Familial Monozygotic Twinning: Report of an Extended Multi-generation Family

Hanan A. Hamamy, Heitham K. Ajlouni, and Kamel M. Ajlouni
National Center for Diabetes, Endocrinology and Genetics, Amman, Jordan

Thirteen sets of monozygotic (MZ) twins from an extended multi-generation family are reported. Zygosity was determined by interviewing families for overall physical similarity and by assessment of facial photographs. A hypothetical gene was traced back five generations to a common grandfather. Familial monozygotic twinning in this pedigree is compatible with autosomal dominant inheritance with reduced penetrance. Other plausible mechanisms of inheritance are discussed.

Monozygotic (MZ) twinning may present an etiologically heterogeneous condition with both genetic and environmental factors playing their roles in the mechanism of production of twins. Familial MZ twinning could also be genetically heterogeneous with several possible modes of inheritance. Autosomal dominant inheritance with variable penetrance was suggested as the underlying etiology for familial MZ twinning (Harvey et al., 1977). Inheritance was reported to occur through both the maternal and paternal lines (Harvey et al., 1977), or only through maternal lines (Lichtenstein et al., 1998; Parisi et al., 1983).

Although the etiology underlying human MZ twinning remains a mystery, several mechanisms for the occurrence of MZ twinning have been proposed. The discordance among cells in the inner cell mass resulting from epigenetic or genetic factors may lead to embryo splitting and MZ twinning (Machin, 1996). Polymorphisms in E-Cadherin were investigated as a probable cause of decreased compaction of cells inside the zona pellucida (Bamforth et al., 2003). The role of hypocalcaemia in the embryo prior to hatching of the zona pellucida and delayed implantation were extensively discussed by Steinman (Steinman, 2001a; Steinman, 2001b; Steinman & Valderrama, 2001; Steinman, 2002; Steinman, 2003). The application of assisted reproductive techniques has enhanced the rates of both MZ and DZ twinning (Alikani et al., 2003). This increase has been attributed to possible mechanical forces affecting the zona pellucida, or to the effects of incubation media and late implantation in IVF procedures (Milki et al., 2003: Steinman, 2003: Abusheikha et al., 2000).

We report an extended pedigree with familial monozygotic twinning and propose a role for autosomal dominant inheritance with reduced penetrance.

Family Data

Data collection included personal interviews with members of the extended family and parents of the twin pairs. This research was conducted by a member of the family acquainted with the particulars of the family pedigree. The parents were specifically asked eight questions evaluating physical resemblance of the twin pair. The questions were extrapolated from the study of Rietveld et al. (2000). Available photographs of the twin pairs were collected and compared for physical similarities. Zygosity was determined according to the response to the questionnaire as well as the degree of resemblance of facial features as judged from photographs. The pedigree was constructed to include MZ twin pairs and all their parents traced back five generations to a common ancestor (Figure 1). Siblings who had no progeny of MZ twinning were included as numbers inside a symbol of unidentified sex. Individuals in the pedigree carrying a probable autosomal dominant gene are marked with a circle inside the symbol. The twin sets were assigned numbers appearing within the pedigree symbol and shaded. Available photographs of 9 twin pairs are presented in Figure 2.

Results

The total number of family members investigated for twinning in the extended pedigree amounted to 2035 individuals. Monozygotic twinning was assigned to 13 pairs based on the response to the questions on physical resemblance, and on the comparison of facial features in the available photographs. Parents of all 13 sets of twins responded that facial features, hair color, face color, and eye color of their twins were

Received 16 February, 2004; accepted 25 March, 2004.

