Chimeric Dizygotic Twins; Twin Study Summaries; News At Home and Abroad

Nancy L. Segal

Department of Psychology, California State University, United States of America

Chimeras, individuals whose genetically distinct cell lines originated from different zygotes, are attracting attention among twin researchers. This is because chimerism may occur more frequently than previously suspected, having been observed among 8% of dizygotic (DZ) twins and 21% of DZ triplets. The presence of separate cell lines in these twins may hold clues to disease susceptibility, developmental complications and histocompatibility features. Next, new twin research on physical development is offering fresh insights on height and hormones, height and education, and pelvic development. Finally, twins having twins, twins deserting the military and twins composing music raise new thoughts about reproduction, behavior and talent.

Chimeric Dizygotic Twins: Implications for Development and Disease

I met the famous author John Barth in the spring of 1973 when he was a visiting English professor at Boston University. I remember that I loved his modern short story course, but I cannot recall when I learned that Barth was part of an opposite-sex twin pair. Perhaps this explains why a novel called *Chimera* (Barth, 1972) is listed among his well-known works. Barth once remarked that less is known about 'opposite-sexers' than about other types of twins. He was right then, and is right now, particularly regarding chimeras (Barth, 1982; see also Segal, 2000).

A chimera is an individual whose genetically different cell lines originated from different zygotes. Chimeras come in different forms (see Johannsen et al., 2003), but the type involving prenatal blood exchange between human dizygotic (DZ) twin pairs is receiving medical attention. Blood stem cells from one twin embryo may enter the bone marrow of the other twin embryo and are tolerated, providing the basis for a lasting blood supply (Pearson, 2002). In some cases, the white blood cells of male twins display characteristics of their female co-twins, whereas white blood cells of female twins display the male XY chromosomal constitution of their brothers (Bird et al., 1980).

The first case of chimerism was documented over 50 years ago in 1953, when it was detected in a female twin — 25 years after her twin brother's infant death. However, scientists are just beginning to appreciate what chimerism implies for development and disease. That it has taken this long for these concerns to gain attention is partly due to the assumption that chimerism occurs rarely. It may not.

By the mid-1970s only 25 cases of chimerism had been described (Race & Sanger, 1975). Even as recently as 2001, forensic investigators reached the same conclusion — in the fascinating report of a DZ male twin suspect who showed 3 alleles at 4 of 9 tested loci, only six case studies were cited published between 1976 and 1993 (Rubocki et al., 2001). Unfortunately, Rubocki et al. (2001) overlooked a crucial report showing that chimerism affects approximately 8% of DZ twin pairs and 21% of DZ triplets (van Dijk et al., 1996; also see Segal, 2002). As van Dijk et al. (1996) pointed out, recent sensitive laboratory techniques were responsible for the detection of chimerism in higher numbers of multiple birth subjects than in the past.

There are other reasons to suspect that chimerism is more frequent than suspected, and may even be on the rise. First, most cases of blood chimerism occur in DZ twins. The DZ twinning rate has escalated considerably since the 1970s, largely due to advanced reproductive technologies (Martin et al., 2002). Close implantation of multiple embryos following in-vitro fertilization could increase the chances of chimerism in multiple birth embryos (Pearson, 2002). Second, prenatal and newborn complications and loss are higher

Address for correspondence: Nancy L. Segal, Department of Psychology, California State University, Fullerton, CA 92834, USA. E-mail: nsegal@fullerton.edu

https://doi.org/10.1375/twin.8.2.178 Published online by Cambridge University Press

among multiples than nonmultiples (Emanual, 1999; Scott-Jupp & Field, 1991). Individuals whose DZ cotwins have died, either during gestation or at birth, may retain the bloodlines of these siblings. Such information may be revealed in unexpected ways — for example, a woman who had not known she was originally a twin showed some chromosomally male blood cells during a routine blood test while pregnant (Pearson, 2002). The question of whether such individuals are at increased risk for disease or other physical complications is yet to be answered.

