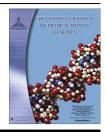Ain Shams University

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REVIEW

Reduced penetrance in human inherited disease

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Abstract   For many inherited diseases, the same mutation is not always expressed in all persons who carry it, moreover, when the mutation is expressed, it is not always expressed in the same way. These findings are the basis for the concepts of penetrance and expressivity. Understanding the factors that control penetrance of disease genes will provide insight into the fundamental disease processes and will help in genetic counselling.

With the advancement of molecular genetics over the last few years, some of the underlying mechanisms of reduced penetrance have been elucidated. These include, mutation type, allelic variations in gene expression, epigenetic factors, gene-environment interplay, influence of age and sex, allele dosage, oligogenic and digenic inheritance mutations, modifier genes, copy number variations as well as the influence of additional gene variants and the effect of single nucleotide polymorphisms.

The aim of this review is to clarify factors affecting gene penetrance as well as some of the underlying molecular mechanisms in some genetic disorders.
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1. Introduction

Penetrance is defined as the percentage of individuals having a particular mutation or genotype who exhibit clinical signs or phenotype of the associated disorder or genotype [1].

Complete penetrance indicates that individuals who have the disease – causing mutation have clinical symptoms of the disease e.g. familial adenomatous polyposis, multiple endocrine neoplasia and retinoblastoma. Incomplete or reduced penetrance indicates that some individuals fail to express the trait, even though they carry the allele e.g. incomplete penetrance of the dominant mutations in the LMNA gene of Emery Dreifuss muscular dystrophy [2]. Low penetrance allele indicates that this allele will only sometimes produce the symptoms at a detectable level e.g. low penetrance of retinoblastoma for p. V654L mutation of RBI gene [3]. Pseudo-incomplete penetrance indicates that the observation of non penetrance is inaccurate because the clinical examination is incomplete or the symptoms have not yet appeared at the time of the examination. It is also seen in germ line mosaicism that is only seen in the first generation when the parents of several affected children with a dominant disease are healthy [3].

Variable expressivity on the other hand means the extent to which a genotype is phenotypically expressed in individuals. Individuals with a certain mutation can exhibit differences in disease severity, even among members of the same family. Examples of diseases that display a range of phenotypes include neurofibromatosis, holoprosencephaly [4] and genetic syndromes [5–8].

Healthy individuals can harbour large number of potentially or mildly disadvantageous variants and perhaps tens of potentially severe disease alleles without suffering any obvious ill effects [9]. These variants may damage the protein in question, but the intact protein may not be necessary for the health of the carrier. The individual may be an asymptomatic carrier of a single recessive mutant allele or the mutation is dominant, but the clinical phenotype might be only mild and lying within the range of normal healthy variations or become apparent in later decades of life [1].

Each individual was found to carry 281–515 missense substitutions predicted with a high degree of confidence to be damaging to the gene product, 40–85 of which were present in the homozygous state. Taken together these studies suggest that a typical healthy individual has about 80 of their genes severely damaged or inactivated in both copies, further emphasising the stark contrast between damage to gene and protein on one hand and damage to health on the other hand [1].

Until recently reduced penetrance is a term used exclusively for autosomal dominant disorders. However the existence of healthy homozygotes of autosomal recessive disorders has been demonstrated by molecular analysis [10]. Irrespective of the mode of inheritance penetrance is likely to be a function of the specific mutation(s) involved. Examples of reduced penetrance in autosomal dominant disorders include, congenital cataract (GJA3 gene) [11], different types of retinitis pigmentosa (PRPF8 & PRPF31) [12], and long QT syndrome [13]. Examples of autosomal recessive disorders include Cys 282tyr (rs1800562), mutation in hemochromatosis gene (HFE) [14], and GBA mutations, (Asn 409ser, rs76763715) in deafness [15].

Reduced penetrance being a widespread phenomenon in human genetics as evidenced from next generation sequencing of entire exomes or genomes of apparently healthy individuals represents a major challenge to genetic counsellors in quantifying the disease risk to the patient's offspring [16]. Also it complicates the recognition of heritable basis of heritable diseases [17], as well as blurring the distinction between monogenic conditions and complex diseases. [18].

