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Identical But Not the Same: The Value of Discordant Monozygotic Twins in Genetic Research

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Monozygotic (MZ) twins show remarkable resemblance in many aspects of behavior, health, and disease. Until recently, MZ twins were usually called "genetically identical"; however, evidence for genetic and epigenetic differences within rare MZ twin pairs has accumulated. Here, we summarize the literature on MZ twins discordant for Mendelian inherited disorders and chromosomal abnormalities. A systematic literature search for English articles on discordant MZ twin pairs was performed in Web of Science and PubMed. A total number of 2,016 publications were retrieved and reviewed and 439 reports were retained. Discordant MZ twin pairs are informative in respect to variability of phenotypic expression, pathogenetic mechanisms, epigenetics, and post-zygotic mutagenesis and may serve as a model for research on genetic defects. The analysis of single discordant MZ twin pairs may represent an elegant approach to identify genes in inherited disorders. © 2010 Wiley-Liss, Inc.

Key words: twins; monozygotic; twin studies; discordant; chromosome disorders; genetic diseases; inborn

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TWINNING

Twins and multiples always have intrigued humans, as illustrated by numerous legends, myths, tales, and anecdotes in which twins play a principal part.

Twins can result from a single ovum, fertilized by one sperm, and are then called monozygotic (MZ) or identical twins. Dizygotic (DZ) or fraternal twins result from two different ova, fertilized by two different sperm. Hence, MZ twins originate from one zygote and are considered to be genetically identical, whereas DZ twins originate from two zygotes and share on average half of the genetic variance present in unrelated individuals (like non-twin sibling pairs). Triplets and higher order multiples can consist of any combination of MZ individuals (including none) together with "additional siblings."

The prevalence of twin births varies between populations, in particular due to differences in the DZ twinning rate. The highest prevalence of twinning is found in Nigeria, where 1 in every 12 persons is a member of a twin pair, and the lowest twinning rates are found in Asia (8/1,000 births in China) [Gan et al., 2007; Hoekstra et al., 2008]. In Europe and the USA, the incidence of twinning is roughly 1 twin pair in every 60 births [Hall, 2003; Hoekstra et al., 2008]. Within Europe and the United States, twinning rates also can vary considerably across time and place [Hoekstra et al., 2008]. As MZ twinning generally occurs at a constant rate of 3–4 per 1,000 maternities around the world [Tong et al., 1997; Hall, 2003], the variation in twinning rates is generally accepted as being the result of variation in DZ twinning rates. The rates of DZ, and possibly also MZ twinning, have increased the past decades, in part due to assisted reproductive technologies (ART) [Chang et al., 2009] and due to increases in maternal age.

The causes of MZ twinning in humans are unknown. Until recently, the process of MZ twinning was considered to represent a random process. However, new data indicate that (epi)genetic mechanisms may be involved in the phenomenon of splitting of the zygote [Shur, 2009]. An excess of females over males has been observed in spontaneous, surviving, MZ twins. This female predominance is observed in particular in monochorionic diamniotic MZ twins, and even more pronounced among monochorionic monoamniotic twins and conjoined twins, suggesting a relationship with the timing of twinning [James, 1975, 1980; Hall, 2003]. Skewed X-inactivation has been suggested to contribute to the process of twinning and as such to the observation of female predominance [Hall, 2003].

Familial MZ twinning has long been recognized [Machin, 2009a] and the MZ twinning rate in ART-induced pregnancies seems to be

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elevated [Chang et al., 2009; Shur, 2009]. Damage to the inner cell mass has been suggested to contribute to twinning in human beings and both familial twinning and ART may be associated with an increased risk of damage to the inner cell mass [Hall, 2003].

Furthermore, and of interest in the context of this review, it has been suggested that genetic differences between cells of the early blastomere may trigger division of the zygote and initiate the process of twinning [Hall, 1996a,b, 2003]. As such, a post-zygotic genetic event may trigger the origin of an MZ twin. In line with this assumption is the observation of an increased prevalence of certain genetic syndromes among MZ twins as compared to singletons, such as Beckwith–Wiedemann syndrome (BWS) [Weksberg et al., 2002; Bliek et al., 2009; Shur, 2009]. Although MZ twin concordance for BWS has been described, most MZ twin pairs are discordant. It has been suggested that unequal splitting of the inner cell mass results in differential methylation between the two cell masses or alternatively that a lack of methylation maintenance in the early zygote results in splitting of the zygote. In both cases a difference in methylation between the two MZ twins may account for phenotypic discordance. Thus, the role of DNA methylation in MZ twinning needs further elucidation.

In the past, zygosity in same-sex twin pairs was mainly determined by blood group and HLA typing, dermatoglyphic studies, and comparison of physical characteristics. Nowadays, DNA polymorphisms are increasingly used (microsatellite markers and/or other polymorphisms such as single-nucleotide polymorphisms (SNPs)) [Hall, 1996b, 2003], although in large-scale epidemiological projects, zygosity still often is reliably determined on a series of questionnaire items [Rietveld et al., 2000]. Correct determination of zygosity is important for individual twin pairs with respect to genetic counseling, preventive medical strategies, or surveillance when one twin has a disease, and to offer optimal guidance in case of organ transplantation [Machin, 2009b]. Obviously, correct determination of zygosity is crucial in research projects involving twins. Methods of zygosity testing are extensively reviewed elsewhere [Machin, 2009b].

