Conference Paper

A. R. Luria and the Twin Method in Modern Medical Genetics

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Abstract

The twin method is one of the classical methods of medical genetics which aids in defining the role of factors of heredity and environment in traits of norm and pathology, to study development of multifactorial diseases and development of genetics of intellectual activity. From the genetic point of view twins may be either monozygotic or dizygotic. The field of intellectual activity, in particular learning ability, attention and memory is most difficult and inaccessible for the genetic analyses of twins.

The very beginning of research of twins' intellectual activity was laid by A.R. Luria in years 1920-1930 and the features of development of twins of various age were revealed. Using tasks that required mental capacities of different levels: immediate memory vs cultural forms of mediated memory, Luria's group compared results of monozygotic and dizygotic twins of different ages (5-7 and 11-13). It has been shown that monozygotic twins are much more similar between themselves concerning mental capacities, natural forms of memory than dizygotic twins. In the older group it was the same difference in natural forma, but much less difference between monozygotic and dizygotic tweens in culturally determined forms of memory. Much more similarity was observed between monozygotic twins who grew separately, than between dizygotic, being raised in the identical social environment. During these researches a number of assumptions have been stated about « the influence of heredity on intellectual activity which will be revealed in the solution of tasks which don't demand special knowledge».

Prospects of modern researches are in comparison of concordance mono-and dizygotic twins, confirming A. R. Luria's assumption of interrelation of natural memory and intellectual endowments of twins with their genotype. Medical genetics confirms that the extent of development of various intellectual traits of monozygotic and dizygotic twins is caused first of all by influence of the environment – training and experience which is revealed is increased in increased variability of most intellectual characteristics at the age of 14–16 years.

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The twin method is based on the principles of comparison of individual traits of mono- and dizygotic twins for revealing the respective degree of influence of environment and genetics in formation of the personality. Monozygotic (MZ) twins arise from the same single cell and have identical genotypes. Dizygotic twins (DZ) arise from different cells. MZ twins are always same sex, whereas DZ twins may be same-sex or opposite-sex. Genotypes of DZ twins differ as common brothers and sisters, but due to simultaneous birth and joint upbringing and education they have the common environment factors hence, the degree of differences is determined by the extent of the difference in genotypes. On condition that the members of twin pairs of any type have a similar environment and education, a greater in-pair similarity of MZ twins as compared with DZ twins may testify to the presence of hereditary influences regarding variability of under investigation trait.

Authorship of the twin method belongs to British anthropologist and eugenicist, Sir Francis Galton (1876), and its main features were stated in his book "The history of twins, as a criterion of the relative powers of nature and nurture".

The methodological bases of the twin method were further developed in 1924 by G. Siemens, who showed the necessity of research of both types of twins and the opportunity of reliable diagnostics of the zygosity based on the analysis of multiple criteria. In addition, G. Siemens formulated the principles of the structure of the twin sample, creating preconditions for studying the genetics of normal variability. Carrying out correlation of two categories of twins, it is possible to find out directly the influence of the genotype on development of one or another trait. Sample selection from MZ twins is necessary in order to reveal principles of influence of environment on a trait. It will make the research clearer and will allow avoidance of influences of collateral factors on results of the experiment.

In spite of gaining considerable popularity, this method by 1920 still was not developed enough in special techniques for genetic analysis of twins. In 1917 H. K. Kol'tsov organized the Institute of Experimental Biology, where for the first time in Russia research on twins was carried out in the department of Eugenics [1]. Up to that time in Russia there was no independent research institute on biology including on genetics. A research program was developed by Professor V. V. Bunak, and implementation of testing of twins was entrusted to G. V. Soboleva. Work consisted of two phases: development of the family trees of sample twins and study of twins themselves for definition of the role of the heredity in formation of one or another trait.

The use of known analytical approaches, relative contribution of genetic factors and factors of environment to phenotype can be evaluated with the aid of this method [2].

Several varieties of the twin method exist:

A classical method is comparison of results of studying MZ and DZ twins. It allows the establishing of reliable patterns of changes in the contribution of environment and phenotype during ontogenesis.

The method of a control twin - is mainly used for studying the influence of environment on a particular psychological trait. MZ twins are an ideal control on each other. If a group of MZ twins is separated to two samples so that in each group there is one equal twin from each pair, a unique situation is created- two samples, equal both by genetic constitution, and by the main environment (general family) parameters. Luria used this method [3].

Method of separated twins - the study is performed with MZ and DZ twins who were separated in early childhood and do not know of each other's existence. Similarity of such children is caused only by the genotype, and environment and its influence is entirely different.

Method of twin families - is mostly used in studying the influence of heredity in development of mental diseases. The twin family method of studying of human heredity is directed to research the members of families of adult twins and their children. Using this method, it is possible to study the role of "maternal" or "paternal" effects of influence on psychological development of children.

Method of single twins is applicable to cases in which only one twin survived after birth. He is good for the identification of the role of perinatal development in subsequent development of the child's personality.

