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One gene, many phenotypes

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ABSTRACT

Phenotype descriptions are valuable information right at the interface of medicine and biology. With the rapid advancement in the field of genetics, thousands of genes involved in human diseases have been cloned. It was expected that knowledge of mutations would lead to consistent genotype-phenotype correlations. The understanding of mechanisms underlying genotype-phenotype discrepancies is important, as it will move clinical genetics towards predictive medicine, allowing better selection of therapeutic strategies and individualized counseling of persons affected with genetic disorders.

Key Words:

Gene, phenotype, mosaicism, epigenetics, pleiotropy.

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INTRODUCTION

Phenotype descriptions are valuable information right at the interface of medicine and biology. Their main value lies in helping to dissect the relationships between diseases and genes[1], in clinical application in genetic counseling and prenatal diagnosis. The phenotype can be thought of as a product of genes interacting with each other and with the environment. A concise definition of a gene, taking into account complex patterns of regulation and transcription, genic conservation and non-coding RNA genes, has been proposed by Gerstein et al.[2] "A gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products".

Mutations in different genes can lead to similar phenotype e.g., hereditary spherocytosis can be due to mutations in the genes encoding for spectrin, ankyrin[3]. In contrast, mutations in one gene could cause multiple phenotypes, as best illustrated in the case of lamin A/C, whereby mutations can cause 13 different diseases.[4]

With rapid advancement in the field of genetics, thousands of genes involved in human diseases have been cloned. It was expected that knowledge of mutations would lead to consistent genotype-phenotype correlations, clarifying why a given genetic change results in a particular phenotype. However, genotype-phenotype correlation is often incomplete. Monogenic diseases provide the simplest models for studying genotype-phenotype relationships. The understanding

of mechanisms underlying genotype-phenotype discrepancies is important, as it will move clinical genetics towards predictive medicine, allowing better selection of therapeutic strategies and individualized counseling of persons affected with genetic disorders.[5]

Monogenic disease with many phenotypes:

I. One gene, many mutations, many phenotypes:

1. Allelic heterogeneity.
2. Non functional vs. partially functional/truncated gene product.
3. Loss of function vs. gain of function.
4. Pleiotropy.

II. One gene, one mutation, many phenotypes.

III. Other mechanisms for phenotypic heterogeneity of monogenic disease:

1. Mosaicism (gene dosage effect).
2. Trinucleotide repeat expansion.
3. X- Inactivation.
4. Phenotypic heterogeneity due to the interaction of alleles at different loci.
5. Modifier genes.
6. Alternative splicing.
7. Epigenetic mechanisms.
8. Gene and environment.

I. One gene, many mutations, many phenotypes.

1- Allelic heterogeneity:

This phenomenon, whereby different mutations at the same locus result in different phenotypes. It is very interesting to know that mutations at a single locus can lead to diseases with entirely different clinical features. For example, mutations in the RET gene have been implicated in the etiology of Hirshprung disease as well as multiple endocrine neoplasia (MEN) Type 2. The underlying mechanism is either quantitative or qualitative change in the gene product. Some of the examples of allelic heterogeneity have been listed in (Table 1).[5]

Table 1: Selected examples of allelic heterogeneity. [5]

Disease	Gene	Disease
Huler syndrome	IDUA	Scheie syndrome
Charcot-marie-tooth neuropathy	PMP22	Hereditary neuropathy with pressure palsy
Hyperkalemic periodic paralysis	SCN4A	Paramyotonia congenita
Creutzfeldt-jacob disease	PRNP	Familial fatal insomnia
Pseudohypoparathyroidism IA	GNAS1	Albright hereditary osteodystrophy
Kennedy disease	AR	Androgen insensitivity
Cystic fibrosis	CFTR	Congenital bilateral absence of vas deference
Duchenne muscular dystrophy	DMD	Becker muscular dystrophy
Hirschsprung disease	RET	Multiple endocrine neoplasia type 2

2- Non functional vs. partially functional/truncated gene product:
Duchenne and Becker muscular dystrophies are caused by mutations in the dystrophin gene. Mutations that partially inactivate the gene product cause Becker muscular dystrophy (BMD), while mutations which completely inactivate the gene product produce Duchenne muscular dystrophy (DMD).

