



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Review Article


July 2016 Vol.:6, Issue:4

© All rights are reserved by G. VinothaPooshan et al.

Inspiration of Gene Mapping in Human Syndromes



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals



ISSN 2349-7203

G. VinothaPooshan*, N.R. Livingstonraja, M. Thiruppathi, P.Vijay Nagendiran

Department of pharmacy, Arulmigu Kalasalingam College of pharmacy, Anand nagar, Krishnankovil, India.

Submission: 26 June 2016
Accepted: 1 July 2016
Published: 25 July 2016

Keywords: Gene mapping, Nanopharmaceuticals, chromosome, gene therapy

ABSTRACT

Gene mapping is the determination of the sequence of genes and their relative distances from one another on a specific chromosome. In this review, we described more about the gene mapping in human disease. Now a day genetic research have been well advanced, thus gene mapping plays major role in the characterisation of specific gene which is responsible for the disease in human. By this characterisation which opens a pathway for the new target to eradicate or control the disease by action of gene therapy and Nanopharmaceuticals.



HUMAN JOURNALS

www.ijppr.humanjournals.com

INTRODUCTION

Gene mapping describes the methods used to identify the locus of a gene and the distances between genes.^[1] The essence of all genome mapping is to place a collection of molecular markers onto their respective positions on the genome. Molecular markers come in all forms. Genes can be viewed as one special type of genetic markers in the construction of genome maps, and mapped the same way as any other markers. Gene mapping studies the relation of genotypes and phenotypes. Its goal is to identify, as precisely as possible, genomic regions affecting particular phenotypes of interest and to estimate the importance of those regions to phenotypic variability of the trait. Phenotypes can include disease status (usually coded 0 or 1), quantitative measurements associated with an individual (blood pressure, fasting glucose), transient molecular measurements associated with organ function (RNA transcript abundance), etc.^[2] Genetic mapping provides a powerful approach to identify genes and biological processes underlying any trait influenced by inheritance, including human diseases. We discuss the intellectual foundations of genetic mapping of Mendelian and complex traits in humans, examine lessons emerging from linkage analysis of Mendelian diseases and genome-wide association studies of common diseases.^[3]

HISTORY

Since the early 1950s, the development of genetics has been exponential with several milestones, including determination of DNA as the genetic material in 1944, discovery of the double-helix structure of DNA in 1953, the development of electrophoretic assays of isozymes^[4] and a wide range of molecular markers that reveals differences at the DNA level^[5,6]. Each of these milestones had led to a huge wave of progress in genetics. Consequently, our understanding of organismal genetics now extends from phenotypes to molecular levels, which can lead to new or improved screening methods for selecting superior genotypes more efficiently and improve decision-making process in breeding strategies. Genetic mapping (also known as linkage mapping or meiotic mapping) is one of the various applications of molecular markers in any species. It refers to the determination of the relative positions of genes on a DNA molecule (chromosome or plasmid) and of their distance between them. Genetic map indicates the position and relative genetic distances between markers along chromosomes, which is analogous to signs or landmarks along a highway where the genes are “houses”^[7,8]. The first genetic map was published in 1911 by T. H. Morgan and his student, Alfred Sturtevant, who showed the locations of 6 sex-linked

genes on a fruit fly chromosome. The principles of genetic mapping and linkage analyses are still used in much the same way but with far more advanced methodologies. During the past two decades, the step from the quite limited polymorphism in morphological traits/mutants and isozymes to the high pace of development of molecular markers resulted in extensive genetic mapping experiments in many species.

PRINCIPLE OF GENE MAPPING:

Independent Assortment

The Principle of Independent Assortment describes how different genes independently separate from one another when reproductive cells develop. This theory was proposed by Gregor Mendel in 1856 which give knowledge about the Independent Assortment of genes and their corresponding traits which were observed in genetic studies in pea plants. Mendel was performing dihybrid crosses, which are crosses between organisms that differ with regard to two traits. He discovered that the combinations of traits in the offspring of his crosses did not always match the combinations of traits in the parental organisms. From his data, he formulated the Principle of Independent Assortment.

We now know that this Independent Assortment of genes occurs during meiosis in eukaryotes. Meiosis is a type of cell division that reduces the number of chromosomes in a parent cell by half to produce four reproductive cells called gametes. In humans, diploid cells contain 46 chromosomes, with 23 chromosomes inherited from the mother and a second similar set of 23 chromosomes inherited from the father. Pairs of similar chromosomes are called homologous chromosomes. During meiosis, the pairs of homologous chromosome are divided in half to form haploid cells, and this separation, or assortment, of homologous chromosomes is random. This means that all of the maternal chromosomes will not be separated into one cell, while the all paternal chromosomes are separated into another. Instead, after meiosis occurs, each haploid cell contains a mixture of genes from the organism's mother and father.

