THE CLINICAL GENETICS OF COMMON DISEASE

Date: September 20, 2005 *
Time: 9:00 am- 9:50 am *
Room: G-202 Biomolecular Building
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Office Hours: by appointment

*Please consult the online schedule for this course for the definitive date and time for this lecture.

The syllabus is meant to accompany the lectures and the material covered (other than that in italics) is considered important to your understanding of the subject.

Lecture Objective
The polygenic aspect of common disease will be discussed and will be contrasted with traditional monogeneic inheritance. Gene environment interactions will be explored as will strategies which have begun to successfully tease out the genetic contribution to common diseases. Diabetes, Alzheimer Disease and AIDS will be featured as clinical examples that serve to illustrate underlying principles about our growing knowledge in this area.
THE GENETICS OF COMMON DISEASE

As discussed at the start of this course we increasingly possess the ability to elucidate the genetic component of common diseases. Virtually every disease examined to date shows a genetic component. The degree of genetic foundation among different disease varies. For example, Type II Diabetes has an extraordinarily high genetic component, breast cancer has a substantial genetic component, but uterine cancer shows little genetic influence in most situations.

Disorders that are transmitted in traditional Mendelian patterns typically result from mutations that have rather high penetrance but rather low frequency in the population (i.e. they are relatively rare). This is in contrast to the genetics of common disease in which we are typically dealing with genes of low penetrance but rather high frequency.

Mendelian vs. Common Disease

| Single Genes vs. Polygenic Inheritance | High Penetrance vs. Low Penetrance |
| Low Frequency Alleles vs. High Frequency Alleles | Limited Environmental Influence vs. Large Environmental Influence |
| Tidy Pedigrees vs. Untidy Pedigrees | Easily Discernible Genetic Role vs. Difficult to Discern Genetic Role |
| Gene Isolation Tractable vs. Difficult to Isolate Genes | Limited Public Health Impact vs. Tremendous Impact |

Figure 13

As can be seen in Figure 13 above, the relatively unusual diseases that follow Mendelian patterns of inheritance are monogenic, with high penetrance and a low population frequency. Many of these characteristics are opposite to those that are seen in common diseases.

The genetics of common disease is beginning to have tremendous impact on our understanding and clinical approach to the disorders which we see every day in the clinic and in the hospital.
A hallmark of the genetics of common disease is that the genetic alterations that pre-dispose to these diseases have significant interactions with the environment. In traditional Mendelian disorder such as Huntington Disease, the environment is relative unimportant in dictating individual’s ultimate destiny. However, gene-environment interactions are critical in common diseases.

At the molecular level, the critical genetic lesions that influence common disease are often not of the type that renders a protein completely inactive as in the more familiar Mendelian disorders. Rather, what appears to be important in dictating an individual’s predilection for many common diseases are polymorphisms that subtly alter the function of a particular gene product making it, for example, more or less efficient or altering its ability to interact with an environmental agent.

Methods of Approaching the Genetics of Common Disease

1. **Twin studies** are an important source of information regarding the genetic foundation of common diseases. Monozygotic (MZ) twins typically share both environment and 100% of their genes, while dizygotic (DZ) twins, like any brothers or sisters, share only 50% of their genes. Thus an excess concordance for a trait or disease in MZ twins is strong evidence of genetic influence.

   Twin studies have led to reproducible estimates of the heritability of a number of traits and diseases. Type II diabetes has an extremely high heritability as do schizophrenia and obesity. Atherosclerosis demonstrates less heritability while Type I diabetes has a modest genetic component of about 25%.

   While twin studies are extremely powerful in detecting a genetic component to disease susceptibility, they offer no clue to the precise genetic mechanism underlying the observed predisposition.

2. **Observational studies** of familial clustering can be important in determining the role of genetics in a disease, but it must be remembered that such familial clustering can be confounded by common environmental exposures among family members and again offers no insight into the precise nature of a genetic component.

3. **Animal studies** have been critical in dissecting the role of genetics in common disease but there is no guarantee that
the same genes found to be responsible for genetic variance in an animal model will also be responsible for genetic variance in humans. Still, immensely useful information can be obtained through animal studies in elucidating the relevant biochemical pathways, and thus the various genes likely to be involved in disease.

4. **Hypothesis generated** approaches to discovering the genetic foundation of disease have been very fruitful. That is, if biochemical information or other clues are present that hint at what genes might be important in a particular disease, then genetic investigation can focus on those genes. For example, we know that the renin-angiotensin system is critical in the regulation of blood pressure. Therefore it is not unreasonable to postulate that perhaps polymorphisms in the genes encoding proteins within this autoregulatory system might be important in determining a predisposition to hypertension. Such approaches based on biochemical knowledge had been very fruitful, but of course demand some level of detailed knowledge about the biochemistry of disease pathogenesis, a body of knowledge which is difficult to come by.

5. **Sib-Pair analysis** represents a genetic technique that requires no assumptions about mode of inheritance or knowledge of a disease’s underlying biochemistry. It has given us important clues to the genetic basis and mechanism of a variety of diseases.