TWIN RESEARCH

From the late 19th century onwards, twin studies played an important role in genetics. In classical twin studies, comparison of the resemblance (concordance rates or correlations) for a disorder or a quantitative trait between MZ and DZ twins facilitates research into the etiology of population variation. The heritability (standardized estimate of the contribution of genetic effects of a (complex) trait) can be estimated through fitting quantitative genetic models to twin data. As such, the results of twin studies are applicable to the whole population the twins originated from and have contributed enormously to current genetic insights. For example, multiple sclerosis (MS) was thought to be a non-genetic disorder until a large study was done in Canadian twins [Martin et al., 1997].

DISCORDANT MZ TWINS

Most MZ twins are remarkably similar and MZ twin pairs are in general expected to be concordant for congenital malformations, chromosomal abnormalities, and Mendelian disorders. However, an increasing number of reports are being published on discordant twin pairs. We performed a systematic literature search in Web of Science and PubMed for English language articles on discordant MZ twin pairs, published before November 1, 2009. The terms used for the PubMed search were: ''Monozyg* OR Twins[mesh] OR ''Twin Studies as Topic''[Mesh] AND Discordan*[tiab]'' and the criteria used for Web of Science were topic = (monozyg*) AND topic = (discordan*). A total of 2,016 publications were primarily screened by P.Z. Four hundred thirty-nine papers concerned reports on individual discordant MZ twin pairs. References were also obtained from articles found through the literature search. It should be noted that some older publications lack the appropriate criteria for establishing monozygosity. Determination of zygosity may be limited in older publications, especially in single discordant pairs [Machin, 2009b]; however, for the purpose of this review we generally assumed that the zygosity status was correctly described.

In this journal, 81 publications on individual discordant MZ twin pairs have been published over the last years. The MZ twin pairs in these reports are informative either because both twins are affected, with a different phenotype in each twin, or because only one twin from an MZ twin pair is affected. Our fascination for twins and the educational value of discordant MZ twins is illustrated by three reports that appear to be based on a one single MZ twin pair [Michalski et al., 1978; Schlegelberger et al., 1984, 1986] discordant for Klinefelter syndrome.

DISCORDANT PHENOTYPES IN MZ TWINS

Tables I and II provide an overview of the publications, which report a difference in phenotype between members from MZ twin pairs. Numerous monogenetic and chromosomal disorders are characterized by significant variability that can be observed between unrelated individuals, sibs, and twins. Since affected sibs and DZ twins share on average only 50% of their segregating genes,

TABLE I. Overview of Publications on Monozygotic Twin Pairs With a Chromosomal Abnormality That Report a Difference in Phenotype Between Both Twins

Chromosomal abnormality	Refs.
del 7q	Tsukamoto et al. [1993]
del 8p23.1	Wat et al. [2009]
dup 11p mosaicism	Marcus-Soekarman et al. [2004]
dup 4q + del 1p36	Angle et al. [2002]
dup 4q28.3-qter	Celle et al. [2000]
inv dup(15)	Peng et al. [2007]
Pseudic 13	Lynch et al. [1995]
Trisomy 13	Loevy et al. [1985], Naor et al. [1987]
Trisomy 18	Lee et al. [2004], Mulder et al. [1989], Schlessel et al. [1990]
Trisomy 21	Beattie et al. [1993], Grynberg et al. [2007]

del, deletion; dup, duplication; inv dup, inverted duplication; psu dic, pseudodicentric chromosome.

TABLE II. Overview of Publications on Monozygotic Twin Pairs With a Monogenetic Disorder That Report a Difference in Phenotype Between Both Twins

