STUDIES ON HUMAN X-CHROMOSOMAL DISORDER

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ABSTRACT

Conditions caused by a change in the number or structure of chromosomes are known as chromosomal disorders. There are over 3000 chromosomal disorders which make a major contribution to human morbidity and mortality. A very high number of both Mendelian and other diseases (some of which are incurable, till today) have been found to have their origins on the X chromosome. Although there are numerous X-linked disorders, few very important diseases were considered to be analyzed using a bioinformatics approach. The discovery may throw some light on various findings which could be very useful in comprehending the mechanisms underlying the causes and occurrence of these diseases at genomic level. Allelic variants of 11 single gene disorders related to X- chromosome were collected from OMIM and their gene expression was obtained from GENE CARDS. The results were compiled and plotted on a pie chart. In X-linked dominant and recessive disorders genes were taken from OMIM, tissue specific expression of these genes and their locus points was obtained. In a total of 41 genes responsible for XLMR which are present on the X-Chromosome, 13 genes which are position specific, were found to cause mental retardation. These 41 genes were analyzed and sufficient information for causing XLMR was found in 39 genes. HEMA was found to have the highest number of allelic variants and expression of the genes causing X-chromosomal disorders were found to be maximum in brain. Mental retardation was found to be the major effect which could be attributed to significant genes present on the X-chromosome. We found that 14 loci were responsible for mental retardation, in which Xp11 coded for 22% genes responsible for it. “X” is the KEY for hereditary LOCK.

Keywords : *Gene Cards, Chromosome, Xlmr, Omim, Omim Key, Hereditary Lock, X-Chromosome*

1. INTRODUCTION

The human X-chromosome has a unique biology that was shaped by its evolution as the sex-chromosomes. Analysis of diseases originating from the X-chromosome is an area of major concern in today’s world of biological research. It has been found that the unique biology of these chromosomes is a result of its evolution into sex- chromosomes in both males and females (Ross MT et al., 2005; Valley CM,

Willard HF 2006; Correia HR et al., 2005). A large number of Mendelian diseases are documented for the X-chromosome. Considerable numbers of disease conditions have been associated with the X-chromosome because the phenotypic consequence of a recessive mutation for any gene that has no active counterpart on the Y chromosome is manifested directly in males. This holds a unique place in the history of medical genetics.

Changes that affect entire chromosomes or segments of chromosomes can cause problems with growth, development, and function of the body systems. These changes can affect many genes along the chromosome and alter the proteins made by these genes. Conditions caused by a change in the number or structure of chromosomes are known as chromosomal disorders. There are over 3000 chromosomal disorders which make a major contribution to human morbidity and mortality (Rasmussen SA et al., 2006; Papavramidis ST et al., 2006; Swerdlow AJ et al., 2005; Christensen MS et al., 2005; de Almeida MQ et al., 2005; Lehrnbecher T et al., 2004; Kockler M et al., 2002; Fasnacht MS, Jaeggi ET 2001; St-Vil D et al., 1996; Schmutz SM et al., 1996). Its impact represents a major cause of fetal loss but the frequency is quite different in neonates (0.7%) as compared to the abortuses (about 50%), since most of the chromosomal aberrations and aneuploidies are lethal in utero (Schmutz SM et al., 1996).

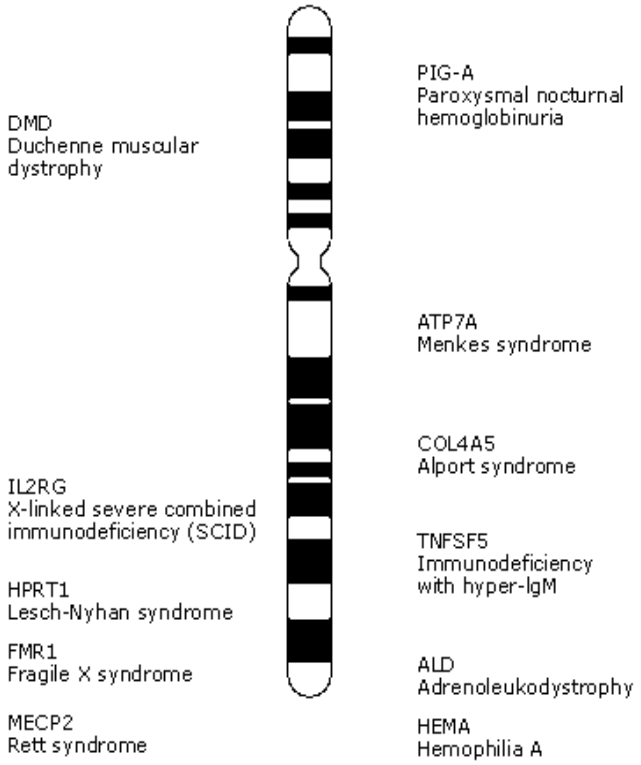
X-Linked diseased genes were manually curated and analyzed using OMIM database. We have classified the genes causing diseases according to X-linked dominants contributing only17%, whereas, X-linked recessive up to 39%. Interestingly, 44% are yet to be classified as recessive or dominant. X-linked dominant disorders are caused by mutations in genes on the chromosome (Mahler M et al 1986) and its recessive disorders are also caused by mutations in genes on the X-chromosome (Davies K E et al 1987).

This observation may certainly give an insight on various findings, which could also be very useful in the understanding of genetic diseases at genomic level. We have analyzed all the genes based on their loci and their percentage in X- chromosomal region. Further, in the analysis to establish the tissue specificity of these genes it is revealed that most of these genes are expressed in neurons. Mental retardation has been found to be the major consequence with a large number of genes contributing to it being located in the X-chromosome. It is also observed that 14 loci are responsible for mental retardation, in which Xp11 codes for 22% genes mainly responsible for mental retardation. A comparative gene localization analysis highlights that, Xq28 gene rich region is with 46%, but Xp22 locus is prone to many diseases with 42%, where as all the other regions form just 12% for its

contribution. No wonder "X" is the KEY for hereditary LOCK!

A review of work has done on both Mendelian and other diseases (some of which are incurable, till today) have been found to have their origins on the X-chromosome. Although there are numerous X-linked disorders, few very important diseases were considered to be analyzed using a bioinformatics approach. Various x-linked disorders: - The X-chromosome likely contains between 900 and 1,200 genes. Genetic disorders that are due to mutations in genes on the X-chromosome are described as X linked. The x-linked disorders are clearly shown in the figure below.

X-linked disorder



Interleukin 2 receptor, gamma (severe combined immunodeficiency) contains 8 exons and spans approximately 4.2 kb whose cytogenic location is Xq 13.1 on the long arm. The IL2RG gene provides instructions for making a protein called the common gamma chain which is located on the surface of immature blood-forming cells in bone marrow. Southern blot analysis suggested that the gene is present in single copy. More than 200 different mutations in the IL2RG gene have been identified in people with X-linked severe combined immunodeficiency (SCID) (Puck JM et al., 1993).

Hypoxanthine phosphoribosyltransferase 1 (Lesch-Nyhan syndrome) located on the long (q) arm of the X-chromosome at position 26.1. It provides instructions for producing an enzyme called hypoxanthine phosphoribosyltransferase-1 which helps to convert the purine hypoxanthine into inosine monophosphate and the purine guanine into guanosine monophosphate which in turn are necessary intermediates in the process of recycling purines to ensure that cells have a an abundant supply of building blocks for the production of DNA and RNA. Lesch-Nyhan syndrome is caused by mutations in the HPRT1 gene. These mutational changes result in either nonfunctional or very low-function hypoxanthine phosphoribosyltransferase 1 which can cause gouty arthritis (arthritis caused by uric acid in the joints), kidney stones, and bladder stones (Rinat C et al., 2006; De

Gregorio L et al., 2005; Mizunuma M et al., 2004; O'Neill JP 2004; Yamada Y. 2003; Schretlen DJ et al., 2001; Rivero MB et al., 2001; De Gregorio L et al., 2000).

The fragile X mental retardation-1 (FMR1) gene, located at Xq27.3, codes for the mRNA-binding fragile X mental retardation protein (FMRP). The fragile X syndrome is the most common form of inherited mental retardation and accounts for approximately 40% of cases with X-linked mental retardation. Other characteristics of the fragile X syndrome include a wide range of cognitive, behavioral, and physical features such as variable IQ (profound to mild mental retardation), autistic-like features, hyperactivity, increased testicular volume, macrocephaly, and large ears (Muddashetty RS et al., 2007; Westmark CJ, Malter JS 2007; Antar LN et al., 2006; Antar LN et al., 2005; Zhang YQ et al ., 2005; Antar LN et al., 2004; Funakoshi T et al 2003; de Diego-Otero Y 2001).

Duhcenne muscular dystrophy located at Xp21.2 is a group of muscle diseases which have three features in common: they are hereditary; they are progressive; and each causes a characteristic selective pattern of weakness. The gene for DMD, found on the X-chromosome, encodes a large protein - dystrophin. Dystrophin is required inside muscle cells for structural support: it is thought to strengthen muscle cells by anchoring elements of the internal cytoskeleton to the surface membrane (De Lima AR et al., 2007).

Phosphatidylinositol N-acetylglucosaminyltransferase subunit A located at Xp22.1, encodes a protein required for synthesis of N-acetylglucosaminyl phosphatidylinositol (GlcNAc-PI), the first intermediate in the biosynthetic pathway of GPI anchor. The distinct and rather peculiar characteristics of paroxysmal nocturnal hemoglobinuria (PNH) is characterized by a decreased number of red blood cells (anemia), and the presence of blood in the urine (hemoglobinuria) and plasma (hemoglobinemia), which is evident after sleeping (Richards SJ et al., 2007; Almeida AM et al., 2006; Krauss JS 2003; Robert D et al., 2003; Rosse WF 1997; Rotoli B, Boccuni P 1995; Kawagoe K et al., 1994; Bessler M et al., 1994).

ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome) located on the long (q) arm of the X-chromosome between positions 13.2 and 13.3, provides instructions for making a protein that is important for regulating copper levels in the body. This protein is found in most cells except liver cells. Menkes' disease is transmitted as an X-linked recessive pattern. Sufferers cannot transport copper, which is needed by enzymes involved in making bone, nerves and other structures (Paulsen M et al., 2006; Madsen E, Gitlin JD 2007; Tumer Z et al., 1999; La Fontaine SL et al.,

1998; La Fontaine S et al., 1998; Mercer JF 1998).

Cytokine receptor common gamma chain (precursor) (CD40LG) encoded by the gene located at Xq26 is expressed on the surface of T cells. It regulates B cell function by engaging CD40 on the B cell surface. A defect in this gene results in an inability to undergo immunoglobulin class switch and is associated with hyper-IgM syndrome (Apoil PA et al., 2007; Schuster A et al., 2005).

ATP-binding cassette, sub-family D (ALD), member 1 located on the long (q) arm of the X-chromosome at position 28, provides instructions for producing one component of a transport protein that is located in the membrane surrounding peroxisomes. X-linked adrenoleukodystrophy is caused by mutations in the ABCD1 gene. In this disease, the fatty covering (myelin sheath) on nerve fibers in the brain is lost, and the adrenal gland degenerates, leading to progressive neurological disability and death (Takahashi N et al., 2007; Ferrer I et al., 2005; Hershkovitz E et al., 2002).

Collagen alpha -5(4) chain (COL4A5) (Alport syndrome) located on the long (q) arm of the X-chromosome at position 22, carries the instructions for making one component of type IV collagen, which is a flexible protein that forms complex networks. Specifically, this gene makes the alpha5 (IV) chain of type IV collagen. Mutations in the COL4A5 gene cause approximately 80 percent of Alport syndrome cases. Alport syndrome (AS) is a genetic disease in which a collagen mutation affects the kidneys, ears, and the eyes (Harvey SJ et al., 2003; van der Loop FT et al., 2000; Kashtan CE 1999; Harvey SJ et al., 1998; Colville DJ, Savige J 1997; Rossetti S et al., 1997).

Methyl CpG binding protein 2 (Rett syndrome) located on the long (q) arm of the X-chromosome at position 28, seems to be important for the function of nerve cells in the brain and is present in high levels in mature nerve cells. Researchers believe that the MeCP2 protein is also involved in processing molecules called messenger RNA (mRNA), which serve as genetic blueprints for making proteins. MECP2 mutations alter the structure of the MeCP2 protein or reduce the amount of protein that is produced. As a result, cells do not have enough MeCP2 protein to bind to DNA and silence other genes. MECP2 gene may also disrupt alternative splicing of proteins critical for communication between nerve cells

Coagulation factor VIII, procoagulant component (hemophilia A) located on the long (q) arm of the X-chromosome at position 28, carries instructions to make a protein called coagulation factor VIII, which is critical for normal blood clotting. After an injury, blood clots protect the body by sealing off damaged blood vessels and preventing

further blood loss. Hemophilia A is a hereditary blood disorder that results in abnormal bleeding (Piétu G et al., 1988; Hoyer LW 1987; Graham JB et al., 1975).

Thus, all the X-linked disorders could be attributed to certain aberrations in the X-chromosome itself, which in turn could be associated with the genes residing on it. The disorders could be directly related to abnormalities either in the gene structure or function. A change in gene structure would give a non-functional or a defective protein product that is instrumental in causing a disease. (Sedlácek Z 1995).

2. LITERATURE REVIEW

X- Linked diseases are single gene disorders that reflect the presence of defective genes on the X-chromosome. This chromosome is present as two copies in females but only as one copy in males. The inheritance patterns of X-linked diseases in family pedigrees are complicated by the fact that males always pass their X-chromosome to their daughters but never to their sons, whereas females pass their X-chromosome to daughters and sons with equal. (Ginns E I *et al., 1998)*

X-linked dominant disorders are caused by mutations in genes on the X-chromosome. Only a few disorders have this inheritance pattern. Males are more frequently affected than females, and the chance of passing on an X-linked dominant disorder differs between men and women. The sons of a man with an X-linked dominant disorder will not be affected, and his daughters will all inherit the condition. A woman with an X-linked dominant disorder has a 50% chance of having an affected daughter or son with each pregnancy. Some X-linked dominant conditions, such as Aicardi Syndrome, are fatal to boys; therefore only girls have them (and boys with Klinefelter Syndrome). (Maheler M *et al., 1986*)

X-linked recessive disorders are also caused by mutations in genes on the X-chromosome. Males are more frequently affected than females, and the chance of passing the disorder differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene. With each pregnancy, a woman who carries an X-linked recessive disorder has a 50% chance of having sons who are affected and a 50% chance of having daughters who carry one copy of the mutated gene. Some of the X-linked genetic disorders are listed below. (Davies K E *et al., 1987)*

A genetic diagnosis of X-linked amelogenesis imperfect found using evolutionary datasets that with amelogenin (AMEL) in 80 amniotes (52 mammalian and 28 reptilian sequences (Delgado S, *et al.*, 2007). Mutations of the X-chromosome amelogenin gene (AMELX) are associated with amelogenesis imperfect (AI) phenotypes. The purpose here was to present a systematic nosology for reporting

the genomic, cDNA and protein consequences of AMELX mutations associated with AI (Hart PS *et al*., 2002).

X-linked agammaglobulinemia (XLA) is a heritable immunodeficiency disorder that is caused by a differentiation block leading to almost complete absence of B lymphocytes and plasma cells. The affected protein is a cytoplasmic protein tyrosine kinase, Bruton's agammaglobulinemia tyrosine kinas' *(Btk)* (Vihinen M *et al*., 2000). X-linked agammaglobulinemia (XLA) is a hereditary immunodeficiency caused by mutations in the gene encoding Bruton tyrosine kinase (BTK). XLA-causing mutations are collected in a mutation database (BTK base), this BTK base is implemented with the MUT base program suite, which provides an easy, interactive, and quality controlled submission of information to mutation databases (Valiaho J *et al*., 2006). XLA gene which codes the BTK tyrosine kinase and were identified as responsible for Bruton's disease which is the most frequently primary X-linked immunodeficiency. This is the most frequent immunodeficiency & infections affected with hypo/ agammaglobulinemia and can be stopped by Genetic advice and constructing a database (Rodriguez C *et al.,* 2006). Bruton's tyrosine kinase (BTK) which is a member of Tec family of protein is encoded by the gene that when mutated causes the primary immunodeficiency disease X-linked agammaglobulinemia (XLA) in humans and X-linked immunodeficiency (Xid) in mice. Mutations affect BTK block B-lymphocyte development. The wealth of information is compiled in the mutation database for XLA (BTKbase) (Lindvall JM *et al*., 2005). Clontech Atlas Human Hematology/Immunology cDNA microarrays, containing 588 genes, and Affymetrix oligonucleotide U95Av2 human array complementary to more than 12,500 genes to get a global view of genes expressed in Epstein-Barr virus (EBV)-transformed B cells and genes regulated by Bruton's tyrosine kinase (BTK). These findings demonstrate for the first time the use of microarray to study the influence of BTK mutations (Islam TC *et al.,* 2002).

The most common congenital deformity of the chest wall is pectus excavatum, a malformation which causes the body of the sternum to be displaced, producing a depression and affects child. Using the Children's Surgical Specialty Group database this can be known and Pedigree analysis of 34 families provides evidence that pectus excavatum is an inherited disorder, possibly of connective tissue (Creswick HA *et al*., 2006).

Mental retardation (MR) is a non-progressive condition characterized by a significant impairment of intellectual capabilities with deficit of cognitive and adaptive functioning caused by mutations in X-chromosome. The XLMR(x-linked mental retardation) bank is an innovative biological database which has the collection

of information. Mental retardation (MR) is a common disorder results from failure to develop cognitive abilities and intelligence level appropriate for the age group. There are more than 1000 entries in Online Mendelian Inheritance in Man (OMIM) database under the name of mental retardation. Mental retardation (MR) poses significant challenges for clinicians and scientists complicated by the extraordinary heterogeneity of genetic MR disorders. (Pescucci C *et al*., 2007; Pandey UB *et al.*, 2004; Inlow JK *et al*., 2004).X-linked nonspecific mental retardation (MRX) accounts for approximately 25% of mental retardation in males. A number of MRX loci have been mapped on the X-chromosome, reflecting the complexity of gene action in central nervous system (CNS) specification and function. The MRX gene oligophrenin (OPHN1) and the brain-specific ephrinB1 (EFNB1) gene, in DNA from affected males excluded their candidacy for MRX81, suggesting a novel disease gene (Annunziata I *et al.*, 2003). Mental retardation segregates as an X-linked trait. Characteristic clinical features include short stature, prominent lower lip, small testes, and muscle wasting of the lower legs, kyphosis, joint hyperextensibility, abnormal gait, tremor, and ion. In summary, this family appears to have a new XLMR syndrome located at Xq24-q25. In this case XLMR databases are used (Cabezas DA *et al*.,2000).

