THE TERMS "DOMINANT" AND "RECESSIVE" SHOULD BE AVOIDED DUE TO GENE THERAPY

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The accumulation of scientific data can conflict with theoretical propositions, requiring their revision. Ptolemy's model of celestial motion was repeatedly "upgraded" until the paradigm fundamentally changed. Today, we not only understand the structure of the solar system but also see the universe across fourteen billion light-years. Similarly, phenotype-based medical genetics still operates with concepts such as dominance, recessiveness, penetrance, expressivity, complementarity, epistasis, and so on. These are descriptive terms of limited accuracy, which are redundant and often confounding in clinical settings. This opinion article re-examines the relationship between molecular inheritance and its phenotypic manifestations in light of the growing role of gene editing and gene therapy. We believe that the use of the classical terms “dominant” and “recessive” in a medical context should be avoided as non-informative and possibly misleading in terms of clinical decisions and treatment choices.

Keywords: dominant, recessive, genotype, phenotype, loss-of-function, gain-of-function, haploinsufficiency, dominant-negative effect, clinical genetics, compensatory gene therapy, genome editing

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В МЕДИЦИНЕ СЛЕДУЕТ ИЗБЕГАТЬ ТЕРМИНОВ «ДОМИНАНТНЫЙ» И «РЕЦЕССИВНЫЙ» ИЗ-ЗА РАЗВИТИЯ ГЕННОЙ ТЕРАПИИ

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Понимание устройства системы ведет к оптимизации описывающей ее модели. Модель движения небесных тел Птолемея многократно усложнялась с целью подгонки под реальность, пока точка зрения исследователей кардинально не изменилась. Аналогично и «фенотипическая генетика» до сих пор пытается описывать наблюдаемое в терминах XIX в.: доминантность, рецессивность, пенетрантность, экспрессивность, комплементарность, эпистаз и т. д. Сегодня мы не просто понимаем устройство Солнечной системы, но видим Вселенную на четырнадцать миллиардов световых лет. Использовать в клинической генетике описательную фенотипическую терминологию — то же самое, что определять расположение небесных тел по гороскопу. В статье рассмотрено соотношение некоторых молекулярных механизмов наследования и их фенотипических проявлений. На фоне возрастающей роли генередактирующей, генозаместительной и генокомпенсаторной терапии использование фенотипических терминов «доминантный» и «рецессивный» становится нежелательным, поскольку не отражает молекулярный профиль заболевания и может вводить врачей в заблуждение при выборе метода лечения.

Ключевые слова: доминантный, рецессивный, генотип, фенотип, потеря функции, возрастание функции, гаплонедостаточность, доминантно-негативный эффект, клиническая генетика, генозаместительная терапия, генокомпенсаторная терапия, геномное редактирование

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Establishing the relationship between a genotype and its manifestation (phenotype) is a key task in genetics, which for diploid organisms is complicated by the interaction of two complete sets of (different) genetic information. Gregor Mendel termed a parental trait expressed in the offspring "dominant", as opposed to cryptic "recessive" traits prone to vanishing. Today, we know that traits represent the realization of the function of proteins (or regulatory RNAs) encoded in DNA, and a dominant phenotype can result from either increased or decreased protein activity/concentration due to various genetic and epigenetic factors: allelic polymorphism of the protein-coding sequence, DNA methylation profile, histone modification and promoter activity, small regulatory RNAs, post-translational protein modification, polygenic interactions, etc. In medical genetics, loss-of-function (LOF) mutations are typically associated with recessive inheritance, while gain-of-function (GOF) mutations are associated with dominant inheritance. However, there are numerous exceptions to this simplistic rule, highlighting the importance of understanding the functional context and biological role of the affected protein or the corresponding regulatory mechanism, particularly in view of gene therapy options.

The rapid development of genetic programming technologies (including the modulation of gene activity by delivering additional copies, CRISPR editing, or using small RNAs) has led to the emergence of a wide range of high-tech drugs prescribed to compensate for genetic disorders (if a function is deficient, it obviously needs to be enhanced; if it is excessive, it needs to be attenuated). At the same time, the "phenotypic" terms dating from the mid-19th century continue to appear in medical records, clinical treatment guidelines, laboratory test reports, and even in gene therapy protocols. According to our estimates, up to 8% of laboratory test reports describing specific molecular events in monogenic diseases are misinterpreted by medical geneticists because of confounding "phenotypic" descriptions.

Terminology: inheritance types and corresponding molecular mechanisms

Autosomal dominant (AD) and autosomal recessive (AR) diseases have clearly distinct patterns of occurrence in a genetic pedigree. With AD inheritance, a single mutant copy of the gene (heterozygous state) is sufficient for the development of the disease, which is characterized by a 50% risk of vertical transmission from generation to generation (examples include Huntington's disease, Thomsen disease, Creutzfeldt-Jakob disease, and over 4,000 other conditions) [1–3].