Address for correspondence: Professor Kamel Ajlouni, Head of National Center for Diabetes, Endocrinology and Genetics, P.O. Box 13165, Amman, Jordan. Email: hhamamy@hotmail.com

https://doi.org/10.1375/twin.7.3.219 Published online by Cambridge University Press

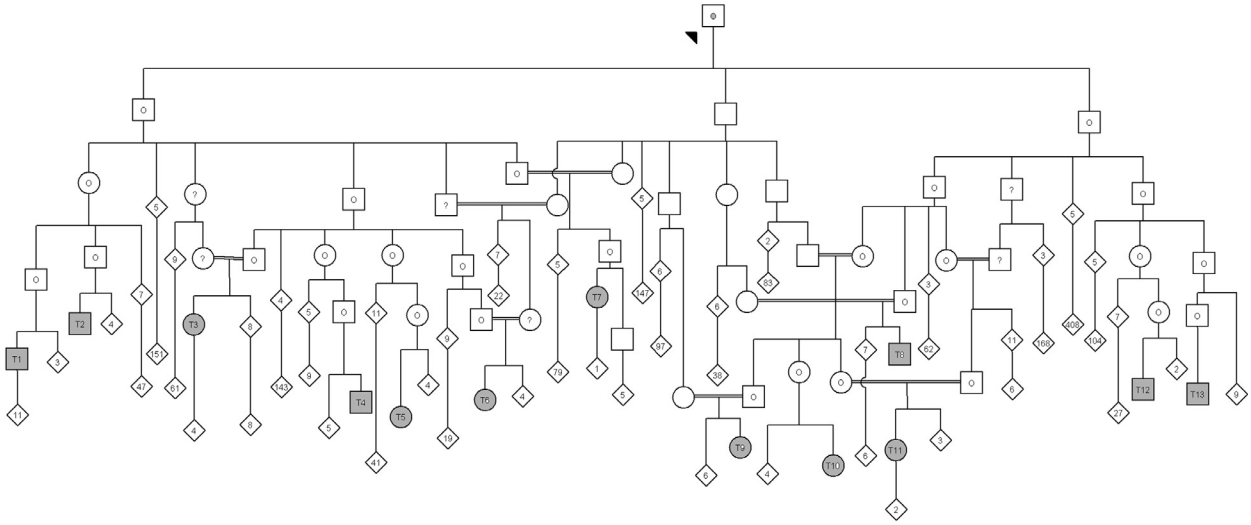

Figure 1
Extended multi-generation pedigree of MZ twins.

exactly similar. All parents said their twins were identical, family members mistake the twins one for the other, and strangers have difficulty telling the twins apart. Six of the parents mistook the twins one for the other, while seven did not.

The photographs of another 4 pairs of like-sex twins showed marked similarities, but data obtained from the verbal questionnaire were controversial, so they were not included as MZ twins.

Individuals in 4 twin pairs were married and between them had 18 children with no MZ twins. Three pairs of dizygotic (DZ) unlike-sex twins were reported. Several pairs of like-sex twins in the earlier generations could not be included in the study due to neonatal or early infant death of one or both twin members, and hence the difficulty in determining zygosity.

Among the 13 sets of MZ twins there were 6 male twins and 7 female twins giving a male/total ratio of

Figure 2
Facial photographs of nine MZ twin pairs.

https://doi.org/10.1375/twin.7.3.219 Published online by Cambridge University Press

.46. There were no instances of parent to offspring transmission of MZ twinning.

The rate of DZ twinning among members of this pedigree is roughly calculated at about 3/1000 offspring. This figure was reached from the presence of 3 pairs of unlike-sex twins in the pedigree with application of Weinberg differential method to estimate the proportion of DZ twins (Hall, 2003). The rate of MZ twinning in the extended pedigree is around 6.39/1000 offspring. The observed ratio of MZ twins among their sibship sizes was 13/68, or 19%.

If familial MZ twinning in this pedigree is following an autosomal dominant mode of inheritance, the penetrance of the gene could be approximated to around 38%.

Discussion

We relied on physical resemblance for designation of zygosity among the twin sets in the studied extended pedigree. It is reported that zygosity can be classified with at least 90% accuracy by physical appearance only (Steinman, 2003). Several studies have likewise shown that establishment of zygosity based on mailed questionnaire evaluating physical resemblance is about 95% accurate (Rietvelt et al., 2000). In this extended family, 13 sets of MZ twin pairs are reported. However, the actual number may be higher due to the presence of several instances of early death of one or both members of like-sex twin pairs in earlier generations. Also there were cases of abortions of twins and in addition, there was controversy on the designation of zygosity in 4 female twins.

The mode of inheritance of MZ twinning in this pedigree is compatible with autosomal dominant inheritance showing variable penetrance. The gene was hypothetically traced back for five generations and assigned to individuals expected to harbor the gene when MZ twins were located in their progeny.