3- Loss of function vs. gain of function:
Phenotype resulting from reduction in the amount of normal protein is called loss of function, while gain of function mutations, also known as neomorphic, are characterized by the ability of the mutant allele product to perform new functions.[6]

Example of that is *RET* gene which codes for a tyrosine kinase receptor. Loss of function mutations in *RET* gene that lead to nonfunctional product or lower expression of *RET* gene give rise to Hirschsprung disease. Gain of function mutations at the same locus that produce constitutively activated receptors lead to MEN Type 2. Similarly, loss of function mutations at FGFR1 locus cause an autosomal dominant form of Kallman syndrome characterized by anosmia and hypogonadotropic hypogonadism, also cause lacrimo-auriculo-dento-digital (LADD) syndrome[7]. The gain of function mutations at the same site lead to a form of craniosynostosis (Pfeiffer syndrome).[8]

Also in the fibroblast growth factor receptor 3 (FGFR3), point mutations in specific domains are associated with autosomal dominant dwarfism and craniosynostosis syndromes such as hypochondroplasia, achondroplasia (the most common form of skeletal dysplasia), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), thanatophoric dysplasia, Crouzon syndrome with acanthosis nigricans and Muenke coronal craniosynostosis[9]. Several reports have demonstrated that these mutations lead to constitutive activation of the receptors[10]. In contrast with the inhibitory role on bone growth, an oncogenic role for FGFR3 in human cancer has emerged. Somatic activating mutations in FGFR3 have been reported in multiple myeloma and, more recently, in two epithelial malignancies, i.e. bladder- and cervix carcinomas[11]. Nearly all mutations identified in bladder tumours are identical to the activating mutations responsible for thanatophoric dysplasia, a lethal form of dwarfism.[12]

Several genes play important role in embryogenesis have also been shown to play a role in causing cancer (Table 2).[13]

Table 2: Genes that can cause both developmental anomalies and cancer.[13]

Gene	Chromosome	Developmental anomaly	Cancer
PAX3	2q35	Waardenburg syndrome type 1	Alveolar rhabdomyosarcoma
KIT	4q12	Piebaldism	Mast cell leukemia
PTCH	9q22	Gorlin	Basal cell carcinoma
RET	10p11	Hirschsprung	MEN2A, MEN2B, thyroid carcinoma
WT1	11p13	Denys-drash	Wilms tumer

4- Pleiotropy:
The term pleiotropy comes from the Greek pleion, meaning "many" and trepein, meaning "influencing". Pleiotropy has been challenged by the remarkably diverse syndromes that can result from different mutations in the same gene, for example the LAMNA gene and X-linked filamin A gene. Mutations in LAMNA gene may cause Emery-Dreifuss muscular dystrophy, a form of limb girdle muscular dystrophy, a form of Charcot-Marie-Tooth disease, dilated cardiomyopathy, Dunnigan type familial partial lipodystrophy, mandibuloacral dysplasia and the very rare condition Hutchinson-Gilford progeria. Mutation in the filamin A gene have recently been implicated in the distinct, though overlapping, X-linked dominant dysmorphic conditions oto-palato-digital syndrome, Melnick-Needles syndrome and frontometaphyseal dysplasia and periventricular nodular hetertopia.[13]

Antagonistic pleiotropy refers to the expression of a gene resulting in multiple competing effects, some beneficial but others detrimental to the organism. This is central to a theory of aging first developed by Williams[14]. Williams[14], suggested that some genes responsible for increased fitness in the younger, fertile organism contribute to decreased fitness later in life.

One such example in male humans is the gene for the hormone testosterone. In youth, testosterone has positive effects including reproductive fitness but, later in life, there are negative effects such as increased susceptibility to prostate cancer. Another example is the p53 gene which suppresses cancer, but also suppresses stem cells which replenish worn-out tissue.[15]

II. One gene, one mutation, many phenotypes:
The phenomenon of allelic heterogeneity is not unexpected, as the gene product may get differentially changed by the different mutations and so the phenotypes. More surprising is the fact that individuals with similar genetic lesions can have significantly different clinical manifestations. This is well observed in autosomal dominant disorders, where 'variable expressivity' and 'reduced penetrance' have been classically described. Expressivity is defined as the severity of the phenotype. When the severity of disease differs in people with same genotype, the phenotype is said to have variable expressivity. Penetrance is the proportion of persons with a particular genotype who manifest the disease. The reduced penetrance leads to 'skipping of generation'. Neurofibromatosis Type 1(NF1) is characterized by extreme clinical variability, not only between unrelated individuals and among affected individuals within a single family but even within a single individual with NF1 at different times in life. The mutation in the NF1 gene can produce different lesions in different tissues such as cafe-au-lait spots, neurofibroma, iris hamartoma, skeletal abnormalities or mental retardation. Each of these pleiotropic effects can have varying severity among the affected family members (variable expressivity). The mechanisms underlying such clinical variations are often unclear. It is supposed to be the result of the modifying effects of other genes, as well as due to interaction with environmental factors.[5]

III. Other mechanisms for phenotypic heterogeneity of monogenic disease:
There are a variety of other mechanisms

that may be responsible for generating phenotypic diversity of diseases that are encoded at a single locus, Some of these, which have been loosely labelled epigenetic, are understood, at least in principle, although the molecular mechanisms involved have not been established and the prediction of the phenotype from the underlying genotype may be extremely difficult.[16]

1- Mosaicism (gene dosage effect):
Mosaicism is the existence of two cell lines with different genetic constitution that have been derived from a single zygote.