X-Linked inhibitor of apoptosis protein (XIAP) is a promising molecular target for the design of new anticancer drugs aiming at promoting apoptosis in cancer cells. We have previously identified embelin as an inhibitor of XIAP through computational structure-based database screening. This database screening lead to the identification of new and more potent inhibitors. Inhibitor of apoptosis (IAP) proteins regulate programmed cell death by using baculovirus IAP repeat (BIR) domain databases thereby inhibiting members of the caspase family of proteases. The X-linked inhibitor of apoptosis (XIAP) is a promising new molecular target for the design of novel anticancer drugs aiming at overcoming apoptosis-resistance of cancer cells to chemotherapeutic agents and radiation therapy. The X-linked inhibitor of apoptosis (XIAP) is a promising new molecular target for the design of novel anticancer drugs aiming at overcoming apoptosis-resistance of cancer cells to chemotherapeutic agents and radiation therapy. (Chen J *et al*.,2006 ; Sweeney MC *et al* .,2006 ; Nikolovska-Coleska Z *et al*.,2004).

Fabry disease is an X-linked lysosomal storage disorder characterized by multi-organ dysfunction, including hearing loss - mainly sensorineural. The recent introduction of enzyme replacement therapy (ERT) has resulted in improvements in renal and cardiac function, and quality of life. When ERT with agalsidase alpha which improves hearing. Fabry disease is caused by a deficient activity of the enzyme alfa-galactosidase A ,which results in

accumulation of globotriaosylceramide (Gb3)leading to multiorgan dysfunction and early death and the database Fabry Outcome Survey (FOS)of Spain gives us the opportunity to assess the efficacy of this therapy. This can be overcome by Enzyme replacement therapy (ERT). (Rivera Gallego A *et al.*,2006; Ramaswami U *et al.*,2006; Beck M *et al.*,2004).

The natural history and mechanisms involved in the cerebrovascular complications of Fabry disease using data reported in FOS-- the Fabry Outcome Survey. Fabry disease leads to accumulation of globotriaosylceramide in nearly all tissues, including the blood vessels, kidney, myocardium, and nervous system. Data were obtained from the Fabry Outcome Survey. ERT (Enzyme replacement therapy) with agalsidase alfa significantly reduces pain and improves quality of life in patients with Fabry disease. Europe-wide database is used for the Fabry Outcome Survey (FOS) (Hajioff D *et al.*, 2006; Hoffmann B *et al.*, 2005; Mehta A *et al.*, 2005; Thadhani R *et al.*, 2002).

X-linked bleeding disorder hemophilia A is caused by congenital deficiency of factor (F) VIII. A mutation database with the largest number of mutations being single nucleotide substitutions distributed throughout the gene. Here, oligonucleotide DNA microarray technique is used to find the mutations. Hemophilia A or B is an X-linked bleeding disorders due to decreased blood levels of coagulants. Clotting factors namely prophylaxis and later placebo were used. This is done by Randomized controlled trials (RCTs). At the last they found placebo more efficient than prophylaxis as a clotting factor. The search strategy uses comprehensive electronic database searches and hand searches of journals and abstract books. Hemophilia B is an X-linked recessive, bleeding disorder caused by mutations in the factor IX gene. The data confirm the remarkable heterogeneity of the mutational spectrum in hemophilia B among affected families. (Stobart K *et al.*,2005; Stobart K et al.,2006 ;Berber E *et al.*,2006; Mahajan A *et al.*,2004). Hemophilia B is an X-linked recessively inherited bleeding disorder caused by heterogeneous mutations spanning the entire factor IX gene. The hemophilia B database is examined to identify specific nucleotides in the FIX gene that are mutated in relatively large number of patients and the variability (if any) in the mutational hotspots at CpG dinucleotides (Mukherjee S *et al.*,2003). Hemophilia a (HEMA) is an X-linked bleeding disorder caused by mutations in the factor VIII gene (F8C). The results of mutation analysis on 89 hemophiliac males showed presence of a disease-causing mutation in 80 individuals (90%, 95% CI of 82%-95%). This finding is supported by similar observations in the international database for hemophilia A mutations (Hamsters). This issue raises the importance of genotypes at other loci that

can act as modifiers for the phenotype (Citron M *et al.,* 2002). Hemophilia A is an X-linked bleeding disorder caused by reduced or absent FVIII (FVIII) protein caused by mutations in the FVIII gene. We have used Southern blotting and chemical mismatch analysis (CMA) to identify the mutations. Seventeen of the base-pair substitutions are missense, two nonsense, and two are splice-site mutations. Unusually, a missense mutation, as well as deletion and splice-site mutations, was found to be associated with exon-skipping events (Theophilus BD *et al.,* 2001).

X-linked nonspecific mental retardation (MRX) accounts for approximately 25% of mental retardation in males. A number of MRX loci have been mapped on the X-chromosome, reflecting the complexity of gene action in central nervous system (CNS) specification and function. The MRX gene oligophrenin (OPHN1) and the brain-specific ephrinB1 (EFNB1) gene, in DNA from affected males excluded their candidacy for MRX81, suggesting a novel disease gene (Annunziata I *et al.,* 2003). The malfunctioning of X-linked genes causes mental retardation. DNA chip technology would hopefully allow (re)screening large numbers of patients. The first edition of the XLMR database describes about this (Chiurazzi P *et al.,* 2001).

X-linked chronic granulomatous disease (CGD) is identified by Molecular identification and clinical characterization of genetic mutations in patient's mutations in patients. The causative gene is CYBB gene. This is described in X-CGDbase but not in detail (von Goessel H *et al*., 2006).

Diagnosis of specific forms of primary hereditary ichthyoses (PHI) was identified by reviewing the epidemiological and clinical features of these patients. Specifically designed protocol forms are used to extract epidemiological and clinical data from the study patients' medical records and entered into a computer database and analyzed using standard statistical software (Al- Zayir AA *et al*., 2006).

About 25% of X-linked genes may escape inactivation at least to some degree and proved that the X-linked genes showed over expression. Comparison is made between male and female and the result shows that female is found to be over expressed when compared to male (Talebizadeh Z *et al.,* 2006).

The human sub-chromosomal region Xq28 is the cause for many diseases and many analysis led to this identification. A relational web-accessible database with comprehensive query options integrating all experimental data has been developed for this purpose (Kolb-Kokocinski a *et al.,* 2006).

A mammalian-specific expansion of more than 20 rapidly-evolving genes on

human chromosome Xq22.1. led to the generation of chimerical genes. Evolution events occurred within and between genes from three separate protein families ([BEX], [WEX] and [GASP]), which often are expressed in mammalian brains and associated with receptor mediated signaling and apoptosis (Winter EE *et al*., 2005).

The data collection for pregnancies and babies was presented by the ESHRE PGD Consortium for one calendar year (2002). The data were collected using a Filmmaker Pro database and divided into referrals, cycles, pregnancies and babies (Harper JC *et al*., 2002).

Kallmann's syndrome corresponds to a loss of sense of smell and hypogonadotrophic hypogonadism. Defects in anosmin-1 result in the X-linked inherited form of Kallmann's syndrome. These solution structures account for the known biological function of anosmin-1, in particular its ability to interact with its three macromolecular ligands. (Hu Y *et al*., 2005).

Massively parallel signature sequencing (MPSS) generates millions of short sequence tags corresponding to transcripts from a single RNA preparation. Genes that are clustered in tandem within a 125-kb region on Xq26.3 are responsible and CT45 was found to be frequently expressed in both cancer cell lines and lung cancer specimens (Chen YT *et al*., 2005).

The esterification of alcohols such as sterols, diacylglycerols, and monoacylglycerols with fatty acids represents the formation of both storage and cytoprotective molecules which several disease pathologies, including atherosclerosis and obesity. The exp of DGAT2 is described here in Saccharomyces cerevisiae strains. In situ hybridizations demonstrate a differentiation-specific expression pattern within the human sebaceous gland for the two AWAT genes (Turkish AR *et al.*, 2005).

Coffin-Lowry syndrome (CLS) is an X-linked semi-dominant condition with learning difficulties and dysmorphism caused by mutations in the gene RSK2. Epilepsy is reported as a feature and cataplexy have been labeled as a startle response and hyperekplexia (Stephenson JB *et al*., 2005).

The cloning and characterization of a novel human lipoma HMGIC fusion partner-like 1 (LHFPL1) gene, isolated from human brain cDNA library, and mapped to Xq23 by browsing the UCSC genomic database. LHFPL1 contains an ORF encoding a protein with a signal peptide sequence and three transmembrane regions (Huang C *et al*., 2004).

The X-linked Emery-Dreifuss muscular dystrophy (X-EDMD) is a hereditary muscle disorder associated with

cardiac involvement. The clinical relevance of X-EDMD in heart conduction system disease is very low. It should, however, be included into the diagnostic work-up of young male individuals with idiopathic cardiac conduction disturbances (Vytopil M *et al.*, 2004).

Obesity shows high heritability and is caused by the genes that affect adipose mass in humans. The majority of obesity syndromes can be distinguished by the presence of mental retardation (Delrue MA *et al*., 2004).

Trichromatic color vision in humans results from the combination of red, green, and blue photopigment opsins. The X-linked long-wave "red" opsin gene (OPN1LW) is the causative gene. The results suggest that subtle changes in L-cone opsin wavelength absorption may have been adaptive during human evolution (Vytopi BC *et al*., 2004).

X-linked dominant hypophosphatemic rickets (XLHR) is a hereditary metabolic bone syndrome rarely associated with progression to irreversible tertiary hyperparathyroidism. Tertiary hyperparathyroidism is a rare but recognized complication of XLHR (Savio RM *et al*., 2004). Inactivating mutations and/or deletions of PHEX (Phosphate-regulating gene with Homologies to Endopeptidase on the X-chromosome) are responsible for X-linked hypophosphatemic rickets in humans. The present study indicates that three homologues are likely involved in the phosphate homeostasis of Drosophila (Ito M *et al.*, 2004).