Disorder	MIM number[a]	Refs.
22q11-deletion syndrome	#611867, #192430, #188400	Fryer [1996], Goodship et al. [1995], Hillebrand et al. [2000], Rauch et al. [1998], Singh et al. [2002], Vincent et al. [1999], Yamagishi et al. [1998]
D-2-hydroxyglutaric aciduria	#600721	Misra et al. [2005]
Alagille syndrome	#118450	Kamath et al. [2002]
Alport syndrome	#301050	Matsukura et al. [2004]
Anophtalmia-esophageal atresia	#206900	Zenteno et al. [2006]
Cystic fibrosis	#219700	Mekus et al. [2000], Picci et al. [2007]
Crouzon syndrome	#123500	Lajeunie et al. [2000], Sher et al. [2008]
Dravet syndrome	#607208	Miyama et al. [2008]
Familial amyloid polyneuropathy	+176300	Holmgren et al. [2004], Munar-Ques et al. [1999], Saporta et al. [2009]
Fragile X syndrome	#300624	Helderman-van den Enden et al. [1999], Kruyer et al. [1994]
Frijns syndrome	%229850	Vargas et al. [2000]
Facioscapulohumeral muscular dystrophy (FSHD)	%158900	Tawil et al. [1993]
G syndrome	%145410	Young et al. [1988]
Gaucher disease	#231000	Lachmann et al. [2004]
Gerstmann–Straussler disease	#137440	Webb et al. [2009]
Huntington disease	#143100	Friedman et al. [2005], Panas et al. [2008], Anca et al. [2004], Georgiou et al. [1999]
Joubert syndrome	%213300	Raynes et al. [1999]
Kallmann syndrome	+308700	Hipkin et al. [1990]
Keratoconus	#148300	McMahon et al. [1999], Weed et al. [2006]
Langerhans histiocytosis	604856	Chen et al. [2004]
LEOPARD syndrome	#151100	Rudolph et al. [2001]
Lymphedema-distichiasis	#153400	Kumar et al. [2007]
McCune–Albright syndrome	#174800	Endo et al. [1991]
Neurofibromatosis type 1	#162200	Kelly et al. [1998], Detjen et al. [2007]
Neurofibromatosis type 2	#101000	Baser et al. [1996]
Goldenhar syndrome	%164210	Ryan et al. [1988], Satoh et al. [1995]
Pai syndrome	155145	Al-Mazrou et al. [2001], Guion-Almeida et al. [2007]
Photosensitive epilepsy	%609569	de Haan et al. [2005]
Primary ciliairy dyskinesia	#242650	Noone et al. [1999]
Severe combined immunodeficiency (SCID)	#102700+	Niehues et al. [1996]
Sickle cell anemia	#603903	Amin et al. [1991]
Thanatophoric dysplasia	#187601/#187600	Corsello et al. [1992], Horton et al. [1983], Horton et al. [1983]
Tibial hemimelia with ectrodactyly	%119100	Dayer et al. [2007]
Tricho-rhino-phalangeal syndrome	#190350	Naselli et al. [1998]
Tuberous sclerosis	#190350/#191100	Humphrey et al. [2004], Kondo et al. [1991], Martin et al. [2003]
WAGR syndrome	#194072	Bremond-Gignac et al. [2005]
Williams syndrome	#194050	Castorina et al. [1997], Maurer et al. [1979], Murphy et al. [1990], Oorthuys [1984], Pankau et al. [2001]
Wilson disease	#277900	Czlonkowska et al. [2009]
(X-linked) adrenoleukodystrophy	#300100	Di et al. [2001], Sobue et al. [1994]

Symbols preceding a MIM number: #, a descriptive phenotype, not necessarily representing a unique locus; +, description of a gene of known sequence and a phenotype; %, a confirmed Mendelian phenotype or phenotypic locus for which the underlying molecular basis is not known; no symbol before a MIM number generally indicates a description of a phenotype for which the Mendelian basis, although suspected, has not been clearly established.[a]Mendelian Inheritance in Man (MIM) numbers correspond to Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) (November 1, 2009). World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/.

phenotypic differences between them may be caused by non-shared genetic variation. Therefore, studying the variability of genetic disorders in MZ twins can be very valuable. Discordant MZ twin pairs have highlighted the possible variability of some diseases, sometimes making us aware of the previously unrecognized ends of the spectrum of disease, such as in Frijns syndrome [Vargas et al., 2000]. An MZ twin pair concordant for a number of dysmorphic features, but discordant for a diaphragmatic defect was described. Twin A came to clinical attention in the context of his twin brother's more obvious clinical characteristics that led to the diagnosis of Fryns syndrome in both twins. At 1 year of age Twin A had mild developmental delay, whereas his twin brother died on day 5. This MZ twin pair indicated that clinically significant diaphragmatic defects are not invariably present, and developmental outcome can be mild in Frijns syndrome, suggesting that the clinical spectrum of this disorder is broader than previously suspected.

A considerable part of research in human genetics is focused on finding explanations for variability in genetically determined diseases, and discordant MZ twin pairs are a valuable source of information in this respect. Numerous reports on MZ twins with 22q11 deletion syndrome, Joubert syndrome, neurofibromatosis, Williams syndrome, and many other diseases with discordant phenotypes emphasize that non-genetic factors may affect the phenotypic variability (see Table II).

A single phenotypically discordant MZ twin pair can contribute to our understanding of the pathogenesis of a disease. Recently, by studying one MZ twin pair, one child with preleukemic and the other one with frank childhood precursor B-cell acute lymphoblastic leukemia, the lineal relationship between several events in carcinogenesis was established [Hong et al., 2008].

Furthermore, discordant MZ twins can guide us toward different manifestations of a genetically determined syndrome. Germline mutations of the gene encoding succinate dehydrogenase subunit B (SDHB) are associated with inherited paraganglioma. Boccon-Gibod et al. [2004] and Pasini et al. [2008] described MZ twin brothers of whom one underwent surgery for a paraganglioma and the other for a stomach gastrointestinal stromal tumor (GIST). They both carried a germline mutation of the *SDHB* gene and subsequent studies in other patients confirmed an association between germline mutations in *SDHB* and GISTs. A careful medical and family history regarding gastrointestinal symptoms and/or tumors is now suggested in patients with germline mutations in *SDHB*.