The phenotypic severity is determined by the proportion of cells carrying the mutation. This is best exemplified in mitochondrial disorders. There are thousands of mitochondrial DNA (mtDNA) molecules in a cell. When a mutation occurs in the mtDNA, it is at first present in only one of the mtDNA molecules. At cell division, the mtDNA molecules replicate and sort randomly among the daughter cells. Each daughter cell may receive very different proportions of mitochondria carrying normal and mutant mtDNA. The phenotype will depend upon three factors: The relative abundance of mutant mtDNA (heteroplasmy), the tissue distribution of the mutant mtDNAs and the vulnerability of each tissue to impaired oxidative metabolism (threshold effect). Thus, reduced penetrance, variable expression and pleiotropy are typical features of kindred with mitochondrial disorders. For example, a deletion of 4977 bp of mtDNA is commonly encountered in Kearns-Sayre syndrome (characterized by the triad of pigmentary retinopathy, external ophthalmoplegia and onset before the age of 20 years). The same deletion has also been identified in cases of Pearson syndrome (sideroblastic anemia, exocrine pancreatic dysfunction) and progressive external ophthalmoplegia. The different phenotypes from the same deletion are due to tissue distribution of the defect. If the defect is present in mitochondria of all tissues, the phenotype is Kearns-Sayre syndrome. In Pearson syndrome, the defect is localized mainly to the hematopoietic tissue, while the defect is confined to the skeletal tissues in progressive external ophthalmoplegia[17]. Another striking example of phenotypic diversity arising from mosaicism is the androgen insensitivity syndrome (AIS). Androgen insensitivity syndrome is the major cause of male pseudohermaphroditism. It is an X-linked disorder caused by mutations in androgen receptor (AR) gene. Androgen insensitivity syndrome can be subdivided into three highly variable phenotypes: complete AIS, when the affected persons have female external genitalia; partial AIS, when the genitalia are ambiguous and mild AIS, when the affected individuals have normal male external genitalia. In a number of cases, identical mutations have resulted in significantly different phenotypes. This is due to somatic mosaicism[18]. The co-expression of wild allele shifts the AIS subtype to a higher degree of virilization than expected from the mutant allele alone.[5]

2- Trinucleotide repeat expansion:
Also known as triplet repeat expansion, is the DNA mutation responsible for causing any type of disorder categorized as a trinucleotide repeat disorder. These are labelled in dynamical genetics as dynamic mutations[19]. At least 12 neurological diseases are known to result from expansion of CTG, CGG, CAG or GAA repeats. Fragile-X syndrome, which is a common cause of mental re-

tardation in males, is a good example of how phenotypic, heterogeneity can be generated by expansion of regions containing trinucleotide repeats, in normal individuals, a DNA segment at Xq27,3 contains between six and 60 copies of the repeat CGG, in some persons, the number is increased to between 60 and 200. In this case, the disorder is clinically silent; premutations of this kind are characteristic of normal-transmitting males and some mentally normal female carriers. Full mutations, which arise in the offspring of pre-mutation carriers, consist of many hundreds or thousands of copies, of the repeat and lead to the full expression of the clinical phenotype. Heterozygous carriers have an extremely variable phenotype: Approximately 50% of females carrying the full mutation, how some mental impairment although those who carry a pre-mutation are usually normal. Similarly, female carriers may or may not show some of the somatic changes associated with the disease in males. Although X inactivation may be partly responsible, this does not seem to be the whole story. Huntington's disease, another neurodegenerative disorder, also shows considerable phenotypic heterogeneity, particularly with respect to age of onset and rate of progression, At the 5`- region of the locus involved there is a CAG repeat sequence, which ranges from ten to 30 copies in normal individuals and which is expanded to beyond 35 copies in patients with Huntington's disease, there appears to be some relationship between the length of the repeats and age of onset. Remarkably, the juvenile onset of cases shows a preponderance of paternal transmission[16]. In 2007 a new disease model was produced to explain the progression of Huntington's Disease and similar trinucleotide repeat disorders, which, seems to accurately predict age of onset and the way the disease will progress in an individual, based on the number of repeats of a genetic mutation[20]. Overall these conditions show considerable phenotypic heterogenity This is reflected at the molecular level, where there is a wide variation in the extension of the length of the repeats required to produce an abnormal phenotype, not all diseases are associated with a premutation length and the relationship between the expansion of trinucleotide repeats and the causation of the disease is not clear. In some cases, those in which the repeats involve promoters, it is thought that methylation of the promoter region lead to gene silencing while in those that involve CAG repeats it is thought that polyglutamine expansion may play a role. But what is clear is that genotypic instability of this type is responsible for neurodegenerative disorders with widely differing phenotypes.[16]

