In response to your many requests for information, we are beginning a newsletter to keep you up to date on our progress.

**Research Goals**

The overall goal of our group's work is to learn more about the genetic causes of mental illness. Available evidence suggests that genetic factors play an important role in who develops OCD. The goal of our genetic research is to identify genes associated with the risk for OCD.

**Our Work to Date:**

Our group has made much progress over the past four years, identifying two genes that are important for OCD in some individuals.

The first gene we identified is called COMT (Catechol-O-methyltransferase) and is thought to end the action of two chemicals that transmit signals between nerve cells. These two neurotransmitters, dopamine and norepinephrine, are involved in many brain activities, including control of emotions, particularly reward and anxiety. We have now tested two large groups of patients and get the same

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**Current Work:**

We are eager to continue our work unraveling the genetic causes of OCD by

- continuing to test specific 'candidate' genes for involvement in OCD *(Association Studies)*
- searching the entire genome for loci that may harbor susceptibility genes for OCD *(Linkage Studies)*

For the linkage studies, we need to recruit extended families (families with more than one affected individual). This is necessary in a disease like OCD, where a large degree of heterogeneity is suspected (i.e. multiple genes are thought to play a role). This is a more recent research initiative. Our current sample consists of 26 extended families, each one having several individuals diagnosed with OCD. We need to recruit several more families before genetic linkage studies can proceed.

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result: Men with OCD are more likely to have the Low-activity form of the COMT gene. This form of the gene carries an alteration, which results to a less active enzyme (three to four times less).

Normally, the chemicals pass form one nerve to the other at the junction called a synapse, then are recycled and finally broken down into smaller substances. When the COMT enzyme is less active, it is likely that the amounts of the two neurotransmitters in the synapse increase possibly because they may not be recycled efficiently, resulting in a biochemical imbalance that contributes to OCD. The Low-activity form of the COMT gene is not absent from the general population, but it is over-represented among men with OCD, which suggests that it is a risk factor for OCD in the magnitude of 2-6 (i.e. increases an individual's risk to develop OCD by 2-6 times). Although this is quite high, it is clear that the COMT gene alone does not explain all genetic risk involved in OCD.

The power of gene discovery is that specific pathways are revealed and are open to further investigation. We can now ask if COMT is involved, what about the other genes that have the same function as COMT? This questioning brings us to examine MAO-A (monoamine oxidase A), which also breaks down dopamine, and additionally serotonin. To our surprise, MAO-A as well has significant contribution to susceptibility to OCD, particularly see this strong sex effect in genes involved in OCD, we still have no proof. It is well known that there are some sex differ-

There is no reason to assume that the OCD syndrome includes only one disorder. The diagnosis of OCD is based on a constellation of symptoms, rather than causes. Genetic studies can be crucial in this regard: when sufficient numbers of patients are examined, genetic variations can also be examined in relation to several variables such as gender, family history, age at disease onset, presence of co-morbid conditions, response to treatment, symptom type, etc. It is likely that this kind of analysis will eventually provide objective criteria to define etiological subtypes of this disorder. It may also allow us to design treatments tailored to the individual patient (patient specific treatments).
The Bottom line/In summary:

- The goal of our genetic research is to identify genes associated with the risk for OCD.
- Two genes, COMT and MAO-A, have been associated with a susceptibility to develop OCD.

GLOSSARY (partly adapted from "Understanding Gene Testing: A Slide Lecture," NCI 8/96)

**Background:**
Gene discovery provides researchers with the ability to identify changes within genes that may predict the future development of specific diseases, help diagnose existing diseases or someday make it possible to treat or even eliminate disease.

**Gene:**
A gene is the working subunit of a DNA molecule. A gene is any given segment along the DNA carrying a particular set of instructions that allows a cell to produce a specific product - typically a protein such as an enzyme. There are between 50,000 and 100,000 genes, and every gene is made up of thousands, even hundreds of thousands of chemical bases.

A sound body depends on the continuous interplay of thousands of proteins, acting together in just the right amounts and in just the right places - and each properly functioning protein is the product of an intact gene. Many, if not most, diseases have their roots in our genes. Common disorders such as heart disease, mental illness and most cancers arise from a complex interplay among multiple genes and between genes and factors in the environment.

**Genome/human chromosomes:**
Genes are strung along chromosomes. Each cell contains two sets of 23 chromosomes, one inherited from the mother and one from the father. A large number of genes reside on each chromosome. Most genes have not yet been identified, but we do know the chromosome location of some. Scientists are developing maps that depict the order in which genes and other DNA landmarks are found along the chromosomes.

**Association Studies:**
In Association Studies, scientists examine specific genes that they have reasons to believe are strong candidates for their disease of interest. In OCD, for example, one might hypothesize that genes involved in serotonin or dopamine pathways may play a role. Variations in these genes are searched for and used to examine if they are present in higher frequencies in patients with OCD than unaffected individuals. If such preferential distribution of a gene variant is detected, scientists can safely hypothesize that the particular gene contributes to the genetic risk of the disease.

**Linkage Studies:**
In Linkage Studies, no a priori hypotheses are made about what genes may be involved. Rather, the entire genome is searched by easily trackable DNA markers - DNA segments with known locations on the chromosomes - for evidence of linkage. Specifically, when a marker is near a disease gene it is expected to be consistently inherited by persons with the disease but not by relatives who are disease free. Linkage studies can only be performed in families which numerous relatives, over several generations, have developed the illness. Even when the rough location of a disease gene is known, much more laboratory work is required to specifically identify it and characterize its alterations or mutations.
Research Team:

Maria Karayiorgou, M.D., Psychiatric Geneticist, Principle Investigator
Maude Blundell, M.S., C.G.C., Genetic Counselor, Research Coordinator
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Carrie Gavigan, M.A., Clinical Interviewer
Claire Haiman, M.A., Clinical Interviewer
Fenia Weiller, M.A., Clinical Interviewer
Adelaide Acquaviva, Secretary

Rockefeller University:

Rockefeller began in 1901 as The Rockefeller Institute for Medical Research, the first U.S. biomedical research center. Rockefeller faculty members have made significant achievements, including the discovery that DNA is the carrier of genetic information. The university has ties to 21 Nobel Laureates. Thirty-three faculty members are elected members of the U.S. National Academy of Sciences.

Funding:

Grant awards from Irma T. Hirschl and G & F Armour Foundations fund our program.

HOW you can stay involved:

● If a relative has been diagnosed with OCD since the time we completed our interview, please contact us.
● If you know of other families that have several members with OCD, please inform them about our studies.

We would like to keep in touch with you, so if you change residence or your phone number please either
● call us at our toll free number: (888) 920-9100, press 1,
● or send an e-mail to: blundem@mail.rockefeller.edu
● or drop us a note to: Maude Blundell · Rockefeller University · 1230 York Avenue, Box #45 · New York, NY 10021

HOW you may benefit:

It is our hope that the research we are currently conducting will lead to the identification of genes involved in OCD. We may know better who is at risk for developing the disease as well as ways to prevent or treat the illness for those who develop it. In addition, by understanding how the genes work, we may be able to develop better treatments to overcome the deficiency of an abnormal gene.

Our Recent Publications