2. Factors affecting penetrance

2.1. Mutation type and penetrance

Incomplete penetrance may be due to the effect of the type of mutation. Some mutations of a given disease may exhibit complete penetrance, where as others in the same gene show incomplete or very low penetrance. e.g. the penetrance of the common mutation for cystic fibrosis, CFTR (Δ Phe 508, rs113993960) is very high, while the penetrance of CFTR Arg 117 His (rs78655421) mutation is very low, so as to suggest its withdrawal from cystic fibrosis mutation panel used for screening programmes [19].

Reduced penetrance in some genetic disorders may also depend on genetic background of gene carriers. In Hirschprung disease (HSCR), although the presence of RET mutations is sufficient to explain HSCR inheritance, a genome scan reveals that new susceptibility locus on 9q-31 is also required to cause the disease [20].

Reduced penetrance may also be due to the type of mutation. Splice site mutations in RBI gene of retinoblastoma lead to reduced penetrance, due to reduction in the amount of Rb protein produced [21]. Null mutations on the other hand tend to exhibit lower penetrance than missense and splicing mutations as in Col3A1. Null mutation reduces the amount of normal collagen produced, while the other mutations produce faulty gene product which disrupt the entire helical collagen molecule [22]. Patients harbouring missense mutations in BMPR2 gene exhibit early and severe pulmonary hypertension than patients harbouring truncating mutations [23]. Double missense mutations may lead to incomplete penetrance in cis as in fabry disease, as one of the two mutations may represent

a hypomorphic (hypofunctional) allele. In recessive disorders clinical penetrance of one mutation may be strongly influenced by the nature of the other mutation in trans. Thus two non-sense/truncating mutations in GJB2 gene produce more severe deafness than two missense mutations [24].

Location of the mutation may also affect penetrance. Thus mutation in cysteine residue of the TNFRSF1A gene causing TNF receptor associated periodic syndrome is more penetrant that mutation in the non-cysteine residue [25].

Penetrance may also be incomplete in compound heterozygotes as in MEFV gene mutations responsible for familial Mediterranean fever [26].

In diseases which exhibit locus heterogeneity clinical penetrance may vary between mutations in different genes as in deafness [24]. Reduced penetrance may also be characteristic of many triplet repeat expansion disorders as in Huntington disease. The possession of intragenic (HTT) CAG repeats of 36–39 copies is often associated with reduced penetrance and later age of onset of clinical symptoms [27].

2.2. Variation in gene expression and penetrance

Humans are characterised by marked inter-individual variation in levels of expression of their genes even in members of the same family which can influence the penetrance of pathological mutations [28]. This may be due to differential contribution of mutant alleles to the clinical profile i.e. allelic heterogeneity as in familial Mediterranean fever, (MEFV gene). M694V homozygotes have a severe form of the disease, while mutations in E148Q and V726A have reduced penetrance [29].

Cis and Trans-acting factors also control gene expression. Cis-acting elements are DNA sequences in the vicinity of the structural portion of a gene that is required for gene expression. Trans-acting factors are considered to be proteins, that bind to the cis-acting sequences to control gene expression. Difference in gene expression may be mediated through polymorphism in any of them (cis acting elements). Differential expression of wild and mutant alleles can also affect penetrance, e.g. unequal allelic expression of the wild type (MYH7-mRNA) and mutated B-myosin transcript and proteins in familial hypertrophic cardiomyopathy. This is characteristic for each mutation, implying cis-acting regulatory mechanisms. [30].

Different degrees of expression in different individuals may also be due to variation in allelic constitution of the rest of the genome or to environmental factors. [31].

Genome sequencing studies indicate that humans carry many genetic variants predicted to cause loss of function (LoF) of protein-coding genes, suggesting redundancy in the human genome. They estimated that human genomes typically contain 100 genuine LoF variants with ~20 genes completely inactivated. About 26 rare and likely deleterious LoF variants were identified as well as 21 severe disease–causing variants and common LoF variants in nonessential genes [32].