3- X- Inactivation:

X-inactivation in females is usually random, because of that female carriers for a particular X-linked trait are in effect, mosaics, with each cell population functionally hemizygous for a particular trait. Hence carriers would be expected to produce approximately half of an abnormal gene product or express about the same amount of a product. However, because X inactivation occurs early during embryogenesis, there is wide variation in the expression of X-linked mutant genes in females; considerable skewing of the distribution of values is encountered. Interestingly, there is a high frequency of discordant phenotypes, among twins with X-linked diseases[21], this may be because X inactivation preceeds twinning and non-randomness reflects asymmetrical splitting of the inner cell mass,

furthermore, it seems likely that some X-linked disorders may have a deleterious effect on cell function during early embryogenesis, a phenomenon that may lead to extreme skewing of the distribution of cell populations. The situation is further complicated by the fact that not all parts of the X chromosome are inactivated. These different issues make for considerable heterogeneity in the expression of mutant gene's in female carriers for X-linked disorders. There is increasing evidence that negative selection may be a major factor for the skewed distribution of cell populations in female carriers. For example, Coleman et al.[22] described a female with the genes for both incontinentia pigmenti and haemophilia A. It appeared that the presence of the gene for incontinentia pigmenti on an X chromosome had unmasked the factor VIII gene mutation on the other chromosome, presumably by negative selection of the former. Another example is female carriers of hemophilia and DMD may occasionally show mild or even full expression of the disease. This is due to nonrandom inactivation of X chromosome, as by chance, most of the X chromosomes carrying the normal allele get inactivated resulting in clinical expression of the disease.[5]

4- Phenotypic heterogeneity due to the interaction of alleles at different loci:

Retinitis pigmentosa is the name given to a set of inherited degeneration of the retina. This condition is very heterogeneous, both clinically and with respect to inheritance. It is X- linked, however both autosomal dominant and recessive forms have been described. Kajiwara et al.[23] reported three families in which a form of retinitis pigmentosa segregated; affected individuals were double heterozygotes for a specific peripherin-RDS gene mutation and a mutation in a second gene, ROM1. It is thought that the products of these two loci. which are on different chromosome, interact non-convalently in the rim region of the photoreceptor outer segment disc membrane. Persons heterozygous for only one of these mutations have no symptoms.

Another condition that shows marked phenotypic heterogeneity is inherited porphyria cutanea tarda. in which heterozygotes are predisposed to photosensitive cutaneous lesions. The phenotype seems to be exacerbated by a variety of enviromental factors, including iron overload and alcohol abuse. The condition results from a deficiency of uroporphyrinogen decarboxylase (URO-D). Not all patients with mutations at the gene that encodes URO-D are symptomatic. Recently it has been found that there is an increased frequency of the alleles of the haemochromatosis gene, notably C282Y AND H63D, in both Argentinian and Italian patients with porphyria culanea tarda. Since the haemochromatosis alleles are associated with increased iron absorption and iron overload and because iron loading exacerbates porphyria cutanea tarda, it seems likely that this is another example of the deleterious interaction of two alleles, in this case with completely different functions.[24,25]

5- Modifier genes:

A modifier gene is defined as an inherited genetic variation that affects the phenotypic expression of another gene. It can affect the pleiotropy, penetrance or expressivity of the disease. Depending upon the nature of modifying effect, modifier genes might cause more severe phenotypes, less severe phenotypes, novel phenotypes or wild-type (normal) phenotypes.[26]