Aarskog syndrome is an X-linked disorder characterized by faciogenital dysplasia and short stature. The present study sets out to determine the effect of growth hormone (GH) therapy in patients with Aarskog syndrome enrolled in KIGS—the Pharmacia International Growth Database (Darendeliler F *et al.*,2003).

Among the possible mechanisms for modifying intron size, it has been suggested that the insertion of transposable elements might have an important role in driving intron evolution. Statistical analysis of total intron length for each pair of paralogous genes provided no evidence for a larger size of introns in the gene copies located on the X-chromosome (Cardazzo B *et al*., 2003).

The microphthalmia with linear skin defects syndrome (MLS) is an X-linked dominant disorder with male lethality. The MLS syndrome is caused by segmental monosomy of the Xp22.3 region. End-sequencing and database analysis revealed a YAC insert of at least 416 kb containing the genes HCCS and AMELX (Kutsche K *et al*., 2003).

Dent's disease is caused by mutations in the CLCN5 gene coding for the chloride channel CLC-5. Extensive databank mining, reverse transcription

polymerase chain reaction (RT-PCR) and automated sequencing were used in the search for novel CLCN5 transcripts (Ludwig M *et al*., 2003).

Ocular albinism type 1 (OA1) is an X-linked disorder, mainly characterized by a severe reduction in visual acuity, foveal hypoplasia, nystagmus, hypo pigmentation of the retina, the presence of macromelanosomes in the skin and eyes, and the misrouting of optic pathways, resulting in the loss of stereoscopic vision (Camand O *et al.*,2003).

Mutations in the X-linked gene double cortex (DCX) result in lissencephaly in males or sub cortical laminar heterotopias (double cortex) in females. According to a search against the human genome database, DCDC1 was mapped to 11p13. Expression analysis showed that DCDC1 was mainly expressed in adult testis (Zeng L *et al.*, 2003).

Rett syndrome (RTT) is a neurodevelopmental disorder affecting primarily females. Mutations in the X-linked gene methyl-CpG-binding protein 2 (MECP2) were first reported in RTT subjects. A new locus-specific database, has been developed RettBASE (http://mecp2.chw.edu.au/), loosely based on the PAHdb website. Rett syndrome (RTT) is a clinically defined disorder that describes a subset of patients with mutations in the X-linked MECP2 gene. A composite phenotype score was developed based on the recommendations for reporting clinical features in RTT of an international collaborative group. (Christodoulou J *et al*., 2003; Weaving LS *et al*., 2003). Geographical clustering has been reported, and it has also been proposed that Rett syndrome is a clinically variable condition and that other neurological disorders may be occurring more commonly in families with Rett syndrome. Both the strengths and the shortcomings of our design are identified, and recommendations are made for future research (Leonard H *et al.*, 2000).

As Human Genome Project exploration continues, the necessity of having a broader spectrum of genomic DNA material from different nationalities to study various aspects of hereditary disease becomes more obvious. During the last five years of investigation they have established a DNA bank, the Iranian Human Mutation Gene Bank , which contains all genetic diseases studied in Iran that have the Mendelian mode of inheritance (Najmabadi *H et al.*,2003).

X-linked RP genes which are retro transposed to form a new class of ribosomal protein (RP) genes. Mammalian ribosomes are composed of four RNA species and 79 different proteins. Unlike RNA constituents, each protein is typically encoded by a single intron- containing gene. Although the role of the autosomal RP genes remains unclear, they may have

evolved to compensate for the reduced dosage of X-linked RP genes (Uechi T *et al.*, 2002).

Pediatric cataract is a major cause of childhood blindness. Several genes associated with congenital and pediatric cataracts have been identified. The Royal Children's Hospital and the Royal Victorian Eye and Ear Hospital have a referral database for almost all pediatric patients with cataracts in south eastern Australia. The database contains cases seen over the past 25 years. Identification of the genes that cause pediatric and congenital cataract should help clarify the etiology of some sporadic and unilateral cataracts (Wirth MG *et al*., 2002).

Wiskott-Aldrich syndrome (WAS) is an X-linked disease characterized by thrombocytopenia, eczema and immunodeficiency of varying severity. The WASP gene, mutations of which are responsible for the phenotype, maps to Xp11.23. We describe here a patient with a large deletion in the Xp11.23 region. Analysis of the 5'-boundary region identified sequences missing in the Human Genome database and recombinogenic element is located downstream of the 5' breakpoint (Lutskiy MI *et al*., 2002).

Human chromosome Xp11.3-Xp11.23 encompasses the map location for a growing number of diseases with a genetic basis or genetic component. These include several eye disorders, syndromic and nonsyndromic forms of X-linked mental retardation (XLMR), X-linked neuromuscular diseases and susceptibility loci for schizophrenia, type 1 diabetes, and Graves' disease. a combination of EST database searches and in silico detection of UniGene clusters are used here (Thiselton DL *et al*.,2002).

X-linked type of albinism that mainly effects pigment production in the eye, resulting in hypo pigmentation of the retina, nystagmus, strabismus, foveal hypoplasia, abnormal crossing of the optic fibers, and reduced visual acuity. The OA1 gene located on chromosome Xp22.32 is responsible for that. Mutation and polymorphism data on this gene is available from the International Albinism Center - Albinism Database (Oetting WS, 2002).

X-linked adrenoleukodystrophy (X-ALD) is caused by mutations in the ABCD1 gene, which encodes a peroxisomal ABC half-transporter (ALDP) involved in the import of very long-chain fatty acids (VLCFA) into the peroxisome. Phenotypes include the rapidly progressive childhood cerebral form (CCALD), the milder adult form, adrenomyeloneuropathy (AMN), and variants without neurologic involvement. a great number of mutations have been identified in the ABCD1 gene (Kemp S *et al*.,2001).

As blast and sequence similarity algorithm are not accurate, the Prospero algorithm was used to perform self-comparisons of all predicted Drosophila melanogaster gene products. These findings demonstrate how completely sequenced genomes can be exploited to further understand the relationships between molecular structure, function, and evolution (Ponting CP *et al*., 2001).

The incidence of mental disability is 30% higher in males than in females and is also higher as compared to all the entries examined in the OMIM database. These conclusions are discussed with regard to the conservation of the vertebrate X-chromosomal linkage group and to human evolution (Zechner U *et al.,* 2001).

The risk of bladder cancer in offspring according to parental and sibling cancer using the national Swedish Family Cancer database. The relatively high ratio of sibling-to-offspring risk as well as observed gender specific effects in bladder cancer may reflect an X-linked susceptibility gene (Plna K and Hemminki K, 2001).

The analysis of disease-associated human genetic variation for seven disease genes: the cystic fibrosis transmembrane conductance regulator, glucose-6-phosphate dehydrogenase, the neural cell adhesion molecule L1, phenylalanine hydroxylase, paired box 6, the X-linked retinoschisis gene and TSC2/tuberin. Overall results demonstrate the usefulness of evolutionary analyses for understanding patterns of human disease mutations and underscore the biomedical significance of sequence data currently being generated from various model organism genome sequencing projects (Miller MP and Kumar S,2001).

X-linked pedigree of posterior lenticonus with cataract was identified further evidence for X-linked inheritance of this condition was sought. Forty-three cases of posterior lenticonus were identified from a database of 354 children with cataract. Posterior lenticonus is a common cause of unilateral infantile cataract, but is thought to be a rare cause of bilateral cataracts. This study suggests that posterior lenticonus is responsible for a significant proportion of childhood cataracts (Russell-Eggitt IM 2000).

In mammals, dosage compensation at X-linked loci is achieved by the process of X-chromosome inactivation in the homogametic sex. X-chromosome (Xi) is subjected to transcriptional inactivation, some escape inactivation and present biallelic expression. The recent development of a database of single nucleotide polymorphisms (SNPs) throughout the human genome enables investigation of allele-specific gene expression in normal human cells. There is potential of this system being studied for X-

linked gene expression in normal human cells (Vasques LR and Pereira LV .2001).

Androgen insensitivity syndrome (AIS) is an X-linked hereditary disorder caused by the mutation of the androgen receptor gene. A national survey of patients with AIS in Hungary has been decided to compose a database for analyzing current practice. Therefore appropriate diagnostic and management strategies for AIS patients, particularly in the case of suspected partial AIS, would be helpful (Solyom J *et al*., 2001).

A database for pentameric short tandem repeat locus DXYS156 from worldwide populations for routine genotyping in forensic identity testing and evolutionary biology reveals that DXYS156 displays a contrasting pattern of X-linked and Y-linked variation among geographic regions, and between X and Y chromosomes (Kersting C *et al*.,2001).

Emery-Dreifuss Muscular Dystrophy (EMD or EDMD) is a rare X-linked recessive disorder, characterized by progressive muscle wasting and weakness, contractures, and cardiomyopathy, manifesting as heart block. A summary of the previously published mutations are described in the EMD Mutation Database (Nevo Y *et al*.,2001).A screening for mutation in the X-linked Emery-Dreifuss muscular dystrophy (X-EMD) gene was performed among patients affected with severe heart rhythm defects and/or dilated cardiomyopathy. Patients were selected from the database of the Department of Cardiology of the University Hospital Brno (Vohanka S *et al*., 2001).

Borjeson-Forssman-Lehmann syndrome (BFLS) is a syndromic X-linked mental retardation that has been mapped by linkage to Xq26-q27. The full coding sequence and genomic structure of the gene for ARHGEF6 was established in silico, based on available genomic, EST, and cDNA sequence information (Lower KM *et al*., 2001).

Comparisons of cancer risks in persons by sibling cancers and parental cancers are informative of elucidating the potential genetic modes in the etiology of the cancers. The Swedish Family-Cancer Database was used to systematically estimate the effects of parental and sibling cancers. The search for pleiotropic recessive/X-linked susceptibility genes should be well motivated based on our results (Dong C *et al.,* 2001).