2.3. Epigenetic changes and penetrance

Epigenetic changes or modifications indicate the sum of heritable changes, such as DNA methylation, histone modification and miRNA expression as well as environmental and stochastic factors which can affect gene expression and reduced penetrance without changing the DNA sequence [33]. Epigenetic variations have been suggested to have an important role in cellular senescence, tumorigenesis and in several diseases including type 2- diabetes, cardiovascular, autoimmune diseases, obesity and Alzheimer's disease. A correlation between epigenetic DNA modifications and human life span has also been shown by Fraga et al. [34] who found that global and local-specific differences in DNA methylation in identical twins of different ages are influenced by environmental factors and lifestyle.

Most studies demonstrated that aging is associated with a relaxation in epigenetic control, due to a decrease in global cystosine methylation mostly in transportable repetitive elements [35].

Epigenetic modifications in the pathophysiology of neuro-degenerative diseases with consequent transcriptional dysregulation might be an important marker of disease status and its progression [36]. Epigenetic allele silencing may also play a role in malignant hyperthermia susceptibility [37].

Epigenetic modification may also account for a specific disease phenotype in twins and in terms of an epigenotype as they are discordant for childhood leukaemia because they have discordant BRCA1 methylation status [38].

A special case of imprinting is provided by X-inactivation, when a disease gene is X-linked. Shewed X-inactivation can cause variable penetrance of pathogenic mutations in female carriers e.g. the EBP gene (XP11.23) in X-linked dominant chondrodysplasia punctata [39].

Genes can also affect one's risk of obesity. However there are several epigenetic influences that alter the expression of our genes and ultimately our risk of becoming obese. Failure of epigenetic markers or imprinting can affect gene expression and cause extreme forms of obesity (e.g. Prader–willi syndrome). [40].

2.4. Gene-Environment interplay and penetrance

The environment will often influence clinical penetrance, either ameliorating or exacerbating the impact of heritable genetic variants. Environmental modifiers of disease penetrance include sex, diet, drugs, alcohol intake, metabolic syndromes and physical activity [41].

In phenylketonuria (PKU), newborns found to have high levels of phenylalanine in their blood can be put on a special low phenylalanine diet to avoid severe effects of PKU. Thus diet can act as an important modifier of clinical penetrance [42].

An inherited predisposition to obesity in carriers of PPARG2 Pro 12A Ala alelle can be modified by low fat intake [43]. The risk of obesity can also be attenuated in persons having genetic variants at the FTO locus by physical activity [44]. Women appear to be more responsive to environmental risk factors causing multiple sclerosis [45].

The most evident environmental influence on penetrance is in cancer susceptibility. Traditionally gene-environment interactions are thought to contribute to tumour suppressor – gene penetrance by facilitating or inhibiting the acquisition of additional somatic mutations required for tumorigenesis. Exposure to environmental factors (diethylstilbestrol) during development can permanently reprogram normal physiologi-

cal tissue responses and this leads to increased tumour–suppressor gene penetrance in genetically susceptible individuals [46].

There is an association between heritable genetic variations at the nicotinic acetylcholine receptor (CHRNA5/CHRNA3/CHRNB4) locus on chromosome 15q 25.1 and lung cancer. Allele T of SNP rs1051730 a synonymous variant located within exon 5 of CHRNA3 gene was found to be strongly associated with smoking quantity, whether this effect is direct or indirect [47]. The risk of lung cancer conferred directly or indirectly by genetic variants on 15q 25 would be small if the individual concerned simply opted not to smoke [48].

Persons who were abused as children and have a genotype conferring high levels of functional polymorphism in the monoamine oxidase A (MAOA) gene promotor which produces high levels of MAO are less likely to develop symptoms of antisocial behavior [49].

2.5. Increasing age and penetrance

The clinical symptoms of some disease mutations are increasingly likely to manifest themselves with increasing age of risk individuals, e.g. MYBPC3 in hypertrophic cardiomyopathy [50], Emery-Dreifuss muscular dystrophy [2] and familial obesity due to melanocortin-4-receptor deficiency [51].

