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Twin zygosity studies with the formula from DNA-View's Kinship Module after molecular analyses by polymorphic markers

U. Ricci[a,*], E. Lapi[a], S. Guarducci[a], E. Andreucci[a], C. Bacci[a], B. Toschi[a], C. Brenner[b], M.L. Giovannucci Uzielli[a]

[a] *Genetics and Molecular Medicine Unit, University of Florence,Via Luca Giordano, 13, Azienda Ospedaliera ⟪A. Meyer⟫, Florence I-50132, Italy*
[b] *Consultant in Forensic Mathematics, California, USA*

Abstract. Human Monozygotic (MZ) Twins estimated to occur once in 250 live births, result from an abnormal behavior by embryonic cell(s) to develop as separate embryos. The MZ twins are considered genetically identical and the reduced phenotypic, genetic or chromosomal concordance represents a very important challenge for geneticists. Determination of zygosity by molecular studies usefully provides a superior replacement for the conventional studies of placenta and chorionic membranes. We utilized a protocol based on the CODIS polymorphic markers battery, by using an infrared LI-COR 4200 instrument (LICOR, Nebraska, USA), and we associated the statistical analysis method with formulae derived by the DNA-View's Kinship Module to better evaluate the genetic identity in a group of MZ twins.

Keywords: Monozigosity twins; Monozigosity discordance; Zygosity analysis; Polymorphic markers

1. Introduction

Human Monozygotic (MZ) twins originate from the cleavage of a single fertilised zygote into two separate zygotes, during the early embryogenesis. Human MZ twins estimated to occur once in 250 live births. Their genome is considered identical. Discordance for well-defined syndrome, or isolated birth defects, or chromosomal abnormalities in MZ twins as well as for complex multifactorial traits and diseases, was described in several instances, in the literature. Environmental factors, but also the origin, development, genetic and epigenetic factors possibly involved in the reduced concordance, must be considered in future studies on MZ twins. A skewed or non-random X-inactivation was also assumed as possible event for discordance in intrapair MZ female twins.

The reduced concordance between MZ twins remains in fact poorly understood, and we need now to compare the genome sequence of MZ twins carefully, in the light of modern

* Corresponding author. Tel.: +39-555662941; fax: +39-555662931.
E-mail address: ricciugo@tin.it (U. Ricci).

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molecular insight of the human genome, to reveal any possible variation and difference between a set of human MZ twins.

2. Materials and methods

We report the preliminary results of a study we are performing in a series of MZ twins referred to the Genetics and Molecular Medicine Unit for different reasons.

In all cases, we performed the zygosity test by using the CODIS polymorphic markers (TPOX, D3S1358, FGA, CSF1PO, D7S820, D8S1179, THO1, D13S317, D16S359, D18S51, D21S11) typed as previously described [1].

In three cases, the MZ twins were concordant for the same genetic disorder: Rett syndrome with the same MECP2 mutation, the same, nonspecific form of mental retardation, a form of autism.

In one case, the intrapair MZ twins showed discordance for a congenital cardiac defect (pulmonary valvular atresia). In another MZ set, the clinical spectrum of an Oculo Auricolo Vertebral syndrome (OAV) was expressed in different way, while in a third MZ twin set, a mosaicism 46,XX/45,X was finally confirmed in both fetuses, but with different percentages of cells with chromosomal defect.

Moreover, we applied the methods to study other four pair of twins, in which the parents are interested just for curiosity.

The scenarios we wish to compare for the twin zygosity study are: (a) **MZ**: C and V are genetically one person; (b) **DZ**: C and V are genetically ordinary full siblings.

The likelihood ratio favoring MZ over DZ is the ratio $P(E|\mathbf{H}_1)/P(E|\mathbf{H}_0)$, where **E** is the event; **E**: Genotypes as stated are observed in the twins C and V.

This likelihood ratio can be evaluated one locus at a time and is the product of the per-locus likelihood ratios. There are only two kinds of locus of concern. Either C and V are identically homozygous QQ or identically heterozygous PQ; the likelihood ratio formulas are respectively $4/(1+q)^2$ and $4/(1+p+q+2pq)$ [2].

3. Results

The molecular analysis of zygosity, performed on the basis of a different number of DNA polymorphic markers of CODIS, confirmed that in all set of twins included in the study, the subjects were MZ twins. The application of the formula from the Kinship Module of the DNA-View program gave us the following results: the likelihood ratio (LR) for MZ for the twins with different mosaicism for 46,XX/45,X was 36,800 (11 markers analysed).

The twins discordant for the cardiac congenital defects were MZ by a LR of 1950, with the use of only nine DNA polymorphic markers. The LR obtained in the MZ control set gave values between 177,000 and 418,000, with the analysis of 13 DNA polymorphic markers. These preliminary data are useful to well evaluate the results of LR with the number of the DNA polymorphic markers included in the molecular zygosity study. The study we performed has never been extended to the parents of the twins, to avoid a paternity/maternity test which was not requested.

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