Another feature of Independent Assortment is recombination. Recombination occurs during meiosis and is a process that breaks and recombines pieces of DNA to produce new combinations of genes. Recombination scrambles pieces of maternal and paternal genes, which ensures that genes assort independently from one another. It is important to note that

there is an exception to the law of independent assortment for genes that are located very close to one another on the same chromosome because of genetic linkage.^[9]

TYPES OF GENE MAPPING

There are two distinctive types of "Maps" used in the field of genome mapping: genetic maps and physical maps.

1. Genetic Mapping

Genetic mapping is based on the use of genetic techniques to construct maps showing the positions of genes and other sequence features on a genome.

- Genetic techniques include cross-breeding experiments or,
- Case of humans, the examination of family histories (pedigrees).

Researchers begin a genetic map by collecting samples of blood or tissue from family members that carry a prominent disease or trait and family members that don't. Scientists then isolate DNA from the samples and closely examine it, looking for unique patterns in the DNA of the family members who do carry the disease that the DNA of those who don't carry the disease don't have. These unique molecular patterns in the DNA are referred to as polymorphisms or markers.^[10] In genetic mapping, any sequence feature that can be faithfully distinguished from the two parents can be used as a genetic marker. Genes, in this regard, are represented by "traits" that can be faithfully distinguished between two parents. Their linkage with other genetic markers are calculated same way as if they are common markers and the actual gene loci are then bracketed in a region between the two nearest neighbouring markers. The entire process is then repeated by looking at more markers which target that region to map the gene neighbourhood to a higher resolution until a specific causative locus can be identified. This process is often referred to as "positional cloning", and it is used extensively in the study of plant species.^[10]

2. Physical Mapping

Physical mapping uses molecular biology techniques to examine DNA molecules directly in order to construct maps showing the positions of sequence features, including genes. Physical maps can be divided into three general types:

- a) **Chromosomal or cytogenetic maps,**
- b) **Radiation hybrid (RH) maps,**and
- c) **Sequence maps.**

The different types of maps vary in their degree of **resolution**, that is, the ability to measure the separation of elements that are close together.

a) Chromosome mapping is a technique used in autosomal DNA testing which allows the test to determine which segments of DNA came from which ancestor. In order to map DNA segments on specific chromosomes it is necessary to test a number of close family relatives. Ideally one should test both parents, one of their children, and a number of first to third cousins on both the maternal and paternal sides of the family. ^[11]

b) Radiation hybrid mapping (also known as RH mapping) is a technique for mapping mammalian chromosomes. Radiation hybrid mapping uses X-ray breakage of chromosomes to determine the distances between DNA markers, as well as their order on the chromosome.

c) Sequence Mapping

Sequence tagged site (STS) mapping is another physical mapping technique. An STS is a short DNA sequence that has been shown to be unique. To qualify as an STS, the exact location and order of the bases of the sequence must be known, and this sequence may occur only once in the chromosome being studied or in the genome as a whole if the DNA fragment set covers the entire genome.

The highly specific and sensitive PCR provides the basis for sequence-tagged sites (STSs), unique landmarks that have been used widely in the construction of genetic and physical maps of the human genome. Electronic PCR (e-PCR) refers to the process of recovering these unique sites in DNA sequences by searching for subsequences that closely match the PCR primers and have the correct order, orientation, and spacing that they could plausibly prime the amplification of a PCR product of the correct molecular weight. A software tool was developed to provide an efficient implementation of this search strategy and allow the sort of en masse searching that is required for modern genome analysis. Some sample searches were performed to demonstrate a number of factors that can affect the likelihood of obtaining a match. Analysis of one large sequence database record revealed the presence of several microsatellite and gene-based markers and allowed the exact base-pair distances among them

to be calculated. This example provides a demonstration of how e-PCR can be used to integrate the growing body of genomic sequence data with existing maps, reveal relationships among markers that existed previously on different maps, and correlate genetic distances with physical distances.^[12]

Gene mapping in human disease:

1. ASTHMA

Laitinen T underwent gene mapping on most common multifactorial diseases like asthma which showed wide significance in genome sequencing. Thus by scanning genome, genome-wide linkage and hierarchical association analysis in six candidate gene, from their gene the asthma-related traits gene marker (ADAM33, PHF11, DPP10, GPR154, HLA-G, and CYFIP2) which cause asthma and also these are carrier gene which transmits the heredity asthma to next generation. Such interaction of the proteins encoded by these genes and the biological relevance of these signalling pathways in the development of asthma are still poorly understood.^[13]

