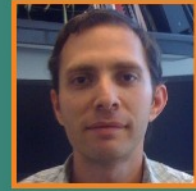




# On the Trail of Genomic Pioneers



Meet Dr. Gene Cutler, PhD  
Principal Scientist Bioinformatics  
ASF Lead Discovery  
Amgen

## 1) Would you tell us a bit about your research interests?

I lead a Bioinformatics group which is embedded within a larger Drug Discovery/High-Throughput Screening group. This puts us at a nexus where large amounts of biological data are being generated and need smart analysis. Our focus is largely on novel target discovery through the mining of disparate data sets. Genomic data is an example of one such class of data. With the growing understanding of the importance of genomic structural variation, we have been working to understand how such variation leads to phenotypic changes, particularly in cases where those phenotypic changes relate to human disease.

## 2) How are Copy Number Variation (CNV) and Single Nucleotide Polymorphism (SNP) studies helping in understanding diseases?

Clearly there are both inherited and spontaneous genomic changes, at various scales, that either directly lead to disease or are permissive for the development of diseases. SNPs can lead to inactivating or activating changes in protein sequence as well as more subtle expression-level changes, while copy number variation generally leads to the elimination of or the increase of gene expression. When those changes occur in disease-related genes, we would expect to see changes in disease rates – usually increases in disease since it is easier to break things than to improve them. Historically, biology had a large focus on forward

genetics – tracking down the genetic causes for disease – until the modern biology revolution (particularly transgenic technology) came along and changed the focus to reverse genetics – making genetic changes and then observing phenotype. We are now swinging back to a major focus on forward genetics as tools such as microarrays and high-throughput sequencing allow us to quantify genetic variability at a scale never before possible.

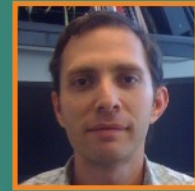
SNP variations between individuals, whether human or from model organisms such as the mouse, can be correlated to phenotype, such as risk of developing diabetes. Phenotype-associated SNPs may be markers or, if you are very lucky, actually causative of the given phenotype. CNVs can be studied in the same way, but they are of particular interest in the field of oncology given the large amount of genomic structural variation that occurs in cancers. The big question there is which of these CNVs are causative, or at least supportive, of cancer development and which are just products of the high genetic instability characteristic of cancer cells.

## 3) Which research study or work has strongly influenced your thought and research goals ?

Rather than point to an individual publication, I would say that a key influence on our work is technological growth. As novel technologies push the boundaries of what is possible in biological research, we work hard to incorporate those into our work. Each new technological advance points the way to new experiments and new analysis strategies. For example, until the advent of high-coverage genome-tiling microarrays,



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our knowledge of CNVs was limited primarily to very large and rare chromosomal abnormalities. Now we know that there is a great amount of structural variation within both human and mouse populations and we expect that some of that variation will be disease-linked.

#### **4) Where do you see your research leading in future?**

Since we try to work at the edge of what is possible, our research can change rapidly in unexpected ways. At the moment, I see Next-Generation sequencing as being a source of vast new data sets, a major leap from microarray technology in both the information content and the complexity of analysis.

#### **5) A great deal of your work focuses on studying mouse genome and variations. What would you say are the most important things that have been discovered in this area over the years? What do you think would be the role of genomics in this area in years to come ?**

The amount of structural genomic variation between strains of mice and the frequency of new CNVs arising are, I believe, the most important observations that have come from this work. For example, in our work we found that about two-thirds of CNVs cover at least one mouse gene and there are around 50 CNVs per strain when compared to the reference C57BL/6 strain. This provides a lot of raw material not only for individual

variation but also for population variation and evolution. There is currently a project underway to sequence the genomes of 17 strains of mice in addition to the already sequenced C57BL/6. Scientifically, this will be very exciting research for furthering our understanding of evolution. SNPs alone just don't cut it as the raw material for the creation of new genes. It's the duplication and translocation events that feed the gene-creation engine.

#### **6) How does the use of mouse as a model organism help in understanding human diseases ?**

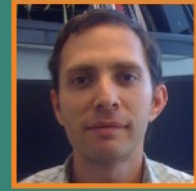
You can only truly understand a human disease when you study humans. With that said, you can't do much in the way of prospective (forward genetics) experimentation in people. Instead you need to find the most relevant and tractable disease models you can. The mouse model tends to be very tractable given the mouse's small size, its high reproductive rate, and our ability to make transgenics. We can identify CNVs that we believe to be linked to specific phenotypes in mice, then introduce the same CNVs in other strains to test our hypotheses.

#### **7) To a broader audience, could you tell more about copy number variation in the mouse genome ?**

We used to think of genome structure as being canonical. There was "the" human genome and "the" mouse genome. Variations were limited to a catalog of point mutations, SNPs, that altered some of the meaning, but none of the structure of the genome. Large structural variations, such as



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the gain or loss of entire chromosomal arms, had been observed in humans but they invariably led to significant birth defects. Replications and deletions of regions of the genome on smaller scales, from tens to hundreds of millions of nucleotides, were not appreciated until the advent of array-based comparative genome hybridization (CGH). CGH technology has allowed us to discover the great variety of copy number variations (CNVs) that occur between individuals within a population and between population subgroups (i.e., mouse strains). This means that one individual may be lacking dozens of genes or have multiple copies of genes present only once in another individual. This has important implications for the use of mouse as a model organism. For example, a given gene that is present once in the canonical genome of the mouse strain C57BL/6, may be present in multiple copies in the mouse strain FVB/NJ. If you had the misfortune to attempt to generate a transgenic strain of FVB/NJ, knocking out that gene, without having that copy number information, you would be at a loss to explain why you did not see the expected phenotype. In fact, the majority of CNVs that we have discovered overlap with known genes. While these genes often belong to certain quickly evolving gene families, such as sensory and immune genes, they are not limited to these multi-member families. Thus we would expect that the phenotypic reach of CNVs to be quite broad. We need a good understanding of these effects in order to truly understand the biology of these important models for human diseases.

**USA: +1-800-436-3564 (Toll free) | India: +91-40-6698-6700**

[www.genelogic.com](http://www.genelogic.com)

[www.ocimumbio.com](http://www.ocimumbio.com)



[outreach@ocimumbio.com](mailto:outreach@ocimumbio.com)

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