Immunodeficiency Resource (IDR) is a comprehensive integrated knowledge base for all the information on immunodeficiencies, including clinical, biochemical, genetic, structural and computational data and analyses (Valiaho J *et al*., 2000). Primary immunodeficiency's (IDs) are a heterogenic group of inherited disorders and this is referred through patient

related mutation databases (Piirila H *et a*l., 2006). The molecular defects responsible for some primary immunodeficiency diseases (PIDs) offers undoubted advantages in establishing a reliable diagnosis. Using the single-stranded conformational polymorphism technique followed by direct sequencing, we are able to find the mutations. Molecular diagnosis was very useful in identifying carriers in these families as well as in making the differential diagnosis among patients with common variable immunodeficiency disease (Garcia Rodriguez MC *et al*., 2001).

Molecular identification and clinical characterization of genetic mutations in patients with X-linked chronic granulomatous disease (CGD). Several mutations take place by insertions, deletions, duplications and missense and in case of splice site mutations could be explained by an age-related variable sensitivity of the splicing machinery to the present splice-site mutation (Heyworth PG *et al*., 2001).

A systematic analysis of cancer risks to offspring and to siblings of cancer cases was carried out based on the nation-wide Swedish Family-Cancer Database (Hemminki K *et al*., 2001).

There is a clear genetic component to prostate cancer susceptibility. Regions reported to be linked to prostate cancer include 1q24-25 (HPC-1), 1q42.2-43, and Xq27-28. Laser micro dissection, DOP-PCR, and CGH is a feasible method for analysis of paraffin-embedded prostate tumors (Verhagen PC *et al.*, 2000).

The full-length cDNA encoding the entire open reading frame (ORF) of rat myotubularin (rMTM) was isolated from a rat testis expression library by PCR. The results indicated that rMTM is a rat homologue of hMTM1 which may be a useful marker in monitoring the events of cell-cell interactions in the testis (Li JC Sammy ET *et al.*, 2000).

Teneurins are a novel family of transmembrane proteins conserved between invertebrates and vertebrates. The entire human teneurin-1 (TEN1) gene is contained in eight PAC clones representing part of the chromosomal locus Xq25. Database searches resulted in the identification of ESTs encoding parts of all four human members of the teneurin family (Minet AD *et al*.,2000).

The Interleukin-1 receptor (IL-1R) and Toll signaling pathways share the evolutionarily conserved Toll homology domain (THD), which is a critical component in the signaling cascade of the host defense responses to infection and inflammation. Evolutionary sequence analyses reinforce that these novel orphan receptors probably form a functionally

distinct subset of the IL-1R super family (Sana TR *et al*., 2000).

Monosomy for the X-chromosome in humans creates a genetic Achilles' heel for nature to deal with. The unexpected difference in the density of coding sequences indicates that our recent, hemophilia B-based estimate of the rate of deleterious mutations per zygote should be increased from 1.3 to 4 (1.3x3) (Giannelli F and Green PM, 2000).

Placental site trophoblastic tumor (PSTT) is a neoplastic proliferation of intermediate trophoblasts that invades the myometrium at the placental site after a pregnancy. Using the X-linked human androgen receptor (AR) gene as a polymorphic marker. In addition, sensitive semi-nested PCR failed to show a human Y chromosome element in any of the five cases of PSTT. Although largely speculative, an active paternal X-chromosome may be of importance in the pathogenesis of PSTT (Hui P *et al.,* 2000).

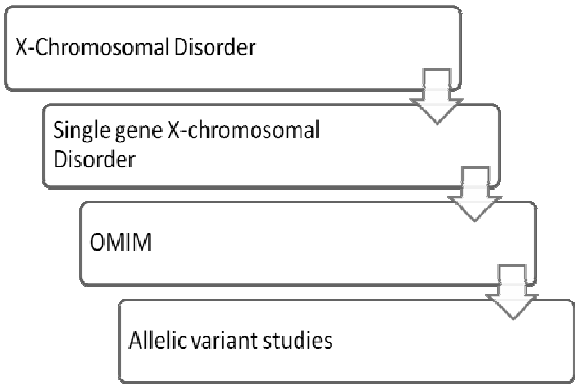
X-linked hypophosphatemia (XLH) is a dominant disorder of phosphate (Pi) homeostasis characterized by growth retardation, rachitic and osteomalacia bone disease, hypo phosphatemia, and renal defects in Pi reabsorption and vitamin D metabolism. The information is centralized on mutations in the PHEX gene by establishing a database search tool, PHEXdb (Sabbagh Y *et al*., 2000).

X-linked error of glycosphingolipid metabolism. Clinical manifestations of the disease are secondary to accumulation of glycosphingolipids in various tissues. The United States Renal Data System Registry database is reviewed. Despite their high risk for cardiovascular complications, patients with Fabry's disease have excellent outcomes after renal transplantation (Ojo A *et al*., 2000).

The large number of redundant sequences available in nucleotide databases provides a resource for the identification of polymorphisms. In this study, we have identified six new X-linked single-nucleotide polymorphisms and determined the inactivation. Expression of only a single allele was seen in females heterozygous for polymorphisms in the BGN, TM4SF2, ATP6S1, VBP1, and PDHA1 genes, suggesting that these genes are subject to X-chromosome inactivation (Kutsche R *et al.,* 2000).

3. MATERIALS AND METHOD

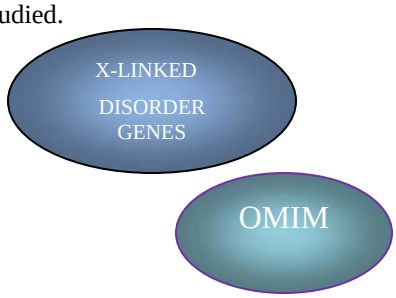
There are 11 single gene disorders related to the X-Chromosome. Their allelic variants were collected from OMIM. All the allelic variants and gene expression associated with these disorders were compiled.

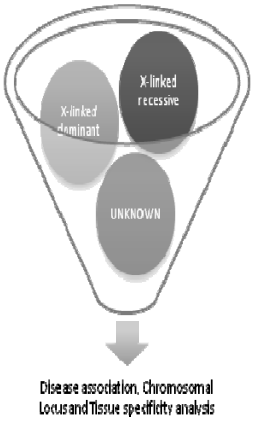


Methodology of analysis of allelic variants

Website: http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM

X-linked dominant genes and X-linked recessive genes were taken from OMIM. Their disease association, tissue specific expression and locus points were studied.

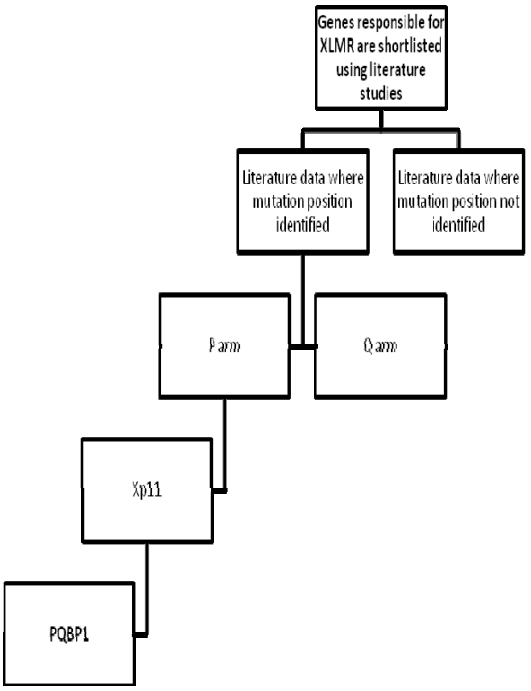




Methodology of analysis of x-linked dominant &recessive gene

Website: http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM

The XLMR (X-Linked Mental Retardation) associated genes were further analysed for screening the target gene for therapy



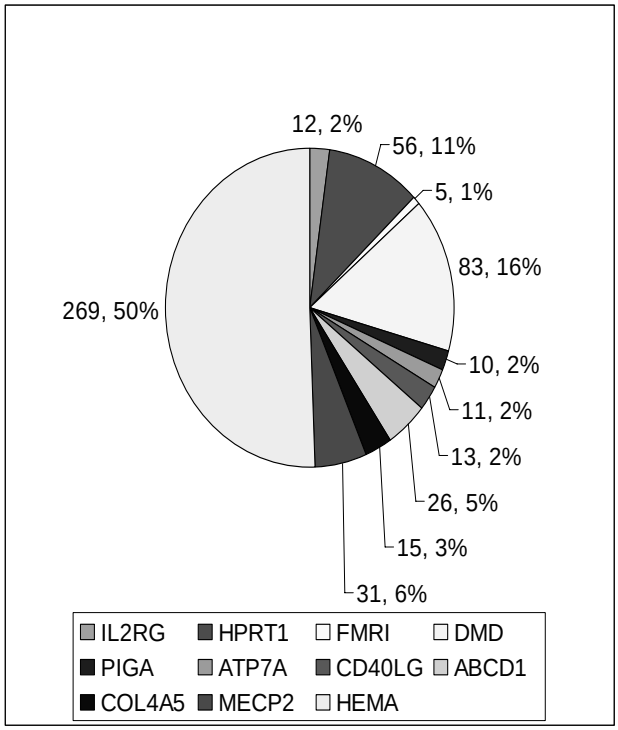
Methadology for functional annotation of target genes associated with XLMR

Website: http://www.ncbi.nlm.nih.gov/sites/entrez/

4. RESULT AND DISCUSION

An analysis of the X -linked disorders was carried out using OMIM for their allelic variants and GENE CARDS for their expression. 11 X -linked single gene disorders were found. The allelic variants were found to be responsible for mental retardation and the maximum number of allelic variants was found for HEMA gene, still further research was carried for all other

genes as well. The genes were looked for their distribution in various tissues. Major expression was found to be in brain. These genes were further divided into dominant and recessive. A large number of genes were not annotated and therefore could not be categorized as dominant or recessive. Of all the X-chromosome disorders, mental retardation was found to be caused by maximum number of genes. Loci on X-chromosome associated with mental retardation were found out. It was discovered that Xq28 had the highest number of genes responsible for mental retardation. Mining of the genes having locus on this region and association with mental retardation were searched for their site of expression and it was found that they are maximally expressed in neurons.