Asthma is caused by a combination of poorly understood genetic and environmental factors. We have systematically mapped the effects of single nucleotide polymorphisms (SNPs) on the presence of childhood onset asthma by genome-wide association. We characterized more than 317,000 SNPs in DNA from 994 patients with childhood-onset asthma and 1,243 non-asthmatics, using family and case-referent panels. Here we show multiple markers on chromosome 17q21 to be strongly and reproducibly associated with childhood onset asthma in family and case-referent panels with a combined P value of $P < 10^{-12}$.^[14]

2. Alzheimer disease

Alzheimer's disease (AD) provides an example of many of these processes. ADtype pathology occurs in middle age in subjects with trisomy 21 (Downs syndrome), so this could be taken as a cytogenetic abnormality suggesting that an AD gene could be situated on chromosome 21. The gene for amyloid precursor protein (APP) was mapped to chromosome 21 ("forward genetics"). Genetic linkage studies with chromosome 21 markers in families with presenile, autosomal dominant AD implicated the region of the APP locus ("reverse genetics"), and when the APP gene was screened for mutations a few mutations were found which occurred in all the subjects with AD in some of these families and which were not

found in any subjects without AD. In cases of senile onset AD weak linkage and association was found to markers on chromosome 19, and one of the genes in this region codes for apolipoprotein E. This protein was known to exist in three common forms, e2, e3 and e4, and when association studies were carried out with this polymorphism it was found that the e4 allele was associated with a higher risk of AD, suggesting that this was directly involved in pathogenesis. Other families with presenile AD demonstrated linkage to markers on chromosome 14, and linkage studies eventually led to a narrow localisation. When genes in this region were screened, one was found to have mutations which again only occurred in subjects with AD and in no normal subjects. This gene was named presenilin 1 (PS1). Other researchers then searched for genes with similar coding sequences to PS1 and very soon afterwards found a second gene on chromosome 1 which contained mutations in other cases of presenile AD, and this was named presenilin 2 (PS2).^[15]

Genetic linkage in Alzheimer disease

Genetic linkage studies with chromosome 21 DNA markers and mutation analysis of the beta-amyloid protein precursor gene located in 21q21.3 have indicated that early-onset Alzheimer's disease (EOAD) is a heterogeneous disorder for which at least one other chromosomal locus exists. We examined two extended histopathologically confirmed EOAD pedigrees, AD/A and AD/B, with highly informative short tandem repeat (STR) polymorphisms and found complete linkage of the disease to a (CA)_n dinucleotide repeat polymorphism at locus D14S43 in 14q24.3 ($Z_{max} = 13.25$ at $\theta = 0.0$). Using additional chromosome 14 STR polymorphisms we were able to delineate the region containing the EOAD gene to an area of, at most, 8.9 centimorgans between D14S42 and D14S53, flanking D14S43 on both sides.^[16]

3. Diabetes mellitus

Mapping of diabetes-susceptibility genes is dependent on several factors, including the existence of a single major gene for susceptibility, genetic homogeneity, and the existence of appropriate clinical material. The power to detect susceptibility genes is dependent on the risks in relatives and the distance of genetic markers from the susceptibility genes. For insulin-dependent diabetes mellitus (IDDM), the best fitting risk models are those with a single major locus with residual polygenic factors. The major locus effect is likely represented by genes in the HLA complex, because specific genotypes have been found to affect IDDM

risk significantly. ^[17]The application of molecular genetic strategies to problems of inherited susceptibility to diabetes mellitus has generated considerable enthusiasm. Recently, mapping disease-susceptibility genes were tedious, time-consuming, and often unrewarding. The likelihood of mapping a disease locus to a known genetic marker locus was small because of the limited number of markers available. The genetic markers for these mapping studies were traits (e.g., the ABO blood group) whose location, number of alleles, and transmission were known in a population. With the strategy of restriction-fragment-length polymorphisms (RFLPs), many DNA markers have become available ^[18].