Currently, there is speculation that genetically different cells within an individual may be linked to conditions such as autism, infertility and Alzheimer's disease. The additional possibility that chimerism could interfere with developing optimal pharmacological treatments for some individuals is also a concern (Pearson, 2002). As DZ twins are the most likely human population to include chimeras, medical investigators working with twins would need to consider this factor in research and practice. Specifically, DZ twins may help identify the genetic bases of certain disorders as well as their treatment. Studying chimeric DZ twins could also increase understanding of the nature and basis of tolerance and reactivity to foreign cells (see Altman, 1999). It was recently reported that opposite-sex infant twins showed little response to in-vitro lymphocyte cultures from each other, but showed normal rejection of cells from a third party (Viëtor, et al., 2000). This finding suggested that the twins' tolerance of one another's cells was preserved, whereas tolerance of foreign cells is acquired. Lastly, physicians aware of chimerism in their DZ twin patients may be able to offer them the best possible treatment. Chimerism poses other curious challenges, however.

Chimerism can affect the classification of twins as either monozygotic (MZ) or DZ. The medical literature includes a case report describing a normal male twin whose female cotwin had trisomy 21 (Gilgenkrantz et al., 1981). The twins' identical blood groups indicated MZ twinning, suggesting that trisomy 21 in one twin was due to a biological error following zygotic division. However, the twins' sex difference offered a more insightful (and accurate) interpretation: the twins' matched blood groups were most likely due to blood exchanges occurring before their birth. Unfortunately, a more recent case had more dire consequences (Johannsen et al., 2003). A twin pair, identified as male through amniocentesis and ultrasound, appeared at birth to be a normal male and a phenotypically normal female. However, the female twin had a 46, XY chromosomal constitution, suggesting that she had 46, XY gonadal dysgenesis. Additional testing indicated increased levels of follicle-stimulating hormone (FSH), as well as undetectable levels of testosterone and inhibin-B (a hormone that suppresses pituitary FSH secretion; increased levels of inhibin-B are associated with the onset of puberty in males; see *Online Medical Dictionary*, 1997–2004). Other biochemical and hormonal indices were also consistent with male sex, and sex-determining region Y (SRY) sequencing was normal. Given the consistency of these results with 46, XY gonadal dysgenesis and its associated risk of gonadoblastoma, the infant underwent a gonadectomy at age 15 months. However, the gonads proved to be normal ovaries, rather than testes. Once this was revealed, subsequent tests using peripheral blood and fibroblasts indicated a 46, XX (female) karyotype. The investigators urged that physicians facing future twin cases of suspected gonadal dysgenesis consider the possibility of chimerism prior to surgical intervention, thus avoiding such difficult mistakes.

What is the best way to diagnose chimerism in DZ twins? Dauber et al. (2003) conducted DNA typing of short tandem-repeat polymorphisms in a pair of twins known to be chimeric from past serological and cytogenetic tests. The conclusion was that results from DNA typing must be interpreted cautiously as DNA methods could not distinguish between cells derived from blood and nonblood tissues. Dauber et al. (2003) emphasized that chimeric DZ twins are mostly those resulting from blood exchanges, whereas dispermic chimeras (those resulting from the fertilization of one or two maternal nuclei and their growth into a single body) show genetically different non–blood cell patches. An additional complication associated with the DNA typing procedure is that blood cells are potentially found in most body tissues.

Another potentially unusual situation involving chimeras has been reported, but did not involve multiple births (Yu et al., 2002). Regardless, this case of tetragametic chimerism has unexpected implications for the development of twins, triplets and more. Tetragametic chimerism involves the creation of two zygotes from two eggs and two sperm followed by zygotic fusion. This condition was identified in a phenotypically normal female. When she required renal transplantation, histocompatibility testing of family members was conducted to determine the best donor. It was revealed instead that she was not the biological mother of two of her three nontwin children. This is because a single cell line predominated in this patient — her children's nonpaternal genes were identified in their maternal grandparents and she was, in fact, the mother of her children. Chimerism was not observed in her peripheral blood samples.