This approach is based on the statistically valid assumption that siblings, on average, share 50% or their alleles. If a polymorphic marker in the genome is near a disease-susceptibility locus, then affected siblings with the given disorder will, more often than not, share the same allele of that polymorphic marker. Given the current saturation of the human genome with highly informative polymorphic markers, such studies are quite feasible. These studies require a large number of well characterized siblings with the disease in question. They have been useful in beginning to understand the genetic basis of such common diseases as Alzheimer disease, Type I diabetes and Multiple Sclerosis.
6. **Quantitative Trait Loci Analysis (QTL)** is a method that synthesizes Sib-Pair analysis with the fact that many diseases are quantitative in nature. For example, hypertension is a quantitative trait, varying continuously in the population. By picking the extremes of affected individuals for a given quantitative trait (e.g. the top 5% of people with hypertension) it is possible to decrease genetic heterogeneity and increase the power of such genetic analyses.

The inherent weakness of these latter two genetic strategies is the immense size of the human genome. Because of this there is always the considerable chance that a purported “linkage” between a specific marker and susceptibility to a disease is spurious. This problem is compounded by the fact that the role of any one individual gene in the genesis of disease susceptibility for a common disorder is likely to be small. Thus, such problems become epidemiologically formable.

Finally, even when a *region* of the genome is found, in a reproducible manner, to be involved in susceptibility to a given diseases, isolating the particular gene within such a region can be difficult. Many regions defined by such techniques span hundreds of kilobases of DNA and encompass dozens of genes. Detecting which gene among all of the candidates is responsible for a small portion of one’s susceptibility to a common disease is a formidable task. It is thus, critical that rigorous replication of such studies be carried out before the results are relied upon.

Can you think of a reason (or reasons) why a study done in Finland might indicate that gene “A” plays a role in susceptibility to a certain common disease, but when the same study is carried out in the US, no association is seen?

**The Genetics of Alzheimer Disease**

Alzheimer Disease is a slowly progressive adult-onset dementia. It results in deterioration of memory and judgment as well as personality changes such as agitation, paranoia and withdrawal. Death typically occurs eight to ten years after diagnosis. The available treatments are grossly inadequate for this devastating and common disease.
Alzheimer Disease is the most common cause of dementia in North America and Europe. By age 70, approximately 10% of all persons have significant memory loss with a substantial percentage of these having Alzheimer Disease. By the age of 90, over 50% of males and 60% of females have Alzheimer-type dementia. Due to our increasing longevity, Alzheimer Disease represents a tremendous medical, economic and social problem in the developed world.

Approximately 25% of Alzheimer Disease is seen in the context of a positive family history. A number of genes have been isolated which pre-dispose to Alzheimer Disease. Mutations in three genes; Presinilin 1, Presinilin 2 and APP are highly penetrant. That is, if one carries a mutation in one of these three genes, the chances of developing Alzheimer Disease by the age of 60 approaches 100%. Fortunately, mutations in these genes, while having high penetrance, are “low frequency” in that they are rare in the general population.

The opposite is true for the ApoE gene. ApoE encodes an Apolipoprotein that has long been known to play a role in lipid transport and be associated with variable risk of cardiac disease. However, in 1992 Sip-pair analysis suggested that ApoE polymorphisms influence age of onset and susceptibility to AD. There are three common Polymorphisms that exist within the ApoE gene, termed E2, E3, and E4. They differ from one another by which amino acids are present at positions 112 and 158 in the ApoE gene. (see Figure 14)

The three polymorphisms of ApoE consist of single aa substitutions, resulting in six possible genotypes
The ApoE4 polymorphism can be thought of as a dose dependent “risk” gene while E2 appears protective. As seen in Figure 14, individuals who inherit two copies of the E4 allele have a very high odds-ratio of developing Alzheimer Disease. A single E4 allele raises the risk substantially over average while, on the contrary, the presence of an E2 allele appears to be protective against Alzheimer Disease.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>E4 / E4</td>
<td>30</td>
</tr>
<tr>
<td>E3 / E4</td>
<td>3</td>
</tr>
<tr>
<td>E2 / E4</td>
<td>1.5</td>
</tr>
<tr>
<td>E2 / E3</td>
<td>0.5</td>
</tr>
<tr>
<td>E2 / E2</td>
<td>insufficient data</td>
</tr>
</tbody>
</table>

The presence of susceptibility alleles for Alzheimer Disease places physicians in a clinically difficult quandary. While possessing an E4 or even two ApoE4 alleles raises one’s odds of Alzheimer Disease, one cannot be certain, even with an unfavorable genotype, that a specific patient will actually develop this disorder. A substantial percentage of autopsy-confirmed Alzheimer Disease cases lack an E4 allele and 5% of centenarians without Alzheimer Disease still carry a single E4 allele. These statistics point out the fact that the development of AD is complex. While it does hinge to a considerable extent on ones underlying genotype, that genotype is not the only important factor. The other factors (presumably having to do with the environment, other genes and chance) remain elusive.