IDDM and IVIDDM are actively being investigated by gene mapping techniques. The pathogenesis of IDDM and that of NIDDM suffer from a common malady-their mode of inheritance is unknown ^[19, 20]. The most powerful predictor of risk for diabetes (either IDDM or NIDDM) is being an identical (monozygotic [MZ]) twin of a diabetic person. An important epidemiological finding for IDDM is that the MZ twin concordance rate is significantly <100%, more likely ranging from 25 to 50% ^[21]. The decreased MZ twin concordance rate implies that nonfamilial environmental factors play an important role in defining an individual's susceptibility to IDDM. The random environmental factors may be heterogeneous (prenatal, perinatal, cultural) and may further obscure the mode of genetic transmission. Heterogeneous environmental factors (environmental "triggers," e.g., viruses and exposures to pathogens) could effectively hide single gene effects. Unlike that for IDDM, the MZ twin concordance rate for NIDDM is close to 100%, indicating that the susceptibility is highly familial, with NIDDM determined by genetic or common environmental factors ^[22].

Estimated risks for diabetes among the relatives of diabetic people from four studies are shown Fig 1. ^[23, 24]. The degree of genetic relationship (the proportion of genes shared identically by descent between relatives) progresses from tertiary relatives (sharing 12.5% of genes) to secondary relatives (sharing 25% of genes) to first-degree relatives (sharing 50% of genes) to MZ twins (sharing 100% of genes).

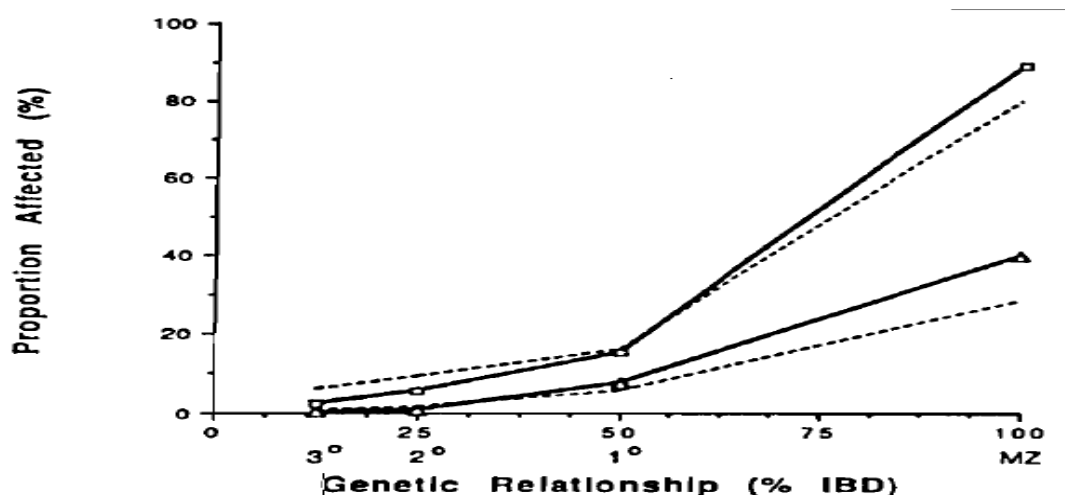


FIG.1. Lifetime risks for insulin-dependent diabetes mellitus (A) and multifactorial threshold model, the genetic factors combine non-insulin-dependent diabetes mellitus (0a) among relatives of diabetic patients. Solid lines observed risk estimates by degree of in an additive fashion to determine the susceptibility to digenic relationship; dashed lines, predicted risks under model. MZ, monozygotic twin; lo, 1st-degree relative; ZO, 2nd-degree relative; 3', 3rd-degree relative; IBD, identical by descent.

4. Schizophrenia

Schizophrenia is a complex biological disorder with multifactorial mode of transmission where non-genetic determinants are also played important role. It is now clear that it involves combined effect of many genes, each conferring a small increase in liability to the illness. Thus no causal disease genes or single gene of major effects, only susceptible genes are operating. Given this complexity, it comes as no surprise of the difficulty to find susceptible genes. However, schizophrenia genes have been found at last. Recent studies on molecular genetics of schizophrenia which focused on positional and functional candidate genes postulated to be associated with schizophrenia are beginning to produce findings of great interest. These include neuregulin (NRG1, 8p12–21), dysbindin, (DTNBP1, 6p22.3), G72 (13q34) / Damino acid oxidase (DAAO, 12q24), proline dehydrogenase (PRODH2, 22q11.21), catechol-O-methyltransferase (COMT, 22q11.21), regulator of G protein signalling (RGS4), 5HT2A and dopamine D3 receptor (DRD3).^[25]

Neuregulin The findings so far regarding the role of NRG1 in schizophrenia are wholly consistent. All published studies to date support an association between NRG1 and schizophrenia, but the functional significance of the risk haplotype is not yet known. There

are, however several clues as to how NRG1 contributes to illness. NRG1 has a role in expression and activation of glutamate and other neurotransmitter receptors as well as role in neurodevelopment, affecting cellular differentiation and neuronal migration. Post-mortem brain studies have shown that the ErbB3 gene, which is of the family of neuregulin receptors, is downregulated in those with schizophrenia.^[26]