The potential family implications of this situation are far-reaching. Had chimerism not been considered, it could have been suspected that the mother had been given the wrong infants at the hospital. The authors of the article note the additional possibility that if the children's father had been the chimera, unfair suspicions of nonpaternity could have been raised. However, the authors did not consider their findings in a multiple birth context. A tetragametic chimeric father of DZ twins might have resulted in alleged superfecundated twins (twins fathered close in time by separate males). A tetragametic mother of DZ twins would be even more baffling unless physicians had read this fascinating report.

https://doi.org/10.1375/twin.8.2.178 Published online by Cambridge University Press

Twin Study Overviews: Body Build

Height and Hormones

The best experiments often occur naturally. Japanese investigators Sato et al. (2003) reported results of the low-dose growth hormone treatment of a MZ male twin whose development lagged behind that of his twin brother. The twins were born at 35 weeks gestation following an unremarkable pregnancy; however, the affected twin was a breech delivery whereas his twin brother was not. The mother's and father's heights were 157.0cm (61.81 inches) and 165.0cm (64.96 inches), respectively. Based on this information, Japanese standards predicted that a son's height should be 169.5 cm (66.73 inches).

The twins' family sought medical assistance when the affected twin was 4.9 years old. At that time, he was 92.4cm (36.38 inches) tall, in contrast with his brother who, at age 5 years, was 106.5cm (41.93 inches) in height. The twins' zygosity was confirmed by the analysis of DNA markers.

The affected twin received low doses of growth hormone several times each week and responded well. His dosage remained low given his family's concerns over adverse side effects from the treatment. He reached his final height of 165.6cm (65.20 inches) at age 16.5 years. His twin brother reached his final height of 166.4cm (65.51) at about the same time (age 16.2 years), making him 0.8cm (0.31 inch) taller than his twin.

The investigators noted that evidence for whether or not hormone therapy enables affected individuals to achieve their full adult height has been mixed. However, their case report suggests that early administration is a key factor in treatment, and may override the severity of the disorder. The availability of a control twin is, of course, an excellent way to assess therapeutic effects. Importantly, the conclusions reached in this case were only possible because the patient had an unaffected MZ twin.

Height and Education

Associations between height and educational attainment are interesting for several reasons. As a group of international investigators point out, both measures reflect social position and resource availability (Silventoinen et al., 2004). In their recent study, twin participants from Minnesota (n = 1598 pairs) were enrolled in the Minnesota Twin Registry and twin participants from Finland (n = 5454 pairs) were from the Finnish Twin Cohort Study. Twins in both countries were born between 1936 and 1955.

Age-adjusted correlations between height and educational attainment were .09 for men and .11 for women in the Minnesota sample, and were .17 for men and .14 for women in the Finnish sample. These associations were attributed to the correlations between shared environmental factors, which were .38 and .36 in Minnesota and .74 and .37 in Finland. Nonshared environmental effects were only detected in the Finnish sample. Differences between the two countries were explained by Minnesota's higher average educational level, which would decrease the effects of childhood environments on education.

Female Pelvic Morphology

The human pelvis increases in size and changes in shape across development. Twin studies have already demonstrated that measured morphological traits, such as height (see above), weight (Segal & Allison, 2002), skinfold measures (Maes et al.,1996), dental characteristics (Boraas, 1988) and brain-size parameters (Pennington et al., 2000) show genetic effects. However, according to the author of a recent twin study, the extent to which genes influence individual differences in pelvic morphology are 'almost nonexistent' (Sharma, 2002, p. 328).

In order to fill this gap, 14 pelvic measurements were obtained for 30 female MZ twin pairs and female DZ twin pairs. The participants were identified through the Twin Registry of the Department of Anthropology at Panjab University. This registry includes 200 twin pairs of all ages. After eliminating several items due to inequality of MZ–DZ variances and other issues, significant genetic effects were found for age at menarche and pelvic area. Bitrochanteric (hip) breadth showed the highest degree of environmental influence.