The most common genetic cause of familial and sporadic amyotrophic lateral silerosis (ALS) and frontotemporal dementia (FTD) is a massive GGGGCC hexanucleotide intronic repeat expansion mutation within C9 or F72. The mean age of onset was 57.9 years for ALS cases and 63.6 years for FTD. Age dependent penetrance rose steeply from 9% at 50 years to 70% by 70 years and 74% by 85 years. Penetrance was not influenced by sex of the proband and was similar for parents and siblings of the probands. However a significantly earlier age of onset was seen in offspring compared to their parents with a mean difference of 6.9 years [52].

Risk of both breast and ovarian cancer is consistently estimated to be higher in BRCA1 than in BRCA2 mutation carriers. The estimated cumulative risks of breast cancer by age 70 years were 55–56% for BRCA1 and 45–47% for BRCA2 mutation carriers. Ovarian cancer risks were 39% for BRCA1 and 1–17% for BRCA2 mutation carriers [53]. Even different BRCA1 gene mutations have distinct effects that influence the age of onset of breast or ovarian cancer. The 185 delAG mutation of the BRCA1 gene is a low penetrance mutation that is age dependent especially when compared with the exon 13 duplication mutations. The median age of affliction with breast cancer was 55 years for 185 delAG in exon 2, 47 years for the 4184 del TCAA mutation in exon 11 and 41 years for exon 13 duplication [54].

In some cases, the clinical penetrance of a particular mutation can change quite dramatically with age. The cumulative incidence among carriers of the Arg 1441 Gly mutation in the LRRK2 gene causing Parkinson disease was found to be 12.5% until the age of 65 years, but 83% until age 80 [55].

However the penetrance of TTR Val 30 Met mutation causing autosomal dominant familial amyloid polyneuropathy has been estimated to be 1.7% until the age of 30 years, 22% until the age of 60 but still only 69% until age 90 [56].

2.6. Effect of sex on penetrance

Sex influenced disorders are disorders that demonstrate gender–related penetrance or the phenotype expression is more likely to occur in a specific gender. The effect of sex on penetrance of inherited mutations was found in a variety of heritable disorders. In cases of hereditary breast/ovarian cancer caused by BRCA2 mutation, about 6% of males as opposed to 86% of females are expected to develop breast cancer by age 70 [57].

The penetrance and attack frequency of hypokalemic periodic paralysis (Hypo PP) due to SCNA4 mutation were lower in females than in males. Males had 100% penetrance and 50–150 attacks/year, compared to 28.27% penetrance and 30–50 attacks/year in females and the attacks disappear during pregnancy. This is most probably due to the effect of estrogens [58].

Sex limited disorders refer to autosomal disorders that are nonpenetrant for a particular gender. Male limited precocious puberty is one example. Males heterozygous for mutations in LCGR gene located in chromosome 2 exhibit this phenotype, but females with the same genotype do not [57].

Allelic variation may also influence the clinical phenotype in a sex specific fashion. The KCNE1 Asp 85 Asn (rs1805128) polymorphism was associated with a Q-T interval prolongation in males but not female type 1 long QT syndrome patients harbouring KCNO1 Gly 589 Asp mutation [1].

Parent of origin effect (Genomic imprinting) was evident in SGCE mutation in myoclonic dystonia. Maternal imprinting ensures that the pathologically effective mutations are almost invariably inherited from the father [59]. There is increased risk for breast cancer in the leaner women especially in the postmenopeusal group, related to the TEXB–alpha. The pesticides aldrin and lindane are also individually associated risk [60]. It is likely that the underlying mechanism is differential gene regulation in males and females particularly in relation to sex steroid–responsive genes [61].

2.7. Allele number and penetrance

The term autosomal dominant implies that the homozygotes exhibit the same or a similar clinical phenotype to the heterozygotes. However in practice, for most dominant human disorders the clinical symptoms in homozygotes tend to be significantly more severe than in the heterozygotes [62]. This is true in low-penetrance mutations e.g. mutations in the RET gene, associated with isolated Hirschsprung disease (HSCR) which are dominant loss-of-function mutations with incomplete penetrance and variable expressivity. Although the heterozygous IVS + 5G- > A mutation is of low penetrance for short segment HSCR, the homozygous state is fully penetrant for total agangliosis or long segment HSCR. Thus the penetrance of RET gene mutations in HSCR depends not only on the nature of the mutation but also on the allele dosage as well as the modifier [63].