Finally, MZ twin pairs concordant for a disease, but discordant for prescribed therapy [Davin et al., 2006] or discordant for compliance [Verougstraete et al., 1999] may serve as a model for the effect of therapy. Comparison of the course of the disease in such twin pairs is informative since many other factors that determine the course of the disease are shared by MZ twins.

There have been a number of reports on MZ twin pairs with a chromosomal abnormality with a significant difference in phenotype. Some of these articles describe severely unbalanced chromosomal patterns in blood from healthy children or adults [Celle et al., 2000; Marcus-Soekarman et al., 2004; O'Donnell et al., 2004; Bourthoumieu et al., 2005]. Chimerism, a condition in which an individual is composed of two genetically different types of cells, originating from more than one zygote, has been demonstrated extensively in DZ twins [van Dijk et al., 1996; Abuelo, 2009]. Blood and buccal DNA likely reflects (in part) ''donor'' DNA in case of chimerism [Thiede et al., 2000; Hong et al., 2007]. The finding of unbalanced chromosomal patterns in healthy MZ co-twins of affected individuals suggests hematopoietic chimerism between the affected and unaffected twin, as in some cases mentioned by the authors.

MZ TWINS DISCORDANT FOR CHROMOSOMAL ABNORMALITIES AND MENDELIAN DISORDERS

Tables III and IV summarize studies of MZ twin pairs where one twin is considered to have a (possibly) Mendelian disorder or chromosomal abnormality and the other twin is unaffected. In the past, MZ twins were considered to be genetically identical. However, it has become increasingly clear that some MZ twins are not fully genetically identical. Figure 1 summarizes possible post-zygotic genetic effects that may account for MZ twin discordance. Obviously, it is important to realize that discordant MZ twins may become concordant over time. In 1993, an MZ twin pair discordant for Leber's hereditary optic neuropathy was reported [Johns et al., 1993]. However, a few years later in 1998 the unaffected twin had become affected as well [Lam, 1998].

MZ twins discordant for aneuploidy have been recognized for several decades; discordant MZ twins have been reported for monosomy X, trisomy 1, trisomy 13, and trisomy 21 [Rogers et al., 1982; Weiss et al., 1982; Gilgenkrantz and Janot, 1983; Uchida et al., 1983; Reiss et al., 1993; Nieuwint et al., 1999; O'Donnell et al., 2004; Rohrer et al., 2004; Cheng et al., 2006; Sethupathy et al., 2007; Dahoun et al., 2008; Gentilin et al., 2008; Taylor et al., 2008]. Moreover, unbalanced chromosomal abnormalities have been described in one member from an MZ twin pair [Marcus-Soekarman et al., 2004; Bourthoumieu et al., 2005].

TABLE III. Overview of Publications on Monozygotic Twin Pairs of Whom Only One Twin Is Considered to Have a Chromosomal Abnormality

Chromosomal abnormality	Refs.
45,X	Gentilin et al. [2008], Nieuwint et al. [1999], Reiss et al. [1993], Rohrer et al. [2004], Uchida et al. [1983], Weiss et al. [1982]
del(10)	Juberg et al. [1981]
der(11)	Bourthoumieu et al. [2005]
Trisomy 1 (partial)	Watson et al. [1990]
Trisomy 13	Taylor et al. [2008]
Trisomy 21	Cheng et al. [2006], Dahoun et al. [2008], Gilgenkrantz and Janot [1983], Nieuwint et al. [1999], O-'Donnell et al. [2004], Rogers et al. [1982], Sethupathy et al. [2007]

del, deletion; der, derivative chromosome.

TABLE IV. Overview of Publications on Monozygotic Twin Pairs of Whom Only One Twin Is Considered to Have a (Possibly) Mendelian Disorder