A- Modifier causing less severe (reduced) phenotype of Beta thalassemia. The severity of anemia in beta thalassemia reflects the degree of globin chain imbalance. The excess of alpha globin chain precipitates in red cell precursors leading to ineffective erythropoiesis. This imbalance can be genetically modified by two factors-variation in amount of gamma globin response and alpha globin chain production[27]. The beta thalassemia patients who coinherit alpha globin gene deletions will have less redundant alpha globin chains and tend to have less severe phenotype. Similarly, increased synthesis of gamma globin chain will reduce the disease severity by increasing HbF level. The gamma globin response is also genetically determined. There are many other loci that are not linked to the beta globin gene but modify HbF response. Linkage studies have mapped these loci to three regions of the genome-chromosome 6q23, 8q11 and Xp22.[28]

B- Modifiers causing more severe (enhanced) phenotype
The severity of anemia in beta thalassemia depends on the degree of globin chain imbalance. It is an autosomal recessive condition. The heterozygotes for beta thalassemia mutations are clinically asymptomatic as the degree of imbalance is insignificant. But, the coinheritance of extra alpha globin genes (alpha triplication) increases the imbalance. This leads to symptomatic disease in heterozygotes, sometimes manifesting as 'intermedia' phenotype.[29]

6- Alternative splicing:
Alternative mRNA splicing is another mechanism responsible for different expression of a similar genotype. Two illustrative examples are given below.

A- Duchenne muscular dystrophy and BMD are caused by mutations in the dystrophin gene. Duchenne muscular dystrophy is a severe muscle-wasting disease arising from defects in the dystrophin gene, typically nonsense or frameshift mutations that preclude the synthesis of a functional protein. Becker muscular dystrophy generally arises from in-frame deletions that allow synthesis of a shorter but still semi-functional protein. But, nonsense mutations which should cause DMD have been reported in BMD. This is due to alternative mRNA splicing- skipping of the affected exon leads to removal of the nonsense mutation from the dystrophin mRNA. This results in production of partially functional dystrophin and BMD phenotype.

B- Cystic fibrosis is an autosomal recessive disorder. The genotype delta F508/R117H can lead to either severe phenotype of cystic fibrosis leading to respiratory failure or the milder phenotype, in which the only manifestation is congenital bilateral absence of vas deferens (CBAVD). The CFTR gene has two intron 8 variants. One is associated with efficient mRNA splicing, while the other causes inefficient splicing. The R117H allele is capable of producing partially functional protein. The R117H allele associated with efficient splicing leads to production of some amount of partially functional protein and hence milder phenotype (CBAVD). On the other hand, severe phenotype results if the intron 8 variant causes inefficient splicing and production of nonfunctional protein.[30]

7- Epigenetic mechanisms:
The term epigenetics refers to changes in gene expression caused by envi-

ronmental factors, not by changes in the underlying DNA sequence. These changes may remain through cell divisions for the remainder of the cell's life. Sometimes the changes last for multiple generations[31]. The Greek prefix epi- in epigenetics implies features that are "on top of" or "in addition to" genetics; thus epigenetic traits exist on top of or in addition to the traditional molecular basis for inheritance. Epigenetic phenomena modulate when and at what level genes are expressed. Thus, the expression of a mutation also depends upon the activity state of the locus carrying it; the mere presence of a genetic defect may not be enough for clinical expression. Epigenetic effects in humans include the following:

A- Genomic imprinting and related disorders:

The term "imprinted gene" refers to genes whose expression is conditioned by their parental origin.[32]

The expression of a gene depends upon the parent who passed on the gene. For example, two different diseases - Prader-Willi syndrome and Angelman syndrome - are due to deletion of the same part of chromosome 15. When the deletion involves the chromosome 15 inherited from the father, the child has Prader-Willi syndrome, but when the deletion involves the chromosome 15 inherited from the mother, the child has Angelman syndrome. This is a striking example of how the parental origin of a genetic defect influences the clinical phenotype. Beckwith-Wiedemann syndrome is also associated with genomic imprinting, often caused by abnormalities in maternal genomic imprinting of a region on chromosome 11.

B- Transgenerational epigenetic observations:

Marcus Pembrey and colleagues also observed that the paternal (but not maternal) grandsons of Swedish boys who were exposed to famine in the 19th century were less likely to die of cardiovascular disease; if food was plentiful then diabetes mortality in the grandchildren increased, suggesting that this was a transgenerational epigenetic inheritance.[33]

8- Gene and environment:

Virtually all human diseases result from the complex interplay of genetic susceptibility factors and modifiable environmental factors. This is most obvious in the context of common illnesses such as diabetes, coronary artery disease or cancer. But, environmental factors play a significant role in the expression of monogenic disorders too. For example, inherited metabolic disorders manifest when there is introduction of the substrate for which the metabolism is defective. Similar genetic defects may have different phenotypes if the environmental factors are not similar.[5]

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