Variants of the melanocortin 1 receptor (MC1R) gene are common in individuals with red hair and fair skin, but the relative contribution to these pigmentary traits in heterozygotes, homozygotes and compound heterozygotes for variants at this locus from the multiple alleles present in Caucasian populations is unclear. The shade of red hair frequently differs in heterozygotes from that in homozygotes/compound heterozy-

gotes and there is also evidence for a heterozygote effect on beard hair colour, skin type and freckling. These data provide evidence for a dosage effect of MC1R variants on hair as well as skin colour [64].

A linear relationship between AGT235T allele number ("dosage") and blood pressure in an ethnically mixed urban population confirmed its role as an independent risk factor for hypertension for men and women when in homozygosity [65].

2.8. Oligogenic inheritance and penetrance

Incomplete penetrance of a mutation can be due to the oligogenic nature of the disease and hence to requirement for multiple genes to be mutated for the condition to manifest [1].

Oligogenic inheritance may occur in cases of nephronophthisis. Nephronophthisis (NPHP) is a recessive cystic renal disease that leads to end stage renal failure. Twenty-five percent of nephronophthisis cases are caused by large homozygous deletions of NPHP1, but six genes responsible for nephronophthisis have been identified. Two mutations in one of NPHP1–4 genes were identified in 44 families with NPHP. Furthermore digenic disease was detected in one patient who carried one mutation in NPHP2 and a second mutation in NPHP4. Also a single mutation was detected in nine families suggesting that the second mutation may be another as yet unidentified NPHP gene [66].

Oligogenic inheritance can also be demonstrated in the Hirschsprung disease (HSCR). Long segment, L-HSCR, sometimes syndromic, is caused by coding sequence mutations at one of several loci including RET, GDNF, SOX10, EDN3 and EDNRB [67,68]. Short segment S-HSCR (80% of cases) reveals complex segregation patterns involving contribution from at least three loci, one of which is the RET gene on chromosome 10q11 with a multiplicative interaction with other loci at 3p21 and 19q12, encompassing currently unidentified gene [68].

Other examples of monogenic inheritance include Holoprosencephaly [69], Bardet–Biedle syndrome [70], sporadic epilepsy [71] familial venous thrombosis [72].

2.9. Digenic inheritance and penetrance

Digenic inheritance occurs in cases where the interaction of mutations in two different genes is required for expression of clinical phenotype. In this situation, a mutation in one copy of each gene is required for full clinical phenotype. The double heterozygous probands exhibit a more severe phenotype than his single heterozygous relative i.e. complete penetrance [73]. In the absence of one of the mutations, the other mutation may be non penetrance or could be responsible for a less severe phenotype or reduced penetrance [1,73] e.gs of digenic inheritance, include Bardet–Biedle syndrome, Q-T syndrome, hypogonadotrophic hypogonadism, nephrotic syndrome and holoprosencephaly.

In hypogonadotrophic hypogonadism(IHH) a significant inter- and intrafamilial variability and apparent incomplete penetrance in familial cases are present. Two different gene defects (FGFR1 and NELF) synergize to produce a more severe phenotype in IHH families (Kallmann syndrome, IHH and anosmia) than either alone [74].

The Bardet–Biedle syndrome is an autosomal recessive disorder where four genes have been identified, BBS1, BBS2,

BBS4 and BBS6. The potential requirement for a third mutation in a second BBS gene in addition to two mutations in the first BBS gene was termed "triallelic" [75].

Digenic inheritance may also occur as a result of mutations in the genes encoding different subunits of the same multimeric protein (e.g. PRpH2 & ROM1), an oligomeric complex (KCNJ 10 & SLC26A4) or simply two proteins may directly interact with each other to form a structural component (e.g. polycystins 1&2). However mutations in receptor/ligand pairs can also result in digenic inheritance (e.g. PROK2 & PROKR2). Digenic inheritance can involve mutations in different genes that compromise the regulatory (e.g. HFE & HAMP), biosynthetic (e.g. ZMPSTE 2484 & LMNA) or degradative pathways (e.g. PC5 kg & LDLR pathway). The two proteins may be in the same signalling pathway, but act at distinct steps e.g. a ligand could induce the activity of a transcriptional factor [1].

