# GENERAL STRATEGIES FOR IDENTIFYING HUMAN DISEASE GENES

**Naila Rozi ssuet**

**Syed khalid Jawaid( ku)**

**Abstract:**

Using information about the function of unidentified disease genes in order to identify the gene. Essentially two approaches are used those which depends on the availability of purified genes product, ands those for which a functional gene assay is required. Some information about the function of the gene is exploited to isolate a gene clone. If the gene product is known partial purification of the product can permit various strategies for identifying the underlying gene. Alternatively a functional assay can be used to screen for the gene. This approach has been useful in only a few cases.

Key Words:

Gene Clone,Human disease

## INTRODUCTION:

Before 1980,only a very few human genes had been identified as disease loci. Such early successes were very largely the result of exceptional characteristics, the biochemical basis of the disease had previously has been established and purification of the gene product could be achieved without too much difficulty .Such advantages do not apply however ,to the great majority of disease resulting from mutation in human genes. In the 1980s the application of recombinant DNA technology offered new approaches to approaching to mapping and identifying the gene underlying inherited single gene disorder and somatic cancers and the number of disease gene identified studies to increase rapidly. With the subsequent advance of rapid PCR based linkage studies and PCR mutation screening technologies, the identification of novel disease gene became commonplaces and is currently occurring on a weekly basis .It is important to note that not all 650000-800000 human genes will be identified as disease genes..some gene are indispensable to embryonic function so that deleterious mutation result in embryonic lethality and go unrecorded in humans. In other case ,abolition of gene function may have no effect on the phenotype because of genetic redundancy, that is another nonallelic genes also supply the same function .Mandelian Inheritance in Men, the catlog of inherited human disorder currently lists only about 5000 mandolin list. The more common inherited disorder are ones that are the most difficult to study by molecular genetics: a combination of different gene is often involved oligogenetics or polygenetics disorders as well as different environmental triggers. similarly ,the more common cancer involve cellular events in which multiple genes are involved. Not expectedly therefore, the human disease gene that have been isolated to date are very largely those responsible for inherited single gene disorder.

## POSITIONAL CLONNING:

This means isolating the gene knowing only its sub chromosomal location, without using any information about the pathogenesis or the biochemical function .The general approach is to try to construct physical and genetics maps of the region ,refine the sub chromosomal localization , and then identify genes in the region to investigate as disease gene candidate. Positional cloning remains androus and is increasingly becoming unnecessary as information accumulates which allows a positional candidate gene approach.

**POSITIONAL CANDIDATE GENE APPROACHES:**

Once a disease has been mapped, it is increasingly becoming possible to use database search to identify candidate genes. With more and more human genes being mapped to specific sub chromosomal regions positional candidate gene approaches are set to dominate the field.

**Genotype Frequencies can be used to calculate mutation rates**:

Mutant genes are being created by fresh mutation but being removed by natural selection. For a given level of selection we can calculate the mutation rate which would be required to replace the gene lost. If we assume that there is equilibrium in the population between the rates of loss and replacement, the calculation tells us the present mutation rate. We can define the coefficient of selection (s) as the relative chance of reproductive failure of a genotype due to natural selection(the fittest type in the population has s=0 ,a genetic lethal has s=1)

For an autosomal recessive condition ,a proportion $q^2$ of the population are affected ,and so the loss of disease genes each generation is $sq^2$ .This is balanced by mutation at the rate of $\mu(1-q^2)$ where μ is the mutation rate per gene per generation. At the equilibrium if q is small

$$sq^2= \mu(1-q^2) \qquad (1)$$

For a rare autosomal dominant condition only the heterozygote's are significantly frequent in the population .Hetrozygotes occur with frequency 2pq( frequency of disease gene=p).Only half the gene lost through their reproductive failure are the disease gene ,so the rate of gene loss is very nearly sp. Again ,this is balanced by a rate of new mutation of $\mu q^2$ which is approximately μ if q is almost 1.Thus

$$\mu=sp \qquad (2)$$

For an X-Linked recessive diseases ,the rate of gene loss through affected males sq. This is balanced by amutation ,but only the one third of x chromosomeswhich are in males are exposed to selection.Thus

$$\mu=sq /3 \qquad (3)$$

Estimated derived using these formulae

$\mu=sq^2$ gives an unexpectedly high mutation rate.

**Mapping In DNA Sequence model**

Mapping the human genome is not the only scientific project supported by the Human Genome Project. Support has also been given to project which aim to sequence the DNA of model organism and to attempt to identify and characteristic genetic variation in different human population .At the outset of the Human Genome Project, it was recognized that comprehensive maps of certain model organisms would be highly desirable. Such organisms include a variety of species. Some of which have been particularly amenable to genetic analysis. The need to study such organisms is evident from numerous examples where information derived from studied of the mathematics of model organism has been essential to interpret data obtain in studies of humans and in understanding human DNA. Research involving such models will continue to provide a basis for analyzing normal gene regulation, genetic diseases and evolutionary process. In addition, large scale sequencing of selected model organisms, notably the roundworm C., are being viewed as pilot projects for sequencing the human genome.