Tracing the hypothetical autosomal dominant gene in the family revealed 3 instances (T3, T6, T11), where both parents could be harboring the gene. This observation and the high consanguinity rate present in the family led to the probability of another mode of inheritance playing a role in the etiology of MZ twinning in this pedigree, and that is autosomal recessive inheritance. We propose that the susceptibility to MZ twinning could be inferred by homozygosity for an autosomal recessive gene in the mother or by homozygosity in the twin pair itself. The homozygosity hypothesis causing MZ twinning could be explained by maternal factors or by embryo factors acting within the internal milieu of the zona pellucida before hatching. Pedigree analysis of this highly consanguineous family could only validate this hypothesis in 6 twin pairs. Among the other twin pairs, 5 were paternally related to the pedigree and their parents were not consanguineous and 2 pairs were related to the pedigree through the mother, but with no consanguinity inferred for the mother or the twin pair. We deduced that these findings could exclude the possibility of autosomal recessive inheritance in this pedigree, at least for half the number of twin pairs, unless the carrier state for the hypothetical allele responsible for MZ twinning is high in the population.

The sex ratio of 0.46 for the MZ twins in this pedigree is close to the reported sex ratio for all MZ twins of 0.484 (Hall, 2003). This may point to the presence of both diamniotic and monoamniotic twin sets in this pedigree. Diamniotic MZ twins could result from inner cell mass splitting up to 7 days post fertilization, while conjoined twins arise when the splitting event happens 14 days after fertilization (Hall, 2003). If the familial susceptibility to MZ twinning is attributed to an autosomal dominant gene, then the effect of this gene would span a period of up to 14 days post fertilization. The excess of female MZ twins could be due to the slower growth of the cells of female embryo with increased risk of missing certain critically timed events (Hall, 2003). Another explanation is that the delay in growth associated with a delay in hatching could expose the female embryos to a milieu inside the zona pellucida with lower calcium concentration and thus lower cadherin activity (Steinmann, 2001a). The cell adhesion molecule E-cadherin is involved in the condensation of cells in early embryonic development (Bamforth et al., 2003). Distribution of E-cadherin genotypes among singletons, DZ twins and MZ twins was reported to show slight overrepresentation of homozygotes for the A/A polymorphism in MZ twins, the difference, however was not significant (Bamforth et al., 2003). The low penetrance of an autosomal dominant gene responsible for MZ twinning may be because that expression of the gene requires certain other genetic or environmental influences.

The rate of DZ twinning of 3/1000 deduced from this pedigree is lower than the birth rate of DZ twins in North America (7–11/1000 births) (Hall, 1996), but is closer to the birth rate of DZ twins in Asia, which is reported to be the lowest in the world at about 3/1000 births. The rate of MZ twinning in this pedigree of 6.4/1000 is more than double the rate of MZ twinning of 3/1000 reported among live births (Hall, 2003).

Among 6874 pregnancies investigated for consanguinity in Jordan, twin rate was reported to be 7.7/1000 pregnancies (Khoury & Massad, 2000). Data on the birth rate of twins from other countries in the Middle East reported figures of 1% in Saudi Arabia (Babay et al., 1994) and 0.85% in Turkey (Duyar & Guntay-Ayaz, 1993).

The hypothesis of The Infertility/Twinning Paternally Dependent syndrome (St Clair & Gobulovsky, 2002) does not fit our pedigree because the lineage of MZ twinning was interchanging between males and females, thus disputing the role of a Y chromosome inheritance.

https://doi.org/10.1375/twin.7.3.219 Published online by Cambridge University Press

The high consanguinity rate among members in this pedigree follows the general trend of favouring consanguinity in the population of Jordan. Among all marriages in the general population in Jordan, 50% are consanguineous and 32% are reported to be between first cousins (Khoury & Massad, 1992). Among parents of the twin sets in this study, five were consanguineous (38.5%), and only one set (7.7%) had parents who were first cousins. Consanguinity does not seem to affect the rate of MZ twinning, at least in the presently reported pedigree.