In practice it is not always clear if a given situation constitutes a true digenic inheritance [76] or it is simply the co-inheritance of two mutations in different genes. In the former case – the expression of disease phenotype requires the presence of both gene lesions. In the latter case, co-inheritance may aggravate the clinical phenotype, but each lesion is associated with its own clinical sequelae [77].

2.10. Modifier genes and penetrance

In single gene disorders there is one gene which is primarily responsible for the disease with one or more independently located inherited modifier genes that influence the phenotype [1]. So any genes involved in the pathogenic process or play a role in phenotypic variation or altered disease severity represent modifier genes [78].

Variants in unlinked modifier genes which affect penetrance have been reported in many diseases including, pancreatitis [79], Gaucher disease [61], and cardiomyopathy [80].

Many different gene loci, have been reported to be responsible for non syndromic autosomal recessive hearing loss. In a large pedigree, linkage to the chromosomal region 4q31 was demonstrated [81]. Also homozygosity of DFNB 26 gene was found in all affected individuals as well as in many unaffected individuals and Zlotogora was able to demonstrate the existence of a dominant modifier (DFNM1) on chromosome 1q24 [10].

In cystic fibrosis, it is not possible to predict the clinical phenotype of a patient based solely on knowledge of the exact mutation in the cystic fibrosis gene, CFTR. In fact at least seven different modifier genes have been described that alter the clinical phenotype [82]. Although numerous environmental factors have been identified as influencing cystic fibrosis (CF) pulmonary phenotype, there is now growing evidence that polymorphic variants in genes beside CFTR play an important role in determining severity of CF lung disease [83]. These modifier gene include MBL2-O (variant alleles of MBL2 gene) which produces mannose binding lectin (MBL), functional polymorphisms in TGFB1 gene in both promoter (-509) and at position $+869$ (codon 10) which influence circulating levels of transforming growth factor B, [84] α1, antitrypsin (SERPINA1), [85] B2 adrenergic receptor (ADRB2), [86] Glutathione S-transferase (GSTM1) [87], Nitric oxide synthase (NOS3) [88], Tumour necrosis factor (TNF), and Glutamate-cysteine ligase (GCLC) [89].

SAA1 is one of the few modifiers identified in humans. This gene influences the risk of renal amyloidosis (RA) in patients with familial Mediterranean fever (FMF), a Mendalian autoinflammatory disorder associated with mutations in MEFV gene. Indeed the SAA1 and homozygous genotype at the MEFV locus are two main risk factors for RA [90].

2.11. Copy number variations and penetrance

Genomic copy number variations (CNVS) are increasingly recognised to contribute to risk for human diseases. CNV involving loss (e.g. deletions) or gain (e.g. duplication) of up to several million base pairs of DNA sequence constitute upward of 5% of human genome. CNV can alter gene dosage and may involve multiple genes and/or regulatory regions. In general CNV deletions show higher penetrance (more severe phenotype) than duplications and longer CNVs often have higher penetrance and/or more clinical features than smaller CNVs [91].

Estimates of clinical penetrance of recurrent pathogenic copy number variations (CNV) vary widely depending upon CNV size, genomic location, disorder in question and genetic variants in vicinity [92].

There is evidence for disease penetrance relating to CNV size in the Pelizaeus Merzbacher disease (characterised by leucodystrophy in which myelin is not formed in CNS) and manifesting carriers with a familial 11 Mb duplication at Xq22 genomic region, including proteolipid protein (PLP1) [93]. Also Mintz demonstrated that CNVs are 19% more common in autism that in controls [94].

Male-biased autosomal effect of 16p13.11 CNV was reported in neurodevelopmental disorders including autism, ADHD, intellectual disability and schizophrenia. Associated analysis revealed an excess of CNV in cases compared with controls and a sex biased effect, with a significant enrichment of CNVs only in the male subgroup of cases and not in females [95].