Dysbindin The evidence for the dysbindin gene having a role in the etiology of schizophrenia is also turning out to be generally consistent. The gene is located within a linkage region previously identified by the same group on chromosome 6p22.3 It codes for a protein which binds to dystrobrevin, part of the dystrophin receptor complex, involved in the pathogenesis of muscular dystrophy. The protein is also found in a small subset of axons. Some of these axons localize to anatomical regions implicated in schizophrenia and are postulated to be involved in synaptic formation and maintenance, signal transduction and receptor gene expression. This may be via N-methyl-D-aspartate (NMDA) receptor functioning.^[27]

Protein dehydrogenase PRODH is another positional candidate for schizophrenia. It is a mitochondrial enzyme involved in transferring redox potential across the mitochondrial membrane, first identified by Liu *et al*^[28] in 2002. It was found on a 1.5Mb region on chromosome 22q11, a region previously implicated in the etiology of schizophrenia both by linkage studies and by work on velocardiofacial syndrome (VCFS)^[29]. In this disorder, the genetic defect is a microdeletion of the 22q11 regions, and sufferers have a 20–30% chance of a schizophrenia like syndrome^[30]. Subsequent studies by other researchers gave conflicting results. Clearly, more work is needed to determine the role of this gene in schizophrenia.

Catechol-O-methyltransferase Although numerous linkage and association studies have been carried out on this candidate gene, but until 2002 these failed to produce any conclusive results. Then a very large case control study, including over 700 probands and 4000 controls, by Shifman *et al*^[31] found a significant association between schizophrenia and COMT haplotype in Ashkenazi Jews. They suggested that the Val/Met polymorphism had only a moderate or no effect on schizophrenia risk and that more than one functional polymorphism within the COMT gene may be responsible. COMT codes for a gene product that inactivates catecholamines including dopamine. It does so by methylation hydroxyl groups. Like PRODH, this gene is located in the 22q11 linkage/VCFS microdeletion region and is, therefore, a prime candidate gene to be involved in the risk of developing schizophrenia.

5. Breast and ovarian cancer

Piri L. Welch et al. has undergone gene mapping on Germline mutations in the tumor suppressor genes *BRCA1* and *BRCA2* predispose individuals to breast and ovarian cancers. Progress in determining the function of *BRCA1* and *BRCA2* suggests that they are involved in two fundamental cellular processes: DNA damage repair and transcriptional regulation. They evaluate current knowledge of *BRCA1* and *BRCA2* functions to explain why mutations in *BRCA1* and *BRCA2* lead specifically to breast and ovarian cancer. The *BRCA1* and *BRCA2* genes contain unusually high densities of repetitive elements. These features of the *BRCA*s genomic regions contribute to chromosomal instability of these genes. They propose that somatic alterations of *BRCA1* and *BRCA2* are common and driven by rearrangements between repetitive elements. Inherited and somatic mutations occur in *BRCA1* and *BRCA2*; virtually all somatic mutations are the result of large genomic rearrangements. What are the consequences of such large somatic mutations of *BRCA1* and *BRCA2* in women with or without inherited mutations? The breast and ovary are estrogen-responsive tissues. Beginning in puberty, the breast epithelium proliferates rapidly in response to fluctuating levels of estrogen. They present a genetic model outlining how *BRCA*-deficient cells may gain uncontrolled proliferation leading to tumor formation. Central to this model of *BRCA*-mediated tumorigenesis is estrogen-mediated proliferation of breast and ovarian epithelium and the distinctive genomic context of the *BRCA* genes.^[32]

6. Haemophilia

Gitschier J *et al* detailed about the gene mapping in Haemophilia A which is most common inherited bleeding disorder in man, affecting approximately 1 male in 10,000. The disease is caused by a deficiency in the gene for factor VIII, a component of the intrinsic coagulation pathway. Due to the broad range of clotting activity in normal and heterozygous females, it is often difficult to confirm the status of women at risk for carrying the disease. A genetic marker in the form of a restriction fragment length polymorphism (RFLP) within or tightly linked to the factor VIII gene would serve as a tag for the haemophilia gene, thus allowing both accurate carrier detection and improved, earlier prenatal diagnosis by chorionic villi sampling. The recent isolation of the factor VIII gene has allowed a search for RFLPs within the gene, and we report here the identification of a common polymorphism within the factor VIII gene, revealed by the restriction enzyme *BclII*, which can be used diagnostically in about 42% of all families. Although the disease haemophilia A has been mapped to the distal

portion of Xq, the BclI RFLP makes possible higher-resolution genetic linkage mapping with respect to other polymorphic markers on this portion of the X chromosome. They have established close linkage of the factor VIII gene to several useful RFLP markers, including the highly informative marker St14. These markers should also be useful for prenatal diagnosis of haemophilia A and for detection of its carriers.^[33]

