely generated the hypothesis that 
TGF-β1, CD14 and IL-4R, but not ADAM33 polymorphisms 
are implicated in asthma in Brazil. The literature is controver-
sial about the effects of ADAM33, with some reporting impor-
tant effects and others finding none. These discrepancies, which the present study cannot resolve, are 
strange; it may reflect the statistical power of the different 
studies, but it could also reflect population differences and the resolution of the discrepancies may lead to new discoveries. These studies now need taking forward in larger cohorts, to find more genes which apparently have different effects in Brazil than in the western world. Confirmatory studies are 
important, but the study that produces the unexpected, and 
is robust, is much more interesting. A prerequisite for suc-
cess will be the generation of focused hypotheses, and rigor-
ous methodology. This has to include the use of both a 
discovery and a second replication population. The rewards 
are potentially very great, because such differences can high-
light novel mechanisms; remember that the observation of the protective effect against asthma of being born on a dairy 
farm, completely counter-intuitive to the received wisdom of
the time, leads to a whole stream of novel mechanistic papers. We will be watching this space!

References


Systemic infection and brain injury in the preterm infant

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In this issue of Jornal de Pediatria, Silveira et al. investigated risk factors for the development of periventricular leukomalacia (PVL) in a cohort of very low birth weight (VLBW) infants. A significantly greater number of infants with PVL had documented sepsis and/or were ventilated for more than 24 hours. This well-designed study adds supportive evidence for the role of postnatal infection in the pathogenesis of PVL. While the data are provocative, it is unclear from this article how the timing of the sepsis episodes is related to the development of PVL. If the study infants all had early-onset sepsis, it is somewhat surprising that coagulase negative staphylococcus was the most common pathogen recovered. In the USA that microorganism would be a rare cause of early-onset sepsis. If the study infants had late-onset infections, the question of timing of the infectious episode with the onset of PVL is particularly important. A major limitation in this study is the lack of data on the likelihood of antenatal infection. That question is particularly important given the high rate of bacteremia with *Mycoplasma* and *Ureaplasma* in infants born prematurely. A third weakness in this study (as noted by the authors) is the lack of magnetic resonance imaging (MRI) information; MRI is a more sensitive way to diagnose PVL. Given these limitations, however, the authors should be congratulated for addressing this question.

PVL is strongly associated with the development of cerebral palsy. The pathogenesis of PVL has been linked with disorders resulting in hypoperfusion of the brain (e.g., hypoxia-ischemia, hypotension patent ductus arteriosus with reversed diastolic flow, etc.) and perinatal (antenatal and postnatal) infection. The final common pathway for both etiologies is likely to include microglial activation, cytokine and glutamate release and free radical production (Figure 1).

Late-onset infections are common among VLBW infants and up to 25% develop a systemic bacterial or fungal infection; 5-10% have documented meningitis. Neurological abnormalities are common among survivors. In a recent prospective observational study by Stoll et al. (n = 6,093) preterm infants with proven systemic infections, clinical infection (negative blood culture), necrotizing enterocolitis (NEC) and meningitis were all more likely to exhibit neurological and growth abnormalities compared with an uninfected control group. Hearing impairment was more common in infants with NEC and in those infected with gram-negative microorganisms. In a case-control study, O’shea et al. also noted an association between clinical chorioamnionitis, sepsis and cerebral palsy.

Over the past 10 years, there has been considerable interest in the relationship of antenatal infection and cerebral palsy.

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