Disorder	MIM[a]	Refs.
Aglossia-adactylia	103300	Robinow et al. [1978]
Aicardi syndrome	%304050	Costa et al. [1997]
Asplenia syndrome	%208530	Hwang et al. [2006], Wilkinson et al. [1979]
Bladder exstrophy	%600057	Bugge [1981], Reutter et al. [2003]
Body stalk anomaly	230750	Daskalakis and Nicolaides [2002], Vidaeff et al. [2005]
Beckwith–Wiedemann syndrome	#122470	Berry et al. [1980], Bose et al. [1985], Chien et al. [1990], Clayton-Smith et al. [1992], Leonard et al. [1996], Litz et al. [1988], Olney et al. [1988], Orstavik et al. [1995], Weksberg et al. [2002], Bliek et al. [2009]
Caudal duplication anomaly	#607864	Kroes et al. [2002], Oates et al. [2006]
Congenital hypothyroidism	#275200/#218700	Rettig et al. [1980]
Colorblindness	+303800	Jorgensen et al. [1992]
Complete congenital heartblock	234700	Cooley et al. [1997]
Congenital bilateral perisylvian syndrome	#300388	Lenti and Triulzi [1996]
Cornelia de Lange syndrome	#122470	Carakushannsky and Berthier [1976], Carakushansky et al. [1996]
Darrier's disease	#124200	Sakuntabhai et al. [1999]
Duane's retraction	#604356, +%126800	Kaufman et al. [1989], Rosenbaum and Weiss [1978]
Duchenne muscular dystrophy	#310200	Burn et al. [1986], Chutkow et al. [1987], Gomez et al. [1977], Lupski et al. [1991], Pena et al. [1987], Richards et al. [1990], Tremblay et al. [1993], Zneimer et al. [1993], Bonilla et al. [1990]
Epilepsy with structural brain abnormalities		Briellmann et al. [1998], Brodtkorb et al. [2000], Kuzniecky et al. [1995], Sisodiya et al. [1999], Supprian et al. [2000]
Fabry disease	#301500	Redonnet-Vernhet et al. [1996]
Fragile X syndrome	#300624	Kruyer et al. [1994], Tuckerman et al. [1985]
Frontonasal dysplasia	136760	Mohammed et al. [2004], Wu et al. [2007]
Facioscapulohumeral muscular dystrophy (FSHD)	%158900	Griggs et al. [1995], Tawil et al. [1993]
Goldenhar syndrome	%164210	Boles et al. [1987], Stoll et al. [1984], Touliatou et al. [2006], Verona et al. [2006], Wieczorek et al. [2007]
Growth hormone deficiency	+139250	Simpson et al. [1999]
Hemihypertrophy	%235000	West et al. [2003]
Hemophilia A	+306700	Bennett et al. [2008]
Hemophilia B	#306900	Kitchens [1987], Revesz et al. [1972]
Holoprosencephaly	%236100	Machin et al. [1985], Peng et al. [2007]
Humero-radial synostosis	%236400/143050	McCredie [1975]
Hunter syndrome	+309900	Winchester et al. [1992]
Idiopathic torsion dystonia (ITD)	#128100/%602124	Chan and Tsui [1997]
Kabuki syndrome	%147920	Shotelersuk et al. [2002]
Kearns–Sayre syndrome	#530000	Blakely et al. [2004]
Klippel–Feil syndrome	%118100	Toyoshima et al. [2006]
Klippel–Trenaunay syndrome	%149000	Hofer et al. [2005], Oduber et al. [2010]
Landau–Kleffner syndrome	245570	Feekery et al. [1993]
Leber's hereditairy opticus atrophy	#535000	Biousse et al. [1997], Johns et al. [1993]
Lesch–Nyhan syndrome	#300322	De et al. [2005]
Mayer Rokitansky Küster syndrome	%277000	Heidenreich et al. [1977], Duru and Laufer [2009]
McCune–Albright syndrome	#174800	Peleg et al. [2009]
Ocular cicatricial pemphigoid	164185	Bhol et al. [1995]
Oculo-oto-radial (IVIC) syndrome	#147750	Elcioglu and Berry [1997]
Oto-palato-digital syndrome	#311300	Robertson et al. [2006]
Oral–facial–digital syndrome	#311200	Shotelersuk et al. [1999]
Primary lateral sclerosis	%611637	Sorenson [2006]
Primary progressive aphasia	#607485	Doran and Larner [2004]
Proteus syndrome	%176920	Brockmann et al. [2008]
Retinitis pigmentosa	#180100 + others	Bernstein and Aptsiauri [2003]
Rett syndrome	#312750	Carter et al. [2008], Migeon et al. [1995], Subramaniam et al. [1997]
Rubinstein–Taybi syndrome	#180849	Kajii et al. [1981]
Say syndrome	181180	Ashton-Prolla and Felix [1997]

(*Continued*)

TABLE IV. (*Continued*)

Disorder	MIM[a]	Refs.
Schimmelpenning–Feuerstein–Mims syndrome	%163200	Schworm et al. [1996]
Silver-Russell syndrome	%180860	Bailey et al. [1995], Sagot et al. [1996], Samn et al. [1990], Yamazawa et al. [2008]
Sotos syndrome	#117550	Brown et al. [1998]
Spondylocostal dysostosis	#277300	Van Thienen and Van der Auwera [1994]
Thumb polydactyly	#174400	Peterson and Rayan [2004]
VACTERL	192350	Becker et al. [2005], Camacho et al. [2008]
Van der Woude syndrome	#119300	Kondo et al. [2002]
X-linked adrenoleukodystrophy	#300100	Korenke et al. [1996]
X-linked hypophosphataemic rickets	#307800	Owen et al. [2009]

Symbols preceding a MIM number: #, a descriptive phenotype, not necessarily representing a unique locus; +, description of a gene of known sequence and a phenotype; %, a confirmed Mendelian phenotype or phenotypic locus for which the underlying molecular basis is not known; no symbol before a MIM number generally indicates a description of a phenotype for which the Mendelian basis, although suspected, has not been clearly established.[a]Mendelian Inheritance in Man (MIM) numbers correspond to Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) (November 1, 2009). World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/.