Result of comparison of two groups of twins is calculation of either identity per cent or concordance of various traits or diseases at each of the pairs of twins. The greater the hereditary component of a trait or disease, the higher concordance value - but the most important is the level of the discrepancy between MZ- and DZ twins. Quantitative evaluation of the share of hereditary trait conditionality is the factor of heritability (H) designated by the following Holzinger concordance formula,

$$HC = (CMZ - CDZ)/(100 - CDZ).$$

CMZ – CDZ – is a concordance expressed in percentage for MZ and DZ twins respectively. If HC>70%, the main role in trait indication belongs to hereditary factors. If H<30%, environmental factors are the main factor in formation of the trait. At intermediate values of H is supposed approximately equal participation of both genetic, and environmental factors [4].

Rather frequently in studying human genetics modifications of the twin method are used, rather than its classical form. Various modifications of twin method for psychogenetics were offered in particular by A.R. Luria [3].

A.R. Luria used the twin method for research of the mutual relation of the heredity and education in mental development. Based on Vygotsky's ideas about the cultural-historical nature of human mental development Luria proposed a heuristic hypothesis, suggesting that during ontogenetic development the structure of higher mental functions changes and as a consequence the relation to genotype is diminished. Using the method of a control twin Luria together with V.N. Kolbanovsky and A.Y. Mirenova introduced differing training programs in these two groups of twins. Both groups were involved in constructing activity of different challenges. In one group the training activity involved more demanding analysis and planning because only a general contour of the example was given, while the second group had to construct objects according to given examples where components of construction were present. The results proved that differential training of genetically equal children can influence their mental functions: the group that was trained with a more challenging construction not only improved construction efficiency, but also other mental functions of the child were improved. Later this method was used by A. R. Luria in his study: in 1956, of A.R. Luria and F. N. Udovich had published work about speech development in twins [5].

Application of the twin method in genetics involve some difficulties: with relatively low frequency of twin birth in most populations (according to the data of the world statistics, twins are 1-2% among newborn) which complicates selection of sufficient pairs of twins with particular trait for analysis with reliable diagnostics of the fact of monozygotic twins that has basic value for drawing of reliable conclusions. Diagnostics of twins zygosity is of great importance, and at the same time researchers are using variety of approaches [6].

Polisimptomic approach, in which comparison is conducted on the main morphological traits: pigmentation of eye, hair and skin, features of scalp and body, as well as form of hair, the form of ears, nose, lips and nails, manual patterns.

Clinically-functional approach, immunologic approach: comparison on erythrocyte antigens, on proteins pf blood serum, on HLA haplotypes (human leukocyte antigens).

Now there is no necessity in such difficult procedure as opportunity emerged to evaluate so called DNA- "fingerprints" - individual nucleotide sequences of the DNA, unique at each person. It entirely proves a genetic identity of twins [4]. The joint

role of factors of heredity and environment is displayed in such pathologies as mental disorders, neurodegenerative diseases, coronary artery disease, insulin-dependent diabetes (IDD) and noninsulin-dependent diabetes (NIDD).

For many years scientists have studied twins, trying to answer the question: what comes first: "nature" or "nurture", as twins present a valuable source of the information for medical and psychological researches. Results of the twins' research influenced discovery and treatment of various diseases (in particular, early breast cancer) and mental disorders [7].

The important role of genes in studying twins' behavior is confirmed by recent molecular-genetic researches. Such studies are based on MZ twins who share a common genotype, however, most monozygotic twin pairs are not identical. There are several possible explanations for these observations, but one is the existence of epigenetic differences. Epigenetics emerged during the first half of the 20th century as the study of biological mechanisms involved in embryonic development and cell differentiation. Twins in early childhood have no marked epigenetic differences but they become greater in older twins [8]. MZ twins constitute an excellent example of how genetically identical individuals can exhibit differences and therefore provide a unique model to study the contribution/role of epigenetic modifications in the establishment of the phenotype. Such markers as DNA methylation and histone acetylation affect repeat DNA sequences and single-copy genes, and have an important impact on gene expression [9]. The role of these epigenetic markers increases in MZ twins who had spent less of their lives together, underlining the significant role of environmental factors in translating a common genotype into a different phenotype. Epigenetic differences influence the discordant frequency of the onset of the disease in MZ twins.

Genes interacting with environment affect the complex nature of behavior. Relatively small differences in epigenetic patterns can have a large impact in phenotype, for instance in cloned animals. In humans, errors in methylation status may lead to such epigenome drift as imprinting defects and cancer [10]. Comparison of MZ twins suggests that external and/or internal factors can have an impact in the phenotype by altering the pattern of epigenetic modifications and thus modulating the genetic information.

Prospects for further research into factors including those affecting mental processes of twins will be related to epigenome changes in MZ twins and aimed at finding out the specific mechanisms responsible for these changes [11]. And furthermore it is

necessary to identify epigenetic markers of environmental risk and molecular mechanisms involved in disease and disease progression, which have implications both for understanding disease and for future medical research (personalized medicine).

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