Genetic Study on IC/PBS/CPPS Update Newsletter

Children's Hospital, Boston
Department of Urology/Program in Genomics

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Possible Gene or Genes for IC/PBS/CPPS

By Steven Boyden, BS

To date, we have collected fifteen extended families from Bulgaria. These families were discovered by Dr. Dimitrakov and provided the first evidence that IC/PBS/CPPS may be an inherited disorder. The Bulgarian families all have multiple members affected with IC/PBS/CPPS, at least one person in each generation, and both males and females affected within families. This type of inheritance pattern is very suspicious of autosomal dominant inheritance (See genetic 101 for definitions pg 2).

We are studying the DNA collected from several of these Bulgarian families with a technique called genetic linkage analysis (see linkage analysis & your DNA for definitions pg 2). We have successfully identified four regions in the genome in five different families. We believe this means that there are likely four different genes, if not more, that may cause the symptoms of IC/PBS/CPPS when altered. These four regions are like knowing the city and state of an address. We are now using another technique to search for the actual gene or street address. We are using DNA sequencing, which is like proofreading a book, to search for the responsible genes in all four regions. Currently, we believe we may have identified a potential altered gene in one promising candidate in one family. Studies are ongoing to determine if this gene is definitively responsible for IC/PBS/CPPS in this particular family. We are hoping this gene's biological activity will give us important clues to finding other IC/PBS/CPPS genes in the other three regions.

We are now realizing that families in the US and Canada also show the same inheritance pattern seen in our Bulgarian families. We are actively collecting the US and Canadian families and will be comparing them to the Bulgarian results.

We believe that the potential identification of up to four different genes that may work together in the body in a common pathway, will provide new drug targets resulting in more effective therapeutics.

Inside this issue:

Special points of interest:

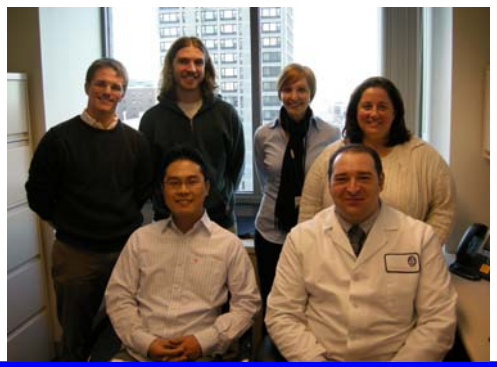
- New Genetic Findings
- Changes in the Reporting of Study Results
- Contact us!!!

Meet the IC/PBS/CPPS Genetics Team!!!

Principle Investigator: Jordan Dimitrakov, MD, PhD

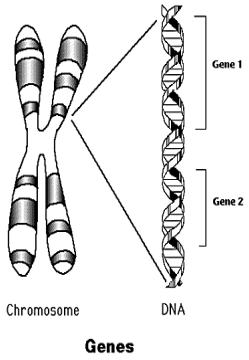
Study Coordinator: Elicia Estrella, MS, CGC

Other Investigators: Louis M. Kunkel, Ph.D (not shown); Steven Boyden, BS; Jaeseop Lee, BS; Michael Smith, BS; Catherine Hasman, MS



Genetics 101

By Elicia Estrella, MS, CGC



Structure of DNA & Genes within a Chromosome

People, animals and many other living organisms are made of cells. All cells within an organism contain **DNA (*D*eoxyribo*n*ucleic *A*cid)**. DNA is the molecule that encodes our genetic information carrying all the instructions for making a person. DNA is made up of two twisted strands of chemical building blocks called bases. There are 4 bases that make up the language of our genes: ***A*denosine, *T*hymine, *G*uanine, and *C*ytosine**. Certain areas of our DNA contain our genes. These genes are considered our genetic blueprint or instructions. Our genes determine all of our features like height and eye color. This is why we have similarities to our parents and grandparents. Our DNA strands are coiled up and tightly packaged into structures called **chromosomes**. We have 46 chromosomes in total. They come in pairs (23 pairs), with one chromosome from each pair inherited from your mother and the other from your father. This is how our parents and grandparents have passed their genes down to the next generation. How our genes are expressed in our family is called the **inheritance pattern**.

We have found many families with symptoms of IC/PBS/CPPS that we believe show evidence of **Autosomal Dominant Inheritance**.

Autosome: a gene is located on chromosome 1-22

Dominant: 1 of 2 copies of a gene is mutated (altered) and trait is expressed

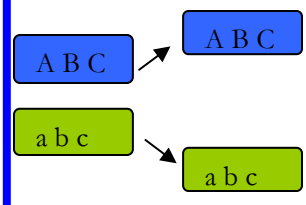
"It is believed that every person has 10-15 mutations within their genome."