Discordant genotypes due to point mutations in one twin have been identified in a few MZ twin pairs. First, in a pair of MZ twins discordant for Darier's disease, a point mutation in *ATP2A2* was identified in the affected twin only [Sakuntabhai et al., 1999]. Furthermore, a mutation in *IRF6* was found in the affected twin from an MZ twin pair discordant for Van der Woude syndrome [Kondo et al., 2002] and discordance for a point mutation in *FLNA* explains the occurrence of otopalatodigital syndrome in one twin from an MZ twin pair [Robertson et al., 2006]. Mosaicism of a mutation in the *COL4A5* gene in the affected twin was suggested to cause discordance of Alport syndrome in an MZ twin pair [Matsukura et al., 2004]. These reports highlight the potential value of discordant MZ twins in identifying new genes [Mansilla et al., 2005]. For complex traits, this approach has not yet seen large-scale application for gene-finding so far.

It has been hypothesized that the inheritance of a single recessive mutated allele of a gene followed by a somatic mutation in the normal allele during critical periods of development in the affected twin may result in discordance for complex diseases in MZ twins [Guidry and Kent, 1999; Singh et al., 2009].

Discordance for many other genetic abnormalities has been demonstrated in the past years. Uniparental disomy (UPD) may occur in only twin from an MZ pair [West et al., 2003; Smith et al., 2006]. In these cases, a post-zygotic mitotic recombination error is believed to result in exclusively paternal origin of a segment of chromosome 11p, resulting in BWS or hemihypertrophy. To our knowledge, no reports are available on discordance for whole chromosome UPD within MZ twin pairs.

Discordance for a triplet repeat expansion length may cause a difference in expression, as illustrated for fragile-X syndrome [Kruyer et al., 1994; Helderman-van den Enden et al., 1999]. Discordance for a phenotype may be the result of different levels of (unrecognized) mosaicism between the two twins. This phenomenon has been demonstrated for monogenetic diseases [Norremolle et al., 2004] and chromosomal abnormalities (45,X). Different rates of mosaicism in 45,X/46,XY or 46,XX/46,XY mosaicism may even result in MZ twins of opposite sex [Schmidt et al., 1976; Schmid et al., 2000; Dallapiccola et al., 1985; Reindollar et al., 1987; Fujimoto et al., 1991; Kurosawa et al., 1992; Costa et al., 1998; Somkuti et al., 2000; Wachtel et al., 2000; Tho et al., 2007; Zech et al., 2008]. Likewise, 45,X mosaicism may result in discordance for symptomatic X-linked disorders, such as Duchenne muscular dystrophy, in women [Bonilla et al., 1990].

In diseases caused by mitochondrial DNA mutations, different levels of heteroplasmy are suggested to be the cause of discordance for Leber's hereditary opticus atrophy [Biousse et al., 1997] and

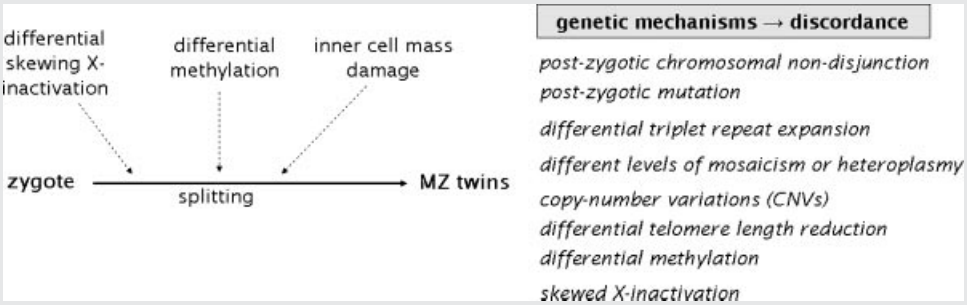

FIG. 1. Possible triggers for splitting of the zygote (left) and (epi)genetic mechanisms that may cause MZ twin discordance (right).

chronic progressive external ophthalmoplegia (CPEO) [Blakely et al., 2004].

The presence of copy-number variations (CNVs) has been demonstrated both within concordant and discordant MZ twin pairs. Bruder et al. studied a total of 19 pairs of MZ twins; 9 of these MZ twin pairs were discordant for probable or possible Parkinson disease, Parkinsonism, or Lewy body dementia and 10 MZ twin pairs were phenotypically unselected. Comparisons within the discordant twin pairs revealed a considerable number of loci suggestive of putative CNV. Analysis of the concordant normal MZ twin pairs also showed discordances in CNVs, suggesting putative de novo somatic CNV events, in addition to the concordant genotypes, including CNVs shared by both twins of a pair [Bruder et al., 2008]. The implications of these findings may be far reaching and the study of CNVs in discordant MZ twin pairs is likely to be an important field of further research.

Telomere length and reduction of telomere length are partly genetically determined, nonetheless significant differences can be found within MZ twin pairs [Slagboom et al., 1994; Andrew et al., 2006; Bakaysa et al., 2007]. The within-pair correlation of telomere length in MZ twins decreases with increasing age [Bakaysa et al., 2007]. The analysis of telomere lengths in lymphocytes from an opposite-sex DZ twin pair with chimerism suggested that telomere length attrition is partly determined by the extracellular factors [Bruderlein et al., 2008]. Twin studies have contributed to our insight into the role of telomere length reduction in the process of aging and the development of age-related disease [Bakaysa et al., 2007; Gilley et al., 2008; Kimura et al., 2008; Valdes et al., 2008].