News At Home and Abroad

Twins Having Twins

Twin sisters Ashlee Spinks and Andrea Springer became famous when they both delivered male–male twin pairs on December 14, 2004, just one hour apart (Associated Press, 2004b). Both new sets of twins were naturally conceived. It was reported that Ashlee's boys are DZ and Andrea's boys are MZ although the methods by which the infants' twin types were determined are unknown. It was also indicated that Ashlee and Andrea were DZ, which they appeared to be from their photo. They are 21 years of age.

According to the twins, multiple births occur both in their own families and in their husbands' families. Genetic effects on DZ twinning are acknowledged by the scientific and medical community, evidence of genetic influence on MZ twinning remains mixed (see Segal, 2000). Twins like Ashlee and Andrea can potentially clarify and confound research in this area.

Military Desertion and Death

Russian twin brothers, Alexander and Dmitry Oparin, deserted their garrison north of Moscow after completing 18 months of their 2-year service (Arvedlund, 2004; Associated Press, 2004a). They killed two policemen who tried to stop them, then took several hostages whom they held at gunpoint.

https://doi.org/10.1375/twin.8.2.178 Published online by Cambridge University Press

When police officers closed in on them, Alexander shot himself and his twin brother was arrested.

There have been other desertions from the Russian army, but the fact that twin brothers did so together seemed to attract attention. The zygosity of the twins was not indicated, but if they were MZ then perhaps their identical features and movements made them easy to track.

Musical Stars

MZ twins, Tegan and Sara Quin, have been called the 'Wonder Twins' (Sinagra, 2004). They are fascinating at many levels. Born in Canada, they began writing songs in high school and released their first album, 'Under Feet Like Ours', when they were 18 years of age. Since then they have toured with Neil Young and The Pretenders, and have produced three other albums. Both twins are also gay.

Working together professionally is an art that many twins master easily and effortlessly. Organizational psychologists might take a closer at what goes on behind such successful scenes.

References

Altman, L. K. (1999, January 12). Keeping harmony in the marriage of cells. *New York Times,* p. F8.

Arvedlund, E. E. (2004, November 16). Russia: Military desertion attempt turns deadly. *New York Times,* p. A6

Associated Press (2004a, November 16). Police free hostages taken by army deserters. *New York Sun*, p. 6.

Associated Press (2004b, December 15). Twin moms double their fun. *Los Angeles Times*, p. A34.

Barth, J. (1972). *Chimera*. New York: Random House.

Barth, J. (1982, May 9). Some reasons why I tell the stories the way I tell them rather than some other sort of stories some other way. *New York Times Book Review*, pp. 3, 29–33.

Bird, G. W., Gibson, M., Wingham, J., Mackintosh, P., Watkins, W., & Greenwell, P. (1980). Another example of haemopoietic chimaerism in dizygotic twins. *British Journal of Haemotology, 46,* 439–445.

Boraas, J. C., Messer, L. B., & Till, M. J. (1988). A genetic contribution to dental caries, occlusion, and morphology as demonstrated by twins reared apart. *Journal of Dental Research, 67*, 1150–1155.

Dauber, E. M., Faé, I., Stadlbacher, S., Glock, B., Schwartz, D. W. M., & Mayr, W. R. (2003). STR typing in a pair of chimeric twins. *International Congress Series, 1239*, 569–571.

Emanual, E. (1999). Eight is too many. *New Republic, 8*, 10–11.

Gilgenkrantz, S., Marchal, C., Wendremaire, P., & Segal, M. (1981). Cytogenetic and antigenic studies in a pair of twins: A normal boy and a trisomic 21 girl with chimera. In *Twin research 3: Twin biology and multiple pregnancy* (pp. 141–153). New York: Alan R. Liss.

Johannsen, T. H., Lundsteen, C., Visfeldt, J., Schwartz, M., Petersen, B. L., Byskov, A. G., & Müller, J. (2003). Erroneous genetic sex determination of a newborn twin girl due to chimerism caused by foetal blood transfusion. *Hormone Research, 60*, 148–151.