We conclude that familial monozygotic twinning in this pedigree is compatible with autosomal dominant inheritance with reduced penetrance. Further studies would be needed to define the responsible gene.

Acknowledgments

We greatly appreciate the cooperation of all family members in this study and the provision of the twins photographs.

References

Abusheikha, N., Salha, O., Sharma., V., Brinsden, P., & Abusheika, N. (2000). Monozygotic twinning and IVF/ICSI treatment: a report of 11 cases and review of literature. *Human Reproduction Update, 6,* 396–403.

Alikani, M., Cekleniak, N., Walters, E., & Cohen, J. (2003). Monozygotic twinning following assisted conception: an analysis of 81 consecutive cases. *Human Reproduction, 18*, 1937–1943.

Babay, Z., Addar, M., & Al-Meshari, A. (1994). Multiple pregnancy management: The King Khaled University hospital experience. *Annals of Saudi Medicine, 14*, 405–408.

Bamforth, F., Brown, L., Senz, J., & Huntsman, D. (2003). Mechanisms of monozygotic (MZ) twinning: a possible role for the cell adhesion molecule, E-cadherin. *American Journal of Medical Genetics, 1*;120A(1), 59–62.

Duyar, I., & Guntay-Ayaz, N. (1993). The frequency of multiple births in central Anatolia. *The Turkish Journal of Pediatrics, 35*, 257–265.

Hall, J. G. (1996). Twinning: mechanisms and genetic implications. *Current Opinion in Genetics & Development, 6*, 343–347.

Hall, J. G. (2003). Twinning. *The Lancet, 362,* 735–743.

Harvey, M., Huntley, R., & Smith, D. (1977). Familial monozygotic twinning. *The Journal of Pediatrics, 90*, 246–249.

Khoury, S., & Massad, D. (1992). Consanguineous marriage in Jordan. *American Journal of Medical Genetics, 43*, 769–775.

Khoury, S., & Massad, D (2000). Consanguinity, fertility, reproductive wastage, infant mortality and congenital malformations in Jordan. *Saudi Medical Journal, 21,* 150–154.

Lichtenstein, P., Kallen, B., & Koster, M. (1998). No paternal effect on monozygotic twinning in the Swedish Twin Registry. *Twin Research, 1,* 212–215.

Machin, G. (1996). Some causes of genotypic and phenotypic discordance in monozygotic twin pairs. *American Journal of Medical Genetics, 61,* 216–228.

Milki, A., Jun, S., Hinckley, M., Behr, B., Giudice, L., & Westphal, L. (2003). Incidence of monozygotic twinning with blastocyst transfer compared to cleavage-stage transfer. *Fertility Sterility, 79,* 503–506.

Parisi, P., Gatti, M., Prinzi, G., & Caperna, G. (1983). Familial incidence of twinning. *Nature, 304*, 626–628.

Rietveld, M., van der Valk, J., Bongers, I., Stroet, T., Slagboom, P., & Boomsma, D. (2000). Zygosity diagnosis in young twins by parental report. *Twin Research, 3*, 134–141.

St Clair, J., & Golubovsky, M. (2002). Paternally derived twinning: a two century examination of records of one Scottish name. *Twin Research, 5*, 294–307.

Steinman, G. (2001a). Mechanisms of twinning. II. Laterality and intercellular bonding in monozygotic twinning. *The Journal of Reproductive Medicine, 46*, 473–479.

Steinman, G. (2001b). Mechanisms of twinning. IV. Sex preference and lactation. *The Journal of Reproductive Medicine, 46*, 1003–1007.

Steinman, G. (2002). Mechanisms of twinning. V. Conjoined twins, stem cells and the calcium model. *The Journal of Reproductive Medicine, 47*, 313–321.

Steinman, G. (2003). Mechanisms of twinning. VI. Genetics and the etiology of monozygotic twinning in in-vitro fertilization. *The Journal of Reproductive Medicine, 48*, 583–590.

Steinman, G., & Valderrama, E. (2001). Mechanisms of twinning. III. Placentation, calcium reduction and modified compaction. *The Journal of Reproductive Medicine, 46*, 995–1002.

https://doi.org/10.1375/twin.7.3.219 Published online by Cambridge University Press