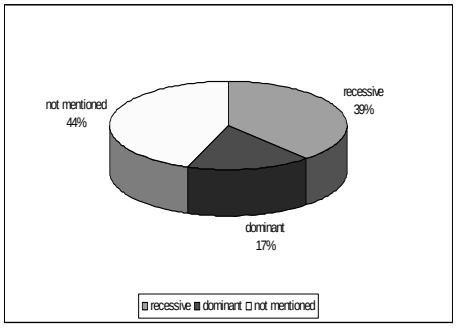


Allelic Variants of single gene X-linked disorder

Percentage of Allelic Variants of All the Genes

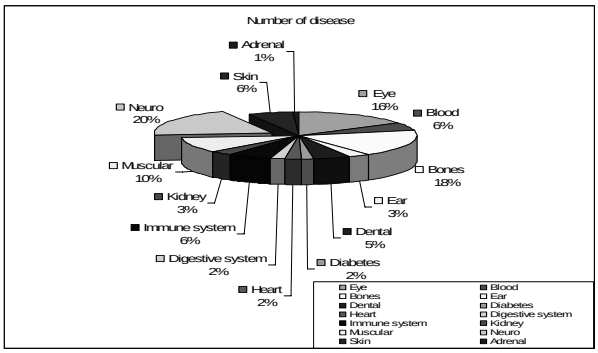
It represents the percentage of allelic variants of all the genes. It shows the number of allelic variants of all the X-linked genes. HEMA gene was found to have the maximum number of allelic variants, equal to 50 percent. All the genes on the X- chromosome were found to have at least more than five allelic variants. HEMA was found to have a maximum of 269 alleles. DMD had 83 variant alleles while HPRT1 was discovered to have 56 alleles. 31 allelic variants could be found for MECP2 gene. ABCD1 had 26 alleles with COL4A5 having just 15. CD4OLG was found to have 13 alleles and ATP7A had 11 alleles. IL2RG had 12 variants while 10 alleles were present in PIGA. FMRI had the minimum number of alleles which was found to be 5 only.

X-linked recessive and dominant gene analysis



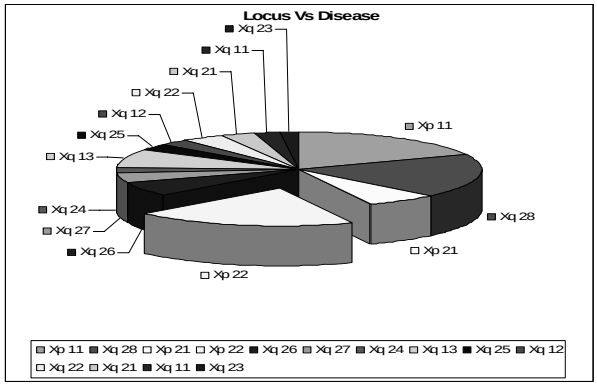
Percentage of X-linked disorder Genes

The complete X-linked disorders are taken from OMIM database and using clinical synopsis the X-linked recessive and dominant genes were manually curated .It was found that almost 44% X-linked disorders were not still annotated.



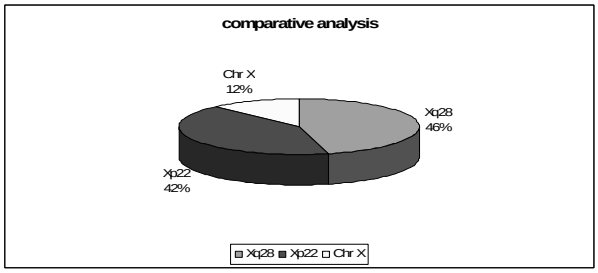
X-linked disorder Gene expression in disease

It is found that X-linked disorders genes were majorly expressed in the nervous system.



Gene Localization in X-linked disorder Genes

It was found that Xq28 and Xp22 genomic region contributed to X-linked disorders and the figure below shows their distribution



Comparative Analysis of X- linked disorders gene locus

From the analysis it was found that around 88 percent contribution was from Xq29 and Xp22.The complete annotation of these genes and the percentage of its expression in various organs are listed below. The percentage of X-linked disorder genes along with their disease association &locus is tabulated below.

Disease Percentage	Locus
Eye 31%	Xp11
Bones 40%	Xp22
Ear 62%	Xp22
Dental 34%	Xp22
Immune system 32%	Xp11
Kidney 50%	Xp11
Heart 49%	Xp28
Mental retardation 22%)	Xp11
Muscular dystrophy 18%	Xp28
Muscular dystrophy 18%	Xp28
Neural 26%	Xp28

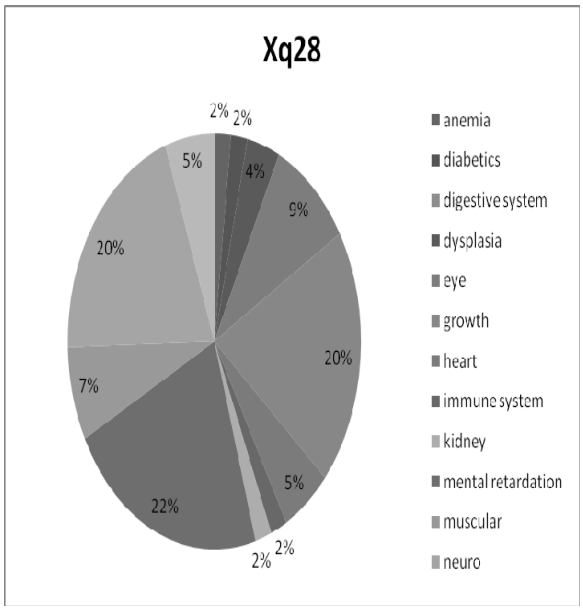
Skin Xq27	Xp22 and 22%
Anemia Xp21	Xp11, Xp22, 20%
Growth retardation 28%	Xp22
Blood related Xq23	Xq28, Xp11 and 22%
Cancer related 23%	Xp11
Dysplasia 33%	Xq28 and Xq13
Goiter Xq27	Xq26, Xp22, Xp11, 25%

Hair related disease 50%	Xq12 and Xq13

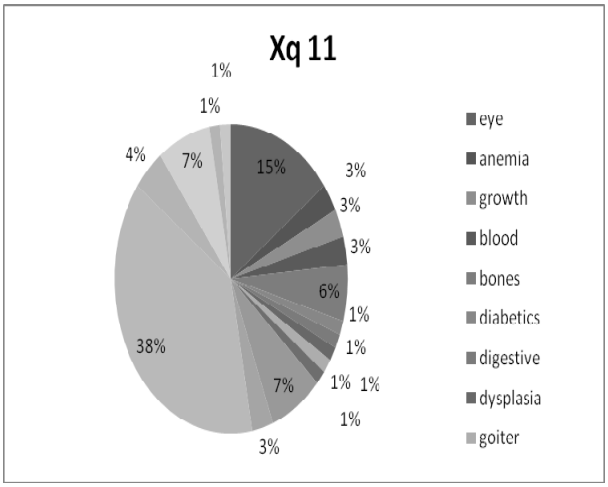
Sexual related disease 32%	Xp22

Percentage of X-linked disorders genes an its disease association

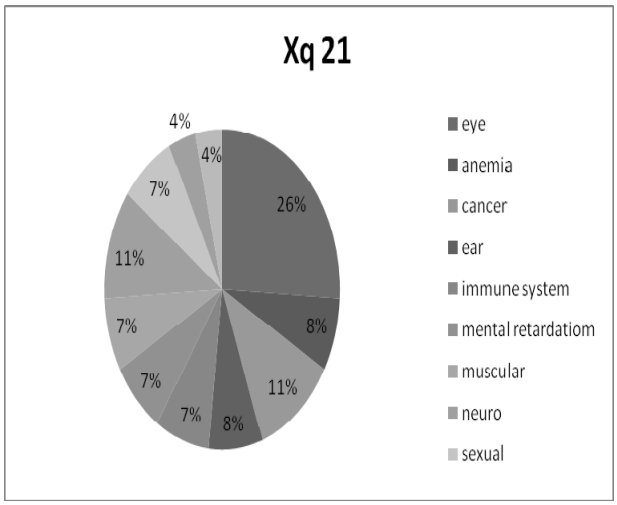
The locus of q arm Xq28,Xq11,Xq21,Xq22,Xq23,Xq24,Xq26, Xq27 which contributes major disorders was studied for its disease association which is listed in the following figures