7. Autoimmune Thyroid Disease

The autoimmune thyroid diseases (AITD) are complex diseases that are caused by an interaction between susceptibility genes and environmental triggers. Genetic susceptibility, in combination with external factors (*e.g.*, dietary iodine), is believed to initiate the autoimmune response to thyroid antigens. Abundant epidemiological data, including family and twin studies, point to a strong genetic influence on the development of AITD. Various techniques have been used to identify the genes contributing to the etiology of AITD, including candidate gene analysis and whole genome screening. These studies have enabled the identification of several loci (genetic regions) that are linked with AITD, and in some of these loci putative AITD susceptibility genes have been identified. Some of these genes/loci are unique to Graves' disease (GD) and Hashimoto's thyroiditis (HT), and some are common to both diseases, indicating that there is a shared genetic susceptibility to GD and HT. The putative GD and HT susceptibility genes include both immune modifying genes (*e.g.*, human leukocyte antigen, cytotoxic T lymphocyte antigen-4) and thyroid-specific genes (*e.g.*, TSH receptor, thyroglobulin). Most likely these loci interact, and their interactions may influence disease phenotype and severity. It is hoped that in the near future additional AITD susceptibility genes will be identified and the mechanisms by which they induce AITD will be unravelled.^[34]

Corresponding causative gene in genetic disease ^[35]

Disease	Type of inheritance	Gene Responsible
Phenylketonuria (PKU)	Autosomal recessive	Phenylalanine hydroxylase (PAH)
Cystic fibrosis	Autosomal recessive	Cystic fibrosis conductance transmembrane
Sickle-cell anaemia	Autosomal recessive	Beta haemoglobin (HBB)
Albinism, oculocutaneous type II	Autosomal recessive	Oculocutaneous albinism II (OCA 2)
Huntington's disease	Autosomal dominant	Huntingtin (HTT)
Myotonic dystrophy type 1	Autosomal dominant	Dystrophiamyotonica-protein kinase (DMPK)
Rett's syndrome	X-linked dominant	Methyl-CpG-binding protein 2 (MECP2)
Spermatogenic failure, nonobstructive, Y-linked	Y-linked	Ubiquitin-specific peptidase 9Y, Y-linked (USP9Y)

Applications of gene mapping

Identification of genes is usually the first step in understanding a genome of a species; mapping of the gene is usually the first step of identification of the gene. Gene mapping is usually the starting point of many important downstream studies.

Molecular Medicine

Through genetic research, medicine will look more into the fundamental causes of diseases rather than concentrating on treating symptoms. Genetic screening will enable rapid and specific diagnostic tests making it possible to treat countless maladies ^[36]. DNA-based tests clarify diagnosis quickly and enable geneticists to detect carriers within families. Genomic information can indicate the future likelihood of some diseases. As an example, if the gene responsible for Huntington's disease is present, it may be certain that symptoms will eventually occur, although predicting the exact time may not be possible. Other diseases where susceptibility may be determined include heart disease, cancer, and diabetes ^[37]

Characterization of inheritance gene

Genetic mapping provides a powerful approach to identify genes and biological processes underlying any trait influenced by inheritance, including human diseases.

Infective disease

The human immunodeficiency virus (or HIV), is a difficult target to find and eradicate. The earliest tests for infection relied on the presence of antibodies to the virus circulating in the bloodstream. However, antibodies don't appear until many weeks after infection, maternal antibodies mask the infection of a newborn, and therapeutic agents to fight the infection don't affect the antibodies. PCR based gene mapping tests have been developed that can detect as little as one viral genome among the DNA of over 50,000 host cells.^[38] Infections can be detected earlier, donated blood can be screened directly for the virus, newborn can be immediately tested for infection, and the effects of antiviral treatments can be quantified.

Some disease organisms, such as that for tuberculosis, are difficult to sample from patients and slow to be grown in the laboratory. PCR-based gene mapping tests have allowed detection of small numbers of disease organisms (both live or dead), inconvenient samples. Detailed genetic analysis can also be used to detect antibiotic resistance, allowing immediate and effective therapy. The effects of therapy can also be immediately evaluated.