A primary goal for physical mapping is identifying the locations of genes within a clone conting that has been localized to a specific chromosomal region. In principal two major features permit the DNA of genes to be distinguished from DNA that does not have a coding function.

SEQUENCE CONSERVATION:

Because gene execute important cellular functions, mutation which alter the sequence of the product will often be disadvantageous and are rapidly eliminated by natural selection. The sequence of coding DNA and important regulatory sequences is therefore more strongly conserved in evolution than that of noncoding DNA.In addition ,premature termination codons in coding DNA are selected against. This means that genes often contain comparatively long open reading frames

(ORFS): In noncoding DNA the DNA triples corresponding to termination codons are not selected against and ORFS are usually comparatively short.Some Exons,however ,may be quite small but can often be detected using computer programs to analyze the relevant DNA sequence.

**Methodology:**

Commonly used methods identifying genes is cloned DNA.

**Zoo-blotting:**

A DNA clone is hybridized at reduced hybridization stringency against a souther bolt of genomics DNA samples from a variety of species,a zoo blot .Depends on coding DNA being more strongly conserved during evolution than noncoding DNA.

CpG island identification

Many vertebrate genes have associated CpGisland,hypothylatedGC-rich Sequences usually having multiple raer-cutter restriction sites.

Identification by restriction mapping :DNA clones are usually hybridized against southern blots of genomics DNA cut with clustering of rare cutter sides.

Island –rescue PCR: This is a way of isolating CpG island sequences from YACs by amplifying sequences between island and neighboring ALU repeats.

Hybirdization to mRNA/cDNA

A genomic DNA clone can be hybridized against appropriate cDNA libraries .

Exon Trapping:

This is essentially an artificial RNA splicing assay .It relies on the observation that avast majority of gene contain multiple exons which need to be spliced together at the RNA level.

c DNA selection or capture:

These techniques involve repeated purification of a subject of genomics DNA clone can be compared against all other available DNA sequence

**Conclusion:**

**It is worth remembering that the medically important mendelian disease are those which are both common and serious ,and they must all have one or another special trick to remain common in the face of selection .This trick may be an exceptionally high mutation rate (Duchene muscular dystrophy),or propagation of non pathological but unstable per mutation.**

**REFRENCES:**


[1] Chelly j,concordat JP,Kaplan CJ.(1989)Proc.NatlAcad.Sci. USA,86,2617-2621

[2] Nelson DL,Ledbetter(1989)proc.NatlAcid USA,86,6686-6690

[3] Naila Rozi, Nasir Uddin Khan,Improve Hidden Markov Model In DNA Sequences ISSN# 2073-7122.Journal of IJCRB,Jan.2011,vol#2,9page#528.

[4] Naila Rozi and Nasir Uddin khan, Journal of Life Sciences ,U.S.A(ISSN-1934-7391),Feb2011,Termination of DNA replication and role of enzymes in recombination

[5] Naila Rozi &Nasir uddin Khan," Improved Hidden Markov Model in DNA Sequence Alignment" Journal of Life Sciences,USA (ISSN -1934-7405)VOL5,.NO.3March2011.page#221-222

[6] Naila Rozi &Nasir uddin khan,"Journal of Mathematics and system science, USA,(ISSN 2159-5291)Jan2012,vol#2

[7] Naila Rozi &Nasir uddin Khan ,Journal of IJRMA,DNA is Double HELIX Geometrically

[8] Naila Rozi,&Nasir Uddin Khan 2ND ICECS Conferenc,28-30DEC 2009Proceeding IEEE, DUBAI,U.A.E,Number Patterns&Geometric representation of DNA,ISBN978-7695-3937-9,page#343-344.

[9]Naila Rozi & Nasir Uddin khan MRI &3D Fourier Transformation ICCAA2012

[10] Naila Rozi and Nasir Uddin khan, design of DNA origami, Proceeding 5th International conference of statistical science Lahore ISBN#978-969-8858-05-6VOL17,279-284 January,2009.

[11]Naila Rozi,Nasir Uddin Khan,2nd ABRC 2009 CONFERNCE COMSAT INSTITUTE LAHORE ON 22-23 october,2009(Geometric Patterns of DNA Help In Signal Processing By Using HMM).

[12]Naila Rozi and Nasir Uddin khan, Proceeding of ICCS-X CAIRO EGYPT,2009 An Evaluation of Contemparary HMM Gene-Finder with Predicted Exon Taxonomy.

[13]Naila Rozi and Nasir Uddin khan, ICCS-X CAIRO EGYPT,2009 Extraction Of Hmm Representation In DNA Sequence.

[14] Naila Rozi and Nasir Uddin Khan ,ICCS-12 Jamai AlQatar ,19-22 Dec,2012,Phase Zero intron interrupt the coding Sequences in DNA by cyclic permutation "978-969-8858-11-7"