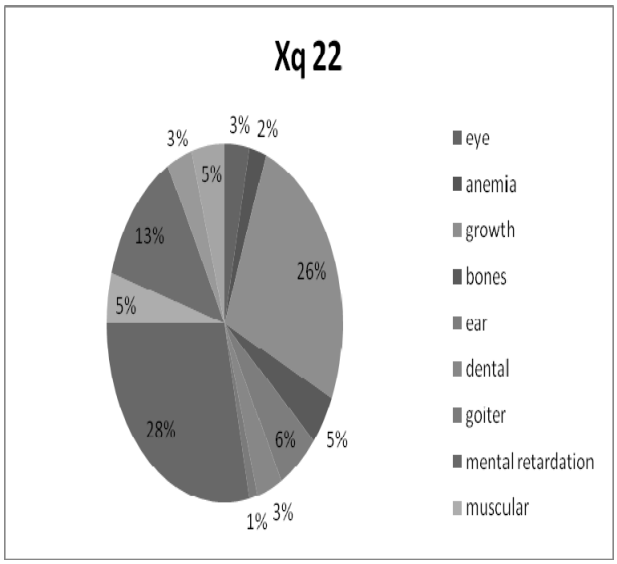
Disease association of Xq28 in biological systems



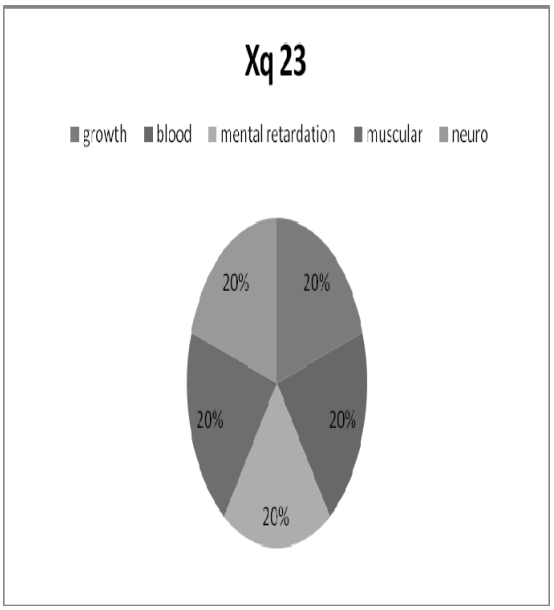
Disease association of Xq11 in biological system



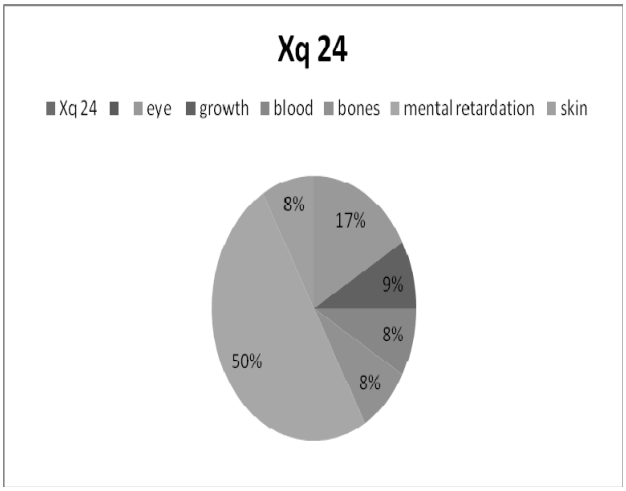
Disease association of Xq21 in biological systeM



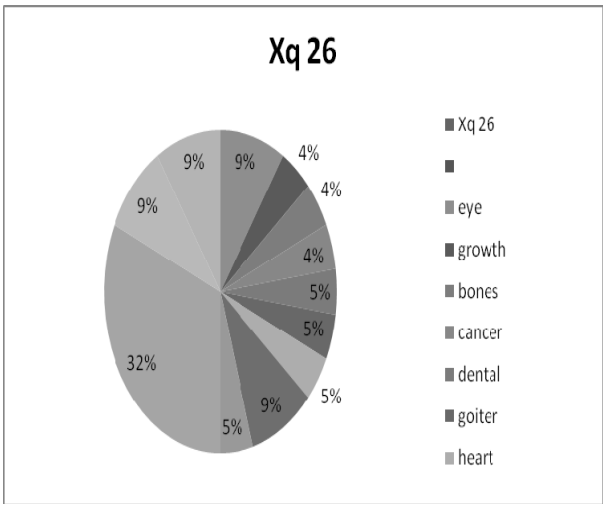
Disease association of Xq22 in biological systems



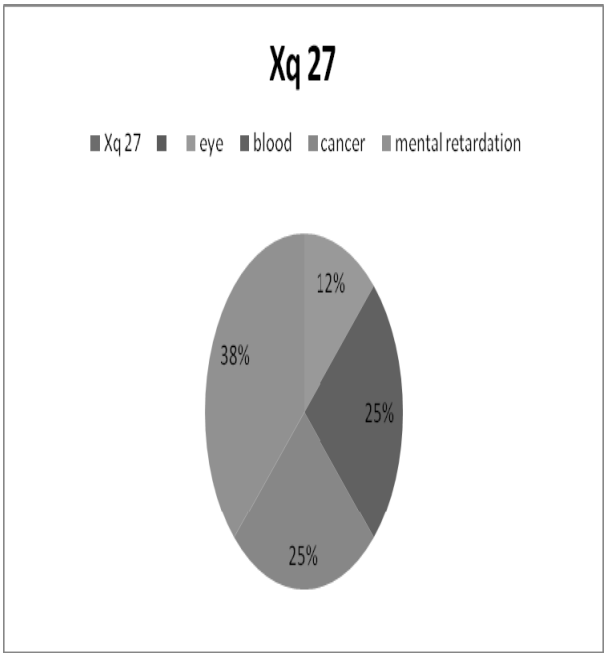
Disease association of Xq23 in biological systems



Disease association of Xq24 in biological systems

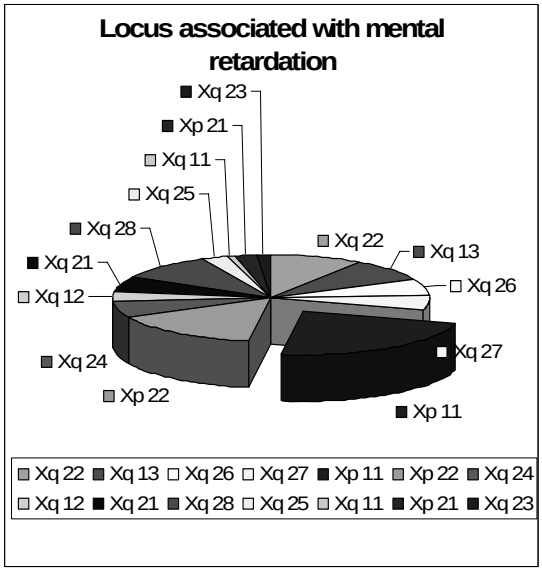


Disease association of Xq26 in biological systems



Disease association of Xq27 in biological systems

The analysis of disease association of all the genes gave us clue that mental retardation was the major X-linked disorder and hence we attempted to find the association of XLMR with all the loci which contributed to X-linked disorders. The graph below shows the percentage of XLMR in all the loci.



Mental Retardation of gene in X-chromosome

From the above results detailed analysis is carried out on XLMR

X-Linked Mental Retardation (XLMR) occurs in two forms, Syndromic and Non -Syndromic. Advances in clinical delineation and molecular understandings of XLMR have now identified 120 syndromic forms of XLMR and 81 families with non-syndromic XLMR (Stevenson et al. 2003). To date, mutations in 47 genes have been linked to XLMR. Of these 47 genes, 29 have been linked exclusively to syndromic XLMR, 11 exclusively to non-syndromic XLMR, and 7 to both (Stevenson and Schwartz 2002).

These 47 genes were analyzed and we found 39 genes which were responsible for causing XLMR. The table gives important information about particular genes.

S. No	Gene Name	Changes in Genomic level	Changes in Proteomic level	Syndromes
1.	ATRX Note-12	CA n time repeat, Splicing mutation[IVS 3+1 G > T]	Code for protein of 280 kDa	Alpha Thalassemia/Mental Retardation Syndrome
2.	ARX	GCG trinucleotide expansion, Deletion of 1517 bp in gene, Missense mutation 1058 C > T	Xp22.1 Duplication at 24 bp in exon 2, Position [428-451], Expansion of polyAlanine tract.	Partington Syndrome, XLAG, Cognitive Impairments
3.	ZDHHC9		Xq26	Marfan Syndrome
4.	PLP2	Alters the core binding site of transcription factor	Xp11.23	
5.	MED12			Lujan Syndrome & Optiz – Kaveggia Syndrome
6.	SCMX	H3K4 ,H3K9 Methylation in Transcriptional repression		
7.	ARHGEF6 Note-10	X/21-reciprocal translocation disrupts Xq26 position, Mutation-[IVS1-11 T→C]	X/21-reciprocal translocation disrupts Xq26 position	XLMR in Telencephalic region of mouse & rat, Borjeson Forssman-Lehmann syndrome
8.	MECP2 Note-7	Interaction with ATRX => XLMR	Missense mutation [R 133 C]	Rett Syndrome, Fatal encephalopathy
9.	AP1S2		Xp22	Hypotonia & delay in walking
10.	CULB4		Xq24	Delyed puberty, Hypogonadism, Macrocephaly, Short Stature
11.	BCOR		b/w Xp11.4-Xq12	Lenz microphthalmia Syndrome
12.	PQBP1	Delets 6 AG dinucleotides in polar AA rich domain(prd)	Xp11.4-Xq12 Changes the conserved residue Tyrosine to Cysteine in WW	Rett syndrome, Proteous Syndrome Choroid coloboma, Renal hypoplasea,

		causing frame shift in 4th coding region.	domain at position 65	
	UBE2A Note-1	Results in Premature UGA codon		
14.	ODF1			Lethality in male, Severe mental retardation
15.	SLC6A8 Note-2		Xq28 , Totally 5 mutation 1-Nonsense mutation [p.Y 317 X] 4-Missense mutation [p.G 87 R] [p.P 390 L] [p.P 554 L] [p.C 337 W]	Mutation causes creatine deficiency in brain
16.	JARID1C Note-4		Affects evolutionarily conserved Serine to Arginine at position 451	Epilepsy ,Short Stature, Behavioral problem
17.	IL1RAPL1		Xp21.3 Stop mutation in exon 10[W 487 X]	Non specific mental retardation
18.	KIAA1202		Xp11.3 - Xq21.1 marked by DXS983	Stocco dos santos XLMR syndrome
19	PHF8 Note-3		Truncating mutation	Mental retardation and midline affect
20.	XLMR-Gene			
21.	ZDHHC15		Xq13.3	Absence of this gene =>skewing of X-ch. =>inactivation=>XLMR
22.	GRIA3		Xq24-Xq25 Markers =>DXS6805-DXS7346	
23.	TM4SF10 Note-5		Xp21.1	Codes for brain cell membrane ptn.1
24.	FTSJ1		Markers =>DXS228-DXS1204, Alteration in the splice site of intron 3 . Mutation is skipping of exon 4 and introducing premature stop	Mutation results in truncated protein=> XLMR