Identification of Genes Involved in Polygenic Disorders

Genetic linkage maps of the human genome are also useful for characterizing inherited diseases caused by more than one factor, often referred to as polygenic disorders. Among the diseases for which more than one gene is likely to be responsible are certain cancers, diabetes, and coronary heart disease [39]. For example, in a complex disorder such as coronary heart disease, blood plasma lipoproteins, the coagulation system, and elements of the arterial walls all play a role, so the number of genes involved can be very large [40]. Some scientists argue that the RFLP maps currently available, with markers spaced an average of 10 centimorgans apart, are a sufficient starting point for studies of polygenic diseases [41]. Higher resolution RFLP maps, such as a 1-centimorgan map, would no doubt simplify the job of identifying the genes responsible for polygenic disorders.

CONCLUSION

Genetic research made in human disease had spread wide range, where gene mapping is great tool in the characterisation of the defective gene which idea for targeting the specific gene to control the disease. Such advancement in gene mapping is rising every day, where above listed disease affects the livelihood of the human. Thus, further research done on gene mapping to attain perfect solution in the diagnosing the heredity disease.

REFERENCES

1. "Gene mapping Glossary Entry". *Genetics Home Reference*. Bethesda, MD: Lister Hill National Center for Biomedical Communications, an Intramural Research Division of the U.S. National Library of Medicine. 20130903. Retrieved 20130906.
2. Abecasis, G.R., Cherny, S.S., Cookson, W.O., Cardon, L.R., (2002). Merlin—rapid analysis of dense genetic maps using sparse gene flow trees. *Nat. Genet.* 30, 97-101. joint2011.stat.sinica.edu.tw/pdf/tutorial-1.pdf
3. David Altshuler, Mark J. Daly, and Eric S. Lander. Genetic Mapping in Human Disease. NIH Public Access Author Manuscript, *Science*. Author manuscript; available in PMC 2009 June 11. *Science*. 2008 November 7; 322(5903): 881–888. doi:10.1126/science.1156409.
4. Markert CL, Moller F (1959). Multiple forms of enzymes: Tissue, ontogenetic and species specific patterns. *Proc. Natl. Acad. Sci. USA* 45: 753-763.
5. Semagn K, Bjørnstad Å, Ndjiondjop MN (2006). An overview of molecular marker methods for plant. *Afr. J. Biotechnol.* 25:2540-2569.
6. Semagn K, Bjørnstad Å, Skinnes H, Marøy AG, Tarkegne T, William M (2006). Distribution of DArT, AFLP, and SSR markers in a genetic linkage map of a doubled-haploid hexaploid wheat population. *Genome* 49: 545–555.
7. Paterson AH (1996). Making genetic maps. In: Paterson AH (ed.) *Genome mapping in plants*, San Diego, California: Academic Press, Austin, Texas, pp. 23–39.
8. Collard BCY, Jahufer MZZ, Brouwer JB, Pang ECK (2005). An introduction to markers, quantitative trait loci (QTL) mapping and marker-assisted selection for crop improvement: The basic concepts. *Euphytica* 142: 169-196.
9. www.nature.com/.../principle-of-independent-assortment-law-of-independent
10. <https://www.genome.gov/10000715>
11. isogg.org/wiki/Chromosome_mapping/en
12. Olson M *et al.* A common language for physical mapping of the human genome. *Science*. 1989 Sep 29; 245(4925):1434-5. PMID: 2781285
13. Laitinen T Gene mapping in asthma-related traits, Ref: *Methods Mol Biol.* 2007;376:213-34, www.ncbi.nlm.nih.gov/pubmed/17984548
14. Miriam F. Moffatt Genetic variants regulating *ORMDL3* expression contribute to the risk of childhood asthma
15. DaveCurtis (dcurtis@hgmp.mrc.ac.uk) <http://www.davecurtis.net/dcurtis/lectures/mapgens.html> December 2000
16. Van Broeckhoven C¹, Backhovens H, Cruts M, De Winter G, Bruyland M, Cras P, Martin JJ Mapping of a gene predisposing to early-onset Alzheimer's disease to chromosome14q24. *Send to: Nat Genet.* 1992 Dec; 2(4):335-9.
17. STEPHEN S. RICH Perspectives in Diabetes Mapping Genes in Diabetes Genetic Epidemiological Perspective.
18. Botstein DR, White RL, Skolnick MH, Davis RW. Construction of a genetic map in humans using restriction fragment length polymorphisms *Am J Hum Genet* 32:314-31, 1980

