Statement on the Genetic Diagnosis of Factors that Predispose to Multifactorial Diseases, Developmental Disorders, and Drug Reactions

German Society of Human Genetics

1. Introduction

Prior to the introduction of molecular genetic methods, a diagnosis and an individual prognosis was based on the medical and family history, physical findings, biochemical or histological tests, and imaging procedures. The discovery of genes and disease-causing mutations has made it possible in recent years to achieve predictive genetic diagnoses for a growing number of monogenic hereditary diseases. For persons known to be at risk for some autosomal dominant diseases with complete penetrance it is possible to predict with certainty whether this disease will occur later in an individual's life. Even for individuals with a high risk of developing a disease that is neither preventable nor treatable, e.g., Huntington's disease, this information can be of value to these individuals in family planning and making other decisions about the future. For dominant heritable diseases with incomplete but high penetrance, predictive genetic testing may contribute to an improved assessment of the probability of an individual becoming affected with the disease. This is true for some familial cancers (e.g., familial breast or intestinal cancer), for which the results of predictive genetic diagnosis can be useful in planning individual diagnostic and preventive measures.

Some other genetic variants that in themselves do not cause disease (polymorphisms) have been shown to occur statistically more frequently in persons with certain manifestations or diseases (ie., they are associated with these manifestations or diseases). Such diseases are assumed to have multifactorial causes, i.e., the effects are due to several genes interacting with external factors. By comparing the frequency of such genetic variants in affected and nonaffected persons, the validity of using certain genetic variants as single parameters but also as combinations of several such parameters (so-called multiparameter tests) can be determined. Depending on the parameters, these data can be applied in individual cases to modify the prediction about the individual's risk of developing the disease in question (modified risk). A typical example is the association of Bechterew disease with the HLA allele B27. While the predictive value of genetic tests for individual monogenic diseases may not always reach 100%, it usually does lie between 50% and 100%. However for diseases associated with polymorphisms, the predictive value of the genetic tests only rarely exceeds a few percent. The reason is that multifactorial diseases are influenced by environmental factors as well as by many genetic factors, each of which in itself contributes little to the overall phenotype. For high blood pressure several hundred such factors are known to date. In addition, it is unclear whether the interrelation of the individual genes is based on additive, multiplicative, or epistatic effects. Even if all the risk factors could be identified, the predictive value for a given individual would be limited, as is well known from the moderate concordance rates of monozygotic twins with their identical genetic complements.

While the genetic diagnosis of monogenic diseases may be useful when considering preventive and therapeutic measures for such disorders, the diagnosis of disease-associated polymorphisms at best identifies predisposing genetic factors for the individual and yields a modified risk assessment that is frequently of questionable value. Therefore, the qualitative and quantitative significance of this type of diagnosis should be weighed carefully not only when used for individuals but also with broader uses, such as for frequently occurring diseases or in population screening.

In the last few years an increasing number of genetic variants have been identified that are thought to be predisposing factors for endemic diseases or for pharmacogenetic reactions to medications and other exogenous influences (Schulz et al. 2002). These kinds of genetic variants differ from the mutations responsible for monogenic hereditary diseases in two important respects for individual and public health assessments: First, the presence of a certain genotype does not mean that the associated phenotype will have a high probability of manifesting. Second, such variants occur frequently in the general population. In view of their complex interactions with probably many other genetic and nongenetic factors, the significance of certain genetic variants for an individual's health and the effectiveness of possible preventive measures geared to that individual's genotype are difficult to determine (Haga et al. 2003). Many of the polymorphism–disease associations that have been published to date could not be confirmed in follow-up studies, and prospective studies to determine the

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usefulness of such analyses for individuals are lacking.