Recent observation in human indicates a tentative link between CNV and weight regulation. Smith-Magenis syndrome (SMS) manifesting obesity and hypercholesterolemia results from deletion CNV at 17p11.2, but is sometimes due to haploinsufficiency of a single gene, RAI1. The reciprocal duplication in 17p11.2 causes Potocki–Lupski syndrome (PTLS). Lacria et al., demonstrated that Dp(11)17 is obesity apposing. It conveys a highly penetrant, strain independent phenotype of reduced weight, linear body composition, lower TC/LDL and insulin sensitivity that is not due to alteration in food intake or activity level in mice and men [96].

There is synergy between multiple large CNVs leading to severe intellectual disability and congenital anomalies [97].

CNV can ameliorate clinical phenotype in spinal muscular atrophy where an increased copy number of SMN2 gene can greatly reduce the severity of the disease caused by the homozygous deletion of SMN1 gene because SMN2 genes, which lack a splicing enhancer, can generate some functional product, therefore can compensate for the loss of the SMN1 gene [98].

2.12. Single nucleotide polymorphism (SNPs) and gene penetrance

It has long been known that mutations in non coding regions which affect gene expression can cause human genetic disease. Classic examples include thalassaemias and hypercholesterol-

emia. However the majority of known functional DNA variants that have been related to disease affect the protein structure. Currently lists of 26,535 missense/nonsense mutations compared to 545 regulatory mutations have been elucidated. This is because their location is generally predictable within or around coding sequence and they are easier to recognise as variants that alter mRNA coding Alternatively, the discrepancy may be due to regulatory polymorphisms, having smaller phenotypic effects that in isolation, they are not sufficient to cause disease [99].

Variation in gene expression occurs and is common in a substantial proportion of genes. The origin of this variation may be in allele-specific variation (cis affect), interindividual variation as a result of polymorphism in other genes that regulates expression of target genes (trans effect), inter-individual variation in environmental factors that control gene expression or as a consequence of phenotypic state as drugs and nutrition [99].

SNPs account for 90% of all polymorphisms in humans. There are about three million SNPs in the human genome (1 per 1000 nucleotides), two thirds of which are in non-coding DNA [100].

There is a significant association between 381T (rs3815188) variant and migraine, specifically in migraine without aura suffers, while the G 684A (rs1043994) variant was found to be significantly associated with migraine, specifically in migraine with aura suffers [101].

Frasen et al. [102] select SNPs for follow up that showed a correlation to gene expression of patients with Crohn's disease (CD). They identified two cis expression quantitative trait loci (cis-e QTL) SNPs that were associated with CD rs2298428 in UBEL3 and rs2927488 in BCL3.

In long QT syndrome, the genotype of a missense polymorphism (lys 897 Thr rs1805123) in KCNH2 gene appears to distinguish symptomatic from asymptomatic individuals carrying a low penetrance Ala 116 val pathogenic mutation [103].

A population allele of one SNP may contribute to pathogeneses only in the presence of a specific allele of another SNP. These SNPs may be linked as in the case of migraine susceptibility or unlinked within different genes as in the transferrin gene [1].

SNPs may also render the pathogenic coding mutation more or less deleterious or penetrant depending on whether the allele harbouring it is more or less expressed than the wild-type allele as in familial hypercholesterolemia [104].

3. To conclude

Some autosomal dominant and autosomal recessive conditions do not follow the Mendelian genetics. So faithfully, these conditions are said to have incomplete or reduced penetrance.

Reduced penetrance is a common phenomenon in genetic disorders. It can explain why genetic disorders can occasionally be transmitted through unaffected parents. It also explains why healthy individuals can have a large number of potentially disadvantageous mutated variants in their genomes, without suffering any obvious ill effects.

An estimate of the percentage of penetrance in autosomal dominant as well as autosomal recessive conditions can be made from pedigree, family history data and now DNA sequencing. In fact large population studies are necessary for measuring penetrance for elucidation of recurrence risks in genetic counselling.

Conflict of interest

The author declare no conflict of interest.

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