Finally, few differences in SNPs [Montgomery et al., 2005] have been recognized within MZ twin pairs. The significance of this finding remains to be elucidated.

Thus, genetic differences between MZ twins may reflect a post-zygotic mutation. In singletons, post-zygotic mutations result in (somatic) mosaicism. Somatic mosaicism is an increasingly recognized phenomenon [Gripp et al., 2006] and is believed to be involved in diseases in which the presumed causative mutation is hypothesized to be lethal in the non-mosaic state, such as Proteus syndrome and McCune–Albright syndrome [Endo et al., 1991; Peleg et al., 2009]. Moreover, somatic mosaicism has been associated with various non-Mendelian disorders and is considered to play a key role in carcinogenesis, ageing and possibly autoimmunity [Youssoufian and Pyeritz, 2002]. Hence, genetic differences between MZ twins may provide insight into early post-zygotic mutagenesis.

Discordant epigenetic phenomena also have been shown to contribute to phenotypic differences in MZ twins. Significant epigenetic differences have been demonstrated in MZ twins [Kato et al., 2005; Wong et al., 2005; Heijmans et al., 2007; Kaminsky et al., 2009]. Fraga et al. found remarkable (age-dependent) discordance within MZ twin pairs for DNA methylation and histone acetylation in one-third of investigated MZ twin pairs [Fraga et al., 2005; Machin, 2009b].

An increased incidence of BWS has been reported in MZ (female) twins [Weksberg et al., 2002; Smith et al., 2006; Bliek et al., 2009]. In most cases the twin pair is discordant for the disease [Weksberg et al., 2002], due to discordance for loss of methylation at imprinting control region 2 (IC2) at chromosome 11p15 [Gaston et al., 2001; Weksberg et al., 2002]. In line with these data, a discordant methylation pattern of differentially methylated region in the upstream of *H19* (H19-DMR) was found in an MZ twin pair discordant for Silver–Russell syndrome [Yamazawa et al., 2008]. In the affected twin from an MZ twin pair discordant for a caudal duplication anomaly, hypermethylation was shown at the promoter region of the *AXIN1* gene [Oates et al., 2006].

Discordance for a monogenetic disease in women may be the result of a difference in randomization of X-inactivation [Lubinsky and Hall, 1991; Tiberio, 1994; Watkiss et al., 1994; Goodship et al., 1996]; this mechanism has been described for hemophilia [Revesz et al., 1972; Kitchens, 1987; Valleix et al., 2002; Bennett et al., 2008], Fabry disease [Redonnet-Vernhet et al., 1996], colorblindness [Jorgensen et al., 1992], Hunter syndrome [Winchester et al., 1992], Fragile-X syndrome [Tuckerman et al., 1985; Kruyer et al., 1994], and Duchenne muscular dystrophy [Gomez et al., 1977; Burn et al., 1986; Chutkow et al., 1987; Pena et al., 1987; Richards et al., 1990; Lupski et al., 1991; Tremblay et al., 1993; Zneimer et al., 1993]. Apparently, non-shared factors can determine randomization of X-inactivation.

The process of MZ twinning may coincide the timing of X-inactivation, randomly resulting in clones with different X-inactivation patterns and unequal blastomere allocation may result in skewed X-inactivation in the smaller clone [Machin, 2009b].

MZ twin pairs discordant for a genetic abnormality elegantly serve as an in vivo model for the genetic defect. In case reports or series on singletons with a (relatively) uncommon disorder the effects related to the genetic aberration may be difficult to extract. Nevertheless, in a single discordant MZ twin pair, sharing many environmental factors and the genetic abnormality being the sole genetic difference, the comparison between the two twins is very illustrative and provides valuable information. The report of an MZ twin pair, of whom one twin has a 45,X genotype and the other twin a 46,XX genotype, increased our insight into the net effect of missing one X-chromosome in females [Rohrer et al., 2004]. Follow-up and comparison of the physical features, growth, and hormone production of both girls, presumably being otherwise genetically identical, indicates the pure effect of the absence of a second X-chromosome on these parameters over time. Likewise, an MZ twin pair discordant for a malformation sequence clearly illustrates the sequential effects of the primary defect. The urinary production from the unaffected twin from an MZ twin pair discordant for renal agenesis prevented the development of sequential abnormalities occurring in Potter sequence in the affected twin [Perez-Brayfield et al., 2004].

Discordant MZ twin pairs may increase our knowledge on a disease upon detailed phenotyping. A thorough analysis of discordant MZ twin pairs may elucidate differences and highlight mechanisms that play a key role in the disease. For example, magnetic resonance imaging (MRI) analysis of MZ twin pairs, discordant for Rett syndrome [Carter et al., 2008], Asperger syndrome [Belmonte and Carper, 2006], ADHD [van 't et al., 2007], and obsessive-compulsive symptoms [den Braber et al., 2008] revealed significant differences in brain structure or functioning.