19. Bartrosa J, Rich SS: Genetics of insulin-dependent diabetes. In Immunogenetics of Endocrine Disorders. Farid NR, Ed. New York, Liss, 1988, p. 1153-202
20. O'Rahilly S, Wainscoat JS, Turner RC: Type 2 (non-insulin-dependent) diabetes mellitus: new genetics for old nightmares. *Diabetologia* 31:407-14. 1988
21. Rotter JI, Vadheim CM, Rimo DL: Genetics of diabetes mellitus. In Diabetes Mellitus. *Diabetes Mellitus: A Practical Approach*. 4th ed. Rifkin H, Porte D Jr, Eds. New York, Elsevier. 1990. p. 378-413
22. Neaman B, Selby JV, King MC, Slemenda C, Fabsitz R, Friedman GD: Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. *Diabetologia* 30:763-68. 1987
23. Zimmet P. Type 2 (non-insulin-dependent) diabetes: an epidemiological overview. *Diabetologia* 22:399-411, 1982
24. Degnbol B, Green A: Diabetes mellitus among first and second degree relatives of early onset diabetics. *Ann Hum Genet* 42:25-47, 1978
25. MohdRazaliSalleh, The Genetics of Schizophrenia, The Malaysian journal of medical science, Malays J Med Sci. 2004 Jul; 11(2): 3–11.
26. Law A. Neuregulin 1 in the human brain. *Am J Psychiatry*. 2003;160:1392. [PubMed]
27. Benson M, Newey S, MartinRebbon E, *et al.* Dysbindin, a novel coiled-coil containing protein that interacts with the dystrobrevins in muscle and the brain. *J Biol Chem*.2001;276:24232–24241. [PubMed]
28. Liu H, Heat SC, Sobin C, *et al.* Genetic variation at the 22q11 PRODH2 / DGCR6 locus presents an unusual pattern and increases susceptibility to schizophrenia. *Proc Natl AcadSci USA*. 2002;99:3717–3722. [PMC free article] [PubMed]
29. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velocardiofacial syndrome. *Arch Gen Psychiatry*. 1999;56:940–945. [PubMed]
30. Murphy KC. Schizophrenia and velocardiofacial syndrome. *Lancet*. 2002;359:426–430. [PubMed]
31. Shifman S, Bronstein M, Sternfield M, *et al.* A highly significant association between a COMT haplotype and schizophrenia. *Am J Hum Genet*. 2002;71:1926–1302. [PMC free article] [PubMed]
32. Piri L, Welch and Mary-Claire King, *BRCA1* and *BRCA2* and the genetics of breast and ovarian cancer, Departments of Medicine and Genetics, Box 357720, University of Washington, Seattle, WA 98195-7720, USA, <http://hmg.oxfordjournals.org/content/10/7/705>
33. Gitschier J, Drayna D, Tuddenham EG, White RL, Lawn RM Genetic mapping and diagnosis of haemophilia A achieved through a BclI polymorphism in the factor VIII gene, *Nature*. 1985 Apr 25-May 1;314(6013):738-40
34. Yaron Tomer, and Terry F. Davies, Searching for the Autoimmune Thyroid Disease Susceptibility Genes: From Gene Mapping to Gene Function, *Endocrine Reviews*, 2003 - press.endocrine.org, <http://press.endocrine.org/doi/abs/10.1210/er.2002-0030#sthash.H8J7IEGT.dpuf>
35. Heidi Chial, Ph.D. , Rare Genetic Disorders: Learning About Genetic Disease Through Gene Mapping, SNPs, and Microarray Data, *Nature Education* 1(1):192
36. What is the Human Genome Project. Obtained 10/13/99. http://www.ornl.gov/TechResources/Human_Genome/home.html
37. What can we expect from the Human Genome Project. Obtained 10/13/99 http://www.accessexcellence.org/AB/IE/What_Can_We_Expect.html
38. Kwok S *et al.* "Identification of HIV sequences by using *in vitro* enzymatic amplification and oligomer cleavage detection." *J. Virol.* vol. 61(5) pp. 1690-4 (1987).
39. Lander, E. S., and Green, P., "Construction of Mul- 28 29 tilocus Genetic Linkage Maps in Humans, " *Proceedings of the National Academy of Sciences USA* 84:2363-2367, 1987,
40. Scott, J., "Molecular Genetics of Common Diseases," *British Medical Journal* 295:769-771, 1987.
41. Donis-Keller, H., Green, P., Helms, C., *et al.*, "A Genetic Linkage Map of the Human Genome," *Cell* 51:319-337, 1987.