Complicating the issue of genetic testing for AD even more than the inherent uncertainty, though, is the fact that we have no suitable treatment for this disorder.
Thus, at present, both physicians and patients are generally not enthusiastic about pursuing predictive testing in AD. This situation would change quickly if effective intervention were discovered that could decrease the risk of AD in susceptible individuals if administered prior to the onset of symptoms. Promising research is ongoing to find such pre-symptomatic therapies.

**Genetic Susceptibility to AIDS**

Certain individuals have been identified that are highly resistant to infection with HIV in spite of dramatic exposure histories. Moreover, some individual infected with Human Immunodeficiency Virus progress rapidly to clinical AIDS, while others progress much more slowly.

An important genetic explanation for the above observation is the fact that an alteration in the CCR5 encoding gene, found in 1-2% of the Caucasian population, has a significant impact on one’s susceptibility to HIV infection and progression to AIDS. Individuals who carry two copies of this polymorphism, termed delta-32, are virtually impervious to infection with HIV. Individuals who are heterozygous for this polymorphism, while able to be infected at essentially normal rates, progress much more slowly to clinical AIDS than do individuals without such polymorphisms.

In the data depicted in **Figure 16** babies infected with HIV showed significant differences in their progression to AIDS depending on their CCR5 genotype; a protective effect is observed in those who carry the delta-32 polymorphism.
Diabetes Mellitus

Diabetes Mellitus is a profoundly important human disease, and its world-wide impact is rising. In the United States alone, it is estimated that more than 100 Billion Dollars of annual healthcare costs are due to diabetes, representing 15% of the cost of all diseases combined! Two distinct types of diabetes exist, Type I, or juvenile onset diabetes, and Type II, or adult onset diabetes.

The overall incidence of Type II Diabetes has been climbing rapidly over the past decade throughout the world. The increase in Diabetes represents a dramatic interaction between culture and evolution. A cultural shift in the availability of calories and a decrease in physical activity, superimposed upon a genetic legacy in which genes have been selected for their ability to promote fat storage, has resulted in the current pandemic of disease.

Type I and Type II Diabetes are distinct diseases, and have different clinical characteristics as detailed in Figure 17

<table>
<thead>
<tr>
<th>Type I diabetes</th>
<th>Type II Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset typically &lt; 30</td>
<td>Onset typically &gt; 30</td>
</tr>
<tr>
<td>Ketosis Prone</td>
<td>Ketosis Resistant</td>
</tr>
<tr>
<td>Absolute insulin deficient</td>
<td>Variable</td>
</tr>
<tr>
<td>Islet Cell Antibodies</td>
<td>None</td>
</tr>
<tr>
<td>Other Autoimmune Dz</td>
<td>No Association</td>
</tr>
<tr>
<td>HLA Associations</td>
<td>None</td>
</tr>
<tr>
<td>MZ Concordance 50%</td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>

Figure 17
Type I Diabetes has a significant genetic component. MZ twin concordance is about 50% as opposed to dizygotic twin concordance of 6%. It is thought that genetic factors account for approximately 25% of susceptibility to Type I Diabetes.

Environmental exposures are critical in the development of this disease. Wide variations are seen in the population risks between countries. For example, Japan has a 15-fold lower incidence of diabetes than the US. The highest known incidence of Type I diabetes is in Finland and Sardinia.

The specific genetic factors involved in susceptibility to Type I Diabetes include genes within the HLA group. This group of genes is critical in the human immune response and it is speculated that a common infectious trigger superimposed upon a susceptible HLA genotype results in autoimmune activity against the pancreatic beta cells and the development of Type I Diabetes. Genetic studies, including candidate gene approaches and Sib-Pair studies, have implicated a number of genes both within the HLA complex and in other areas of the genome that seem to confer an elevated risk of type I diabetes.

Type II Diabetes represents a clash of our evolutionary past and our current culture, serving to highlight the interplay of genetics and environment. The MZ Concordance for Type II Diabetes approaches 100%, indicating an extremely strong genetic predisposition to this disorder. Candidate gene approaches have not been particularly fruitful in elucidating the genetics of Type II Diabetes. Sib-pair analyses have implicated polymorphisms in the CAPN10 gene in Type II Diabetes susceptibility.

WHAT WILL WE DO WITH OUR KNOWLEDGE ABOUT THE GENETICS OF COMMON DISEASE?

It is hoped that further insight into the genetics of common disease will lead to the early identification of susceptible individuals at which point preventative measures can be taken. In addition, insight into the genetic basis of disease should form the basis for new knowledge and new therapies.

A significant (and one of the more realistic) hopes for our new knowledge in this area is the emergence of pharmacogenomics.
At this point in medical history we basically practice a “one-size fits all” form of medicine. Our initial approach to a patient with hypertension or diabetes is focused almost exclusively on the disease and we try a variety of therapies until we hit upon one that seems to work best for that individual patient. This empiric process is time consuming, frustrating and, most importantly, fraught with dangers regarding adverse reactions that some individuals demonstrate to certain drugs.

As we begin to understand the genetic basis for disease we will be able to tailor our therapy towards the individual. By analyzing polymorphisms present in a particular individual we will have a much better idea of how to treat them for their particular type of diabetes or hypertension by taking into account their individual genotype.