Based on the present state of knowledge, in the foreseeable future only very few genetic variants will have sufficiently scientifically validated predictive values—and the therapeutic and preventive options derived from them—to warrant adding a respective diagnostic test to health care programs. Nonetheless, these types of diagnostic procedures are being offered in increasing numbers, not the least via internet, by medical practices and institutions and also by nonmedical facilities, whereby the prevailing quality standards for medical genetic diagnoses are often blatently ignored. The dissemination and application of "genetic disposition" tests or "risk profiles" in this manner disregard elementary principles such as validation, quality control, and cost effectiveness. In addition, essential aspects of patient-protection policies, such as appropriate explanations and individual interpretation of findings are ignored. The German Society of Human Genetics is deeply concerned about these developments. As a society of specialized scientists who are directly affected, it has the responsibility to emphasize that these unacceptable practices should not be allowed to proceed uncontrolled. To prevent their expanding use, a standardized regulation should be introduced that requires the diagnosis of genetic variants to adhere to scientifically recognized criteria. In the following we would like to present the criteria that should be applied when the diagnosis of genetic variants is carried out as a part of health care and when the legally required or private health insurance companies assume the costs of the examination.

2. Scientific Validation and Quality Control

2.1 Clinical Validation

The clinical validity of each genetic variant must be appropriately demonstrated before it is used as a diagnostic or prognostic parameter. To be confirmed scientifically, a variant generally must be studied epidemiologically in the population for whom its diagnostic test will be used. It is especially important to identify the following:

- the allele frequency of the variant in the population in question,
- the clinical phenotype or risk of disease associated with the corresponding genotype,
- the influence of the genotype on the probability of manifestation of the phenotype or the disease (positive and negative predictive values), and
- the influence of preventive measures on the probability that the phenotype associated with the variant will be manifest.

2.2 Analytic Validation

The analytic procedures used in diagnosing genetic variants must meet the same standards of precision and reproducibility as those used for the diagnosis of monogenic hereditary diseases. The guidelines used by the GfH (German Society of Human Genetics) for molecular genetic diagnosis are to be followed (Berufsverband medizinische Genetik e.V., Deutsche Gesellschaft für Humangenetik 2001).

2.3 Quality Control and Evaluation

The technical standards of the applied diagnostic procedures in clinical use must be regularly monitored, as with any other molecular genetic procedure (internal and external quality control). The clinical validity and cost effectiveness of the procedures should also be checked regularly (accompanying prospective epidemiological studies, Kristoffersson 2000).

3. Counseling and Informed Consent

3.1 In General

Since the diagnosis of genetic disposition variants is important for the future of the person being investigated, explanations of the procedure, interpretation of the results, and relevant counseling must meet high standards of quality.

Before being tested for genetic disposition variants, an individual must be appropriately informed of the significance of a genetic disposition to the disease in question and of the preventive or therapeutic options available in case of such a disposition. An individual must be offered genetic counseling prior to being tested, especially if the individual has a family history of a specific disease. As with other predictive diagnoses, written informed consent to carry out the diagnostic procedure should be obtained. Results of the investigation must be explained with reference to the patient's history and other findings.

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3.2 Problems Related to Multiparameter Investigations

Broadly defined "genetic risk profiles" encompassing several genetic variants, some of which may not be individually named or are poorly outlined, are available. These types of investigations are permissable only when

- the physician arranging for the investigation is informed about each individual parameter and has explained them and their significance to the person being investigated,
- both the individual parameters and their combinations have been validated in the manner described in Section 2.1, and
- the test is carried out with reference to a defined clinical phenotype, to have been discussed with the patient during consultations.

Thus it will be clear that global "multiparameter screening" for several or many different health risks is not permissible if it is not feasible to explain all aspects of such a test to the person to be tested and therefore it is not possible to attain his legally binding consent for the test.

4. Scope of Testing and Cost Effectiveness

From the above discussion it is apparent that it should be left solely to physicians to determine whether the diagnosis of a genetic variant is necessary for a given individual. With rising costs of health care, only those forms of genetic diagnosis will be economically tenable for which the costs of an analysis and the medical or psychosocial significance of the results obtainable for the person tested are reasonably related. The application and realization of diagnostic procedures for genetic variants should therefore remain reserved for appropriately qualified medical or nonmedical specialists in human genetics. The general conditions should be regulated in a law for genetic diagnosis.

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