The intrauterine environment is not necessarily equal for both twins from an MZ twin pair because of the number of cells allocated

to each twin, the timing of the twinning process, and the vascular distribution from the placenta [Machin, 1996]. An increased prevalence of deformations is observed in MZ twins compared to DZ twins and singletons. A substantial part of these deformations is present in only one twin [Hall, 1996b, 2003]. Evidently, discordance for congenital deformations or malformations in an MZ twin pair may also reflect environmental origins [van der Knaap and Barth, 1994; Mohammed et al., 2004].

In addition to descriptions of discordance for genotypes or phenotypes in Mendelian and chromosomal disorders, discordant MZ twin pairs also have been investigated for aspects of multifactorial traits and disorders, by comparing the affected (high-scoring) and unaffected (low-scoring) twin. For example, the immunologic responses in MZ twins discordant for rheumatoid arthritis [Gulwani-Akolkar et al., 1995] and Crohn's disease [Gulwani-Akolkar et al., 1994] were compared and cerebral glucose metabolism was studied in MZ twins discordant for Alzheimer disease [Virta et al., 2009]. Similarly, cytokine profiles in MZ twins discordant for myasthenia gravis differed significantly, suggesting a role of these mediators in the pathogenesis of the disease [Kakoulidou et al., 2004]. The amount of exercise in a pair of MZ female twins discordant for adolescent idiopathic scoliosis (AIS) was evaluated by Potoupnis et al. [2008], and this case report questioned the ''cause and effect'' relationship between AIS and exercising, as both girls were elite athletes twins.

Discordant MZ twin pairs also comprise a unique source of information on the effects of acquired diseases such as HIV [Agrati et al., 2006] or lifestyle factors [e.g., smoking, Kaprio and Koskenvuo, 1989; van Leeuwen et al., 2007 and drug use, Ferguson et al., 2007]. In population-based case–control studies, it is often difficult to distinguish the cause and the effect of a disorder (or, e.g., of medication use) on gene expression. MZ twins, discordant for the disorder, may be very valuable in the analysis of the effect of the disease on gene expression, as demonstrated for acquired obesity [Pietilainen et al., 2008]. In these pairs, mtDNA copy number was reduced by 47% in the obese twin's fat and pathway analyses of the adipose tissue transcription profiles showed significant down-regulation of mitochondrial branched-chain amino acid (BCAA) catabolism. These findings pointed to a substantial role of mitochondrial energy and amino acid metabolism in obesity.

MZ twins, both exposed to toxics may suggest variability of the effect that is probably not genetically determined, as published, for example, for diethylstilbestrol (DES), [Sandberg and Christian, 1980], thalidomide [Jorgensen et al., 1970], and alcohol [Streissguth and Dehaene, 1993] exposure.

The Human Genome Project and its associated technologies have opened up many new opportunities for gene finding and positional cloning has been successful in the identification of genes involved in many human disorders [Khoury and Yang, 1998; Landegren, 2000; Collins and McKusick, 2001]. However, the genetic basis of many heritable disorders remains unclear and the identification of a causative mutation responsible for a phenotype still represents a very demanding task. With today's whole-genome sequencing technologies and increasing evidence for genetic and epigenetic differences in some MZ twins, twin research provides new opportunities. The genetic analysis of discordant MZ twin pairs may identify new genes, as demonstrated in Darier's disease and Van der Woude syndrome [Sakuntabhai et al., 1999; Kondo et al., 2002]. The occurrence of a possibly monogenetic disorder in only one twin from an MZ twin pair has been used as an argument against Mendelian inheritance. In 1992, an MZ twin pair discordant for Fuchs' heterochromic uveitis (FHU) persuaded the authors to state that ''regular Mendelian inheritance is now proved to be impossible'' [Jones and Read, 1992]. Recognizing numerous reports on discordance for genetic abnormalities in MZ twins, such a conclusion would nowadays probably be drawn more carefully. Also in prenatal testing, awareness of the possibility of genetic or phenotypic discordance is justified.

The exact extent of genetic differences between (unselected) MZ twins still remains to be elucidated. Based on the very first results of studies in which both members of MZ twin pairs were genotyped, such differences seem rare in unselected samples. It is therefore unlikely that such differences would significantly bias the results of large-scale epidemiological studies that analyze data from twins to estimate heritability. However, the precise effect of this possible variance in twin studies remains to be established based on empirical data.

Genetic difference within a discordant MZ twin pair may guide us toward causative genes in monogenetic diseases, without the confounding effect of polymorphisms [Kruglyak and Nickerson, 2001]. As such, hunting for genetic differences between discordant MZ twin pairs appears to be an encouraging strategy for future twin research. In the era of large-scale genome-wide association studies including thousands of patients in each study, single discordant MZ twin pairs may serve as an alternative to increase our knowledge on the spectrum of diseases, factors contributing to variability, pathogenic mechanisms, and post-zygotic mutagenesis. The search for differences in genotypes within discordant MZ twin pairs seems to be a promising approach in gene-finding. With future possibilities for human genome sequencing of large numbers of individuals [e.g., Drmanac et al., 2010] it may even become feasible to turn this strategy around and sequence large numbers of unselected MZ twin pairs, after which differences within pairs can be correlated with differences in phenotypes or transcription profiles.

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