Maes, H. H., Beunen, G. P., Vlietinck, R. F., Neale, M. C., Thomis, M., Vanden Eynde, B., Lysens, R., Simons, J., Derom, C., & Derom, R. (1996). Inheritance of physical fitness in 10-yr-old twins and their parents. *Medicine and Science in Sports and Exercise, 12*, 1479–1491.

Martin, J. A., Hamilton, B. E., Ventura, S. J., Menacker, F., Park, M. M., & Sutton, P. D. (2002). Births: Final Data for 2001. *National Vital Statistics Reports, 51*, 1–103.

On-Line Medical Dictionary (1997-2004). CancerWEB Department of Medical Oncology, University of Newcastle on Tyne. Retrieved December, 2004, from CancerWEB: http://cancerweb.ncl.ac.uk/omd/

Pearson, H. (2002). News feature. Human genetics: Dual identifies. *Nature, 417*, 10–11.

Pennington, B. F., Filipek, P. A., Lefly, D., Chhabildas, N., Kennedy, D. N., Simon, J. H., Filley, C. M., Galaburda, A., & DeFries, J. C. (2000). A twin MRI study of size variations in the human brain. *Journal of Cognitive Neuroscience, 12*, 223–232.

Race, R. R., & Sanger, R. (1975). *Blood groups in man.* Oxford: Blackwell.

Rubocki, R. J., McCue, B. J., Duffy, K. J., Shepard, K. L., Shepherd, S. J., & Wisecarver, J. L. (2001). Natural DNA mixtures generated in fraternal twins in utero. *Journal of Forensic Sciences, 46*, 120–125.

Sato, H., Miyamoto, S., Noda, H., & Sasaki, N. (2003). Comparison of final height in monozygotic twins, one with idiopathic and isolated growth hormone deficiency treated with low dose growth hormone. *Hormone Research, 60*, 152–155.

Scott-Jupp, R., & Field, D. (1991). Multiple pregnancies resulting from assisted conception: Burden on neonatal units. *British Medical Journal, 302*, 1079.

Segal, N. L. (2000). *Entwined lives: Twins and what they tell us about human behavior.* New York: Plume.

Segal, N. L. (2002). Commentary on: Rubocki RJ, McCue BJ, Duffy KJ, Shepard KL, Shepherd SJ, Wisecarver JL. Natural DNA mixtures generated in fraternal twins in utero. *Journal of Forensic Sciences, 47*, 1174.

Segal, N. L., & Allison, D. B. (2002). Twins and virtual twins: Bases of relative body weight revisited. *International Journal of Obesity, 26*, 437–441

Sharma, K. (2002). Genetic basis of human female pelvic morphology: A twin study. *American Journal of Physical Anthropology, 117*, 327–333.

Silventoinen, K., Krueger, R. F., Bouchard, T. J., Jr., Kaprio, J., & McGue, M. (2004). Heritability of boy height and educational attainment in an international context: Comparison of adult twins in Minnesota and Finland. *American Journal of Human Genetics, 16*, 544–555.

Sinagra, L. (2004, September 5). Wonder twins activate a sound that isn't crunch folk or riot-grrl punk. *New York Times*, p. 20.

van Dijk, B. A., Boomsma, D. I., & de Man, A. J. M. (1996). Blood group chimerism in human multiple births is not rare. *American Journal of Medical Genetics, 61*, 264–268.

Viëtor, H. E., Hamel, B. C. J., van Bree, S. P. M. J., van der Meer, E. M. W., Smeets, D. F .C. M., Otten, B. J., Holl, R. A., & Claas, F. H. J. (2000). Immunological tolerance in an HLA non-identical chimeric twin. *Human Immunology, 61*, 190–192.

Yu, N., Krusall, M. S., Yunis, J. J., Knoll, J. H. M., Uhl, L., Alosco, S., Ohashi, M., Calvijo, O., Husain, Z., Yunis, E. J., Yunis, J. J., & Yunis, E. J. (2002). Disputed maternity leading to identification of tetragametic chimerism. *New England Journal of Medicine, 346*, 1545–1552.

https://doi.org/10.1375/twin.8.2.178 Published online by Cambridge University Press