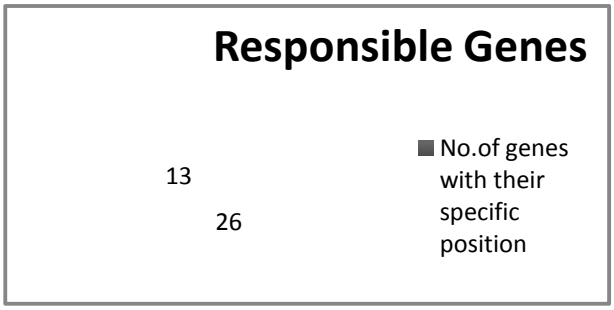
			codon in exon 5	
25.	PAK3 & FACL4 Note-6		Xp22.3 DXS1106-DXS8067 2 Null mutations	Nonspecific MR
26.	NXF5 Note-13	4 Nucleotide changes 1 Intronic, 2 Silent, 1 Missense	Xp21.1 - Xq22.1, 1 Missense [K 23 E]	Syndromic XLMR
27.	FMR1	Unstable CGG repeat		Methylation of FMR1=> Transcriptional block=> FragileX Syndrome
28.	TM4SF2 Note-9		Xp11.4 DXS564-DXS556	
29.	ZNF741	KLF8 gene shows no mutations in the coding region	Xp11.21	
30.	TEN1		Xq25 Terminal of TEN1 has 26 YD repeats	TEN1 with neuronal expression is responsible for XLMR
31.	RPS6KA3			Coffin Lowry Syndrome
32.	OPHN1			Cerebellar hypoplaia
33.	ZNF674		Substitution mutation P.[T343M] P.[P412L]	
34.	Shashi XLMR Note-11		Xq26 – Xq27	
35.	SOX3		Xq26.3 PolyAlanine expansion	Affects Transcription pathway and regulation of gene
36.	MRX73		Xp22.2 DXS8019-DXS365	Coffin Lowry Syndrome
37.	MRX58		Xp11.3-Xq13.1 DXS6673E, Encode hydrophilic protein of 1358a.a	
38.	MRX51		DXS8012-DXS1003 Xp11.3-Xp11.23	
39.	XLMR7		DXS8063-DXS1047 Xq23-Xq26.1	

Mutated genes responsible for XLMR

Gene	Contents
1.UBE2A	It do not contribute significantly to XLMR but they are found in them
2.SLC6A8	Out of 478 males with XR, only 1% has SLC6A8 mutation. Frequency of this mutation is similar to that of CGG expansion in FMR1
3.PHF8	PHF8 harbors 2 functional domains. 1-PHDfinger domain, 2-JmjC domain (Jumonji like C terminus).
4.JARID1C	This gene belongs to conserved ARID protein family which contains several DNA motifs that regulates transcription and remodels chromosomes. This gene was formerly known as SMCX.
5.TM4SF10	It is not a frequent cause for XLMR
6.PAK3	This gene should be considered as important factor for MRX location
7.MECP2	70-80% of Rett syndrome is due to MECP2 mutation. Studies have been performed on mouse and human.
8.IL1RAPL	We are unable to confirm the involvement of SOX3 gene in XLMR , so it is not advisable to take SOX3 gene. Dysfunction of SOX3 gene is due to polyAlanine expansion
9.TM4SF2	The association of this gene with XLMR is hypothesis
10.ARHGEF6	Guanine nucleotide exchange factor which act as a potential candidate for XLMR. Mutation is skipping of exon2 and predicts protein which lacks 28 amino acids.
11.Shashi	This gene has interval
XLMR	flanked by ATA 59 DO5 and GATA 31 EO8
12.ATRX	All the mutations occur only with in this two domains 1-PHDZinc finger, 2-ATPase Helicase domain.
13.NXF5	Good candidate for Syndromic form of XLMR

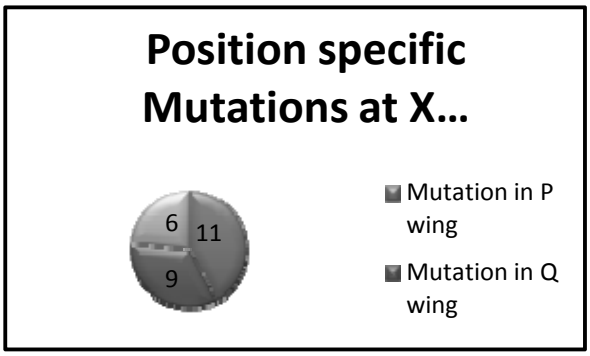
List of XLMR genes and its contribution

The method of focusing the PQBP1 gene which causes Renpenning syndrome for study has been shown in the following pictorial representations. The shows that out of 47 genes , information about position of mutation is available for 26 genes only.

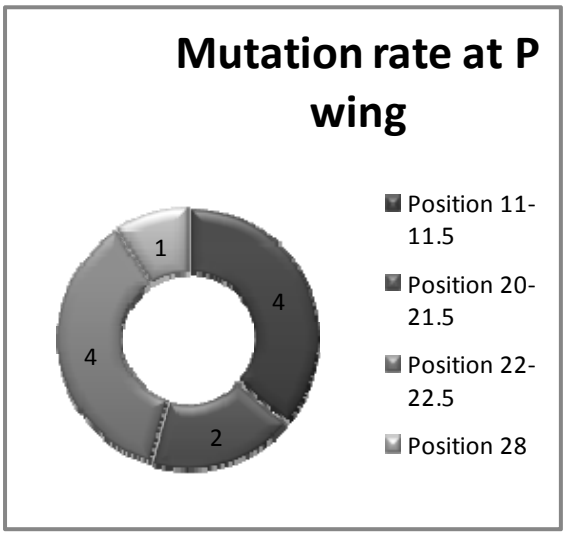


XLMR causing genes with information on specific mutational position

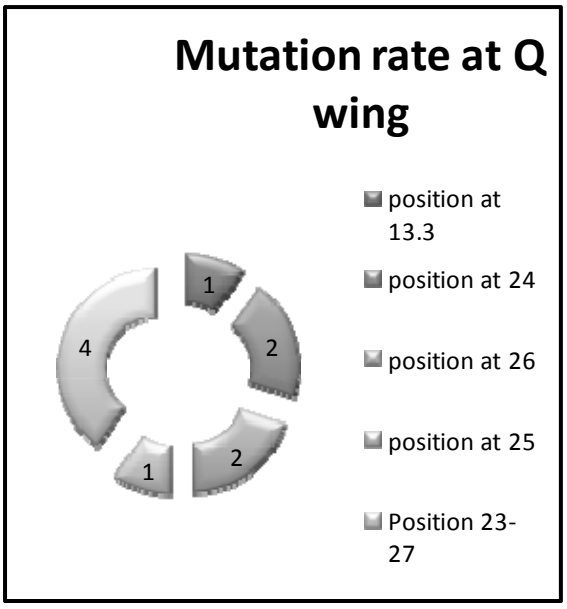
Neglecting the 13 genes for which information on position of mutation was not available, the remaining 26 genes were classified on the basis of occurence and position of mutation at P-wing, Q-wing and at both the wings.



Position specific mutation at X-chromosome



Mutation rate at p wing



Mutation rate at Q wing

Mutation rate at both the P and Q wing

Gene Position	Gene Name
Xp11.3-Xq12.1	1-KIAA1202
Xp11.3-Xq13.1	1-MRX58
Xp11.4-Xq12	2-BCOR,PQBP1
Xp21.1-Xq22.1	NXF5
451	JARID1C

Mutation rate at both the P and Q wing

Considering these 26 genes at X-chromosome, there are totally 8 genes which have their starting position ranging from Xp11.1 - Xp11.5. Out of these 8,the only gene which has all the information on position, type of mutation and the exact mutation which it has undergone is PQBP1 which causes Renpenning syndrome by a missense mutation p.Y65C. It consists of six exons that code for a protein of 265 amino acids in which a WWW domain is encoded by the amino acid positions 47–78, which has been shown to play an important role in regulation of transcription activity by interacting with the carboxyl-terminal domain of the RNA polymerase II. The WWW domain is much attractive for a Proline rich compound APPTPPPLPP which shows much optimal energy minimization while docking to the WWW domain.

Renpenning syndrome is one of the rare diseases to be analyzed and cured (http://rarediseases.info.nih.gov/asp/diseases/diseaseinfo.asp?ID=9509). The proline rich compound APPTPPPLPP can be suggested to prevent the missense mutation p.Y65C by docking to the WWW domain which is the sole cause for Renpenning syndrome.

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