With AR inheritance, a mutation in both copies of the gene is required for the development of the disease (homozygous/compound heterozygous state). In such cases, the parents are usually healthy carriers, and the disease in the offspring occurs due to the coincidence of nonfunctional alleles with a 25% probability (examples include hereditary hearing loss, cystic fibrosis, phenylketonuria, and over 3,000 other conditions) [4–6].

In the case of X-linked recessive inheritance, the trait is phenotypically manifested in males in the hemizygous state, while homozygosity/compound heterozygosity for the mutation is required for manifestation in females. Classic examples of this group of diseases are hemophilia A and color blindness, and over 100 similarly inherited conditions have been described [7, 8].

In X-linked dominant inheritance, the presence of a single mutant allele is sufficient for manifestation. This type of inheritance is characterized by more severe consequences in males, sometimes lethal early in development. An affected woman has a 50% chance of transmitting the disease to offspring of both sexes, while an affected man transmits the mutant allele to all of his daughters and none of his sons. About 40 diseases have this pattern of inheritance. A striking example of X-linked dominant condition is Rett syndrome [9]. Importantly, in women, the pathogenic allele in each individual cell will be either active or not as a result of X-inactivation; the ratio can vary, which explains the phenomenon of varying symptom severity in heterozygous carriers.

The classical Mendelian scheme assumes 100% phenotypic expression of any allele (penetrance) with full strength (expressivity), and that the presence of a mutant variant in a particular number of copies is unambiguously linked to the phenotype. However, for many hereditary conditions, both autosomal dominant and X-linked, so-called incomplete penetrance is observed (when some carriers of a pathogenic allele remain clinically asymptomatic throughout their lives due to the genomic landscape and environmental factors). Incomplete penetrance creates significant difficulties for medical genetic counseling, as a phenotypically healthy individual can transmit a mutant allele to an offspring who unexpectedly develops the disease. Age-dependent penetrance and variable expressivity are recognized as well; it should be noted that manifestation of any trait is age-dependent and variable in strength, even in identical twins. For example, for autosomal dominant neurofibromatosis type 1 or hereditary cancer syndromes caused by mutations in tumor suppressor genes (such as BRCA1 or TP53), the penetrance is considered age-dependent, while the expressivity varies [10].

Conventionality of "dominance" and "recessiveness" in the context of gain- and loss-of-function mutations

From a molecular perspective, different inheritance patterns are typically associated with functional types of mutations. Gain-of-function mutations confer a new or enhanced function to the protein, which is pathogenic even with a normal second allele. This mechanism most often underlies dominant diseases. However, the disease typically occurs only in heterozygotes, as homozygosity for such critical defects leads to embryonic death early in development.

By contrast, loss-of-function mutations result in complete or partial loss of protein function (for example, due to promoter inactivation or severe disruption of protein structure) and are usually associated with recessive diseases [11, 12].

However, under certain conditions, LOF mutations can lead to dominant pathologies (in heterozygotes). This occurs through two main mechanisms: haploinsufficiency and dominant-negative effects. Haploinsufficiency occurs when the level of normal protein synthesized from a single functioning allele is insufficient to fully implement the necessary functions, leading to the development of disease (examples include Marfan syndrome, DiGeorge syndrome, Williams syndrome, and approximately 500 other diseases) [13–15]. In the context of incomplete penetrance, haploinsufficiency can predispose to disease (examples include tumor suppressor genes, such as TP53 in Li-Fraumeni syndrome, BRCA1 in ovarian cancer, etc.) [16, 17].

A dominant-negative effect is observed when the LOF mutant protein not only loses function but also actively disrupts the functioning of intracellular systems, for example, through inclusion in multimeric complexes, changes in receptor titer, and other methods of competitive inhibition. Thus, LOF mutations can manifest as either recessive or dominant mutations (examples include Brugada syndrome, Culler-Jones syndrome, and approximately 700 other diseases) [18, 19].

Thus, comparing the heterozygous GOF effect of protein hyperactivity/overconcentration and the heterozygous dominant-negative LOF effect of competitive inhibition of multicomplexes, it can be argued that the key factor in understanding the molecular mechanisms of pathology and choosing the correct pathogenetic therapy (gene delivery or genome editing) is the deficiency or excess of function, not homo/heterozygosity (and, especially, not the phenotype).

Incomplete penetrance adds uncertainty to the decision to use a gene therapy, especially when prescribing treatment before the clinical manifestation of a monogenic hereditary disease [20]. In such cases, it is necessary to weigh the reversibility of pathological processes with delayed phenotypic manifestation against the safety of the gene therapy.

CONCLUSION

Thus, in modern medical genetics, the phenotypic terms "dominant" and "recessive" are losing their diagnostic and prognostic value. Their persistent use can mislead the clinical interpretation of molecular-genetic findings and critically undermine the choice of therapeutic strategy. With the rapid development of gene replacement, gene compensatory therapy, and genome editing, the emphasis should be shifted from formally classifying the mode of inheritance to accurately determining the molecular routes of pathogenesis — whether the cause of a disease is a consequence of a deficiency or excess of a specific macromolecule (protein, tRNA, etc.). This functional approach is essential for the prescription of pathogenetically based and personalized therapy.

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