Linkage Analysis and your DNA

By Elicia Estrella, MS, CGC

Which of our 23 pairs of chromosomes from both parents we have inherited is a matter of chance. There are 8,324,608 possible combinations of 23 chromosome pairs. Each chromosome contains many different genes. The total possible combination of gene copies for those genes in humans is approximately 10^{963}. This accounts for the fact that everyone, except identical twins, is genetically unique.

Genes on the same chromosome are passed on together as a unit. Such genes are said to be linked. For example, the "A" and "B" alleles (in the illustration on left) are both be passed on together. "A" and "B" are linked due to their occurrence on the same chromosome.



Genes A and B linked on a chromosome are more likely to be inherited together

Linked genes most likely account for such phenomena as red hair being strongly associated with light complexioned skin among humans. If you inherit one of these traits, you will most likely inherit the other.

Linkage is the tendency for genes and genetic markers to be inherited together because of their location near one another on the same chromosome.

A genetic marker is a segment of DNA with an identifiable physical location on a chromosome whose inheritance can be followed. A genetic marker can have a function and thus be a gene. Or a marker can be a section of DNA with no known function.

Because DNA segments that lie near each other on a chromosome tend to be inherited together, markers are often used as tools for tracking the inheritance pattern of a gene that has not yet been identified but whose approximate location is known.

Linkage analysis of a family's DNA sample allows us to make a statistical estimate of whether two gene locations or loci are likely to lie near each other on a chromosome and are therefore likely to be inherited together or linked. Scientists use linkage analysis as a way of gene-hunting for diseases believed to be inherited .

Study Changes: Results Reporting

We are still recruiting patients for our genetic study on IC/PBS/CPPS.

Do you have symptoms for at least 3 months in a 6 month period of;

- Pain in the Pelvic area
- Bladder Pressure, Discomfort or Pain (which ease with urination)
- Urinary frequency
- Urinary urgency
-

Are you willing to provide a saliva and urine sample?

Agree to complete several brief questionnaires?

Live in the USA or Canada?

Enrollment is voluntary !

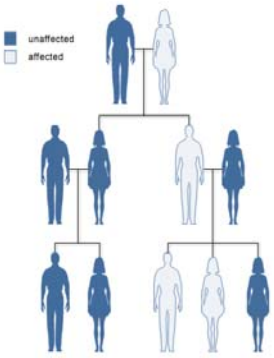
No Travel Required !

Participate from home or through your doctor!

No cost to participate in this study!

Family members with or without symptoms are eligible!

We are *changing our consent form* to allow participants to receive individual results ONLY if results are confirmed by a diagnostic laboratory. This is a change from our previous consent which only allowed general study results to be released. If you are already a participant and are interested in obtaining your individual results, we welcome you to re-consent. Send in the REPLY CARD below and we will contact you.



An example of autosomal dominant inheritance in a family tree. Lightly shaded people are affected with an "inherited condition"

Contact us!!!

REPLY CARD

NAME: _____

(please PRINT)

Contact information Changes:

Address: _____

Phone: _____

Email: _____

Clinical updates:

_____

_____

_____ **Place a check here to be contacted about our new consent form**

_____ **Place a check here to be taken off our mailing list**

Please sign to authenticate: _____

We would love to hear from you! Let us know:

1. Give us feedback on the newsletter
2. What would you like to see in future issues of our newsletter?
3. Update us on your contact info! (phone/email/address)
4. Take me off your mailing list!
5. Request a copy of the newsletter to be sent to someone not on our mailing list ! (family member, new study participant, your doctor, etc.)

Review of Current Pharmacological Therapies

More than 180 different types of therapy (pharmacological, dietary, interventional, and behavorial) have been used in the treatment and management of IC/PBS, yet evidence of efficacy from clinical trials has been inconclusive. Dr. Dimitrakov has reviewed 21 of the most common pharmacologic treatment approaches in an attempt to evaluate treatment efficacy in a recent publication.

His review showed that unfortunately the majority of pharmacologic agents were not beneficial. From clinical trials only pentosan polysulfate (Elmiron) was believed to modestly help in managing the symptoms of IC/PBS. Dr. Dimitrakov designed this study with the aim to attempt to begin a clinical consensus of treatment and treatment efficacy for IC/PBS.

To read the article for more specifics please see the reference below;

Dimitrakov, J., Kroenke, K., Steers, WD., Berde, C., Zurakowski, D., Freeman, MR., Jackosn. JL., **Pharmacologic Management of Painful Bladder/ Interstitial Cystitis: A Systematic Review**. *Arch Intern Med*. 167 (18):1922-9.2007.

Look for us on the web soon!!!

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