Epidemiology of Down Syndrome

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Down syndrome (DS) is the most commonly identified genetic form of mental retardation and the leading cause of specific birth defects and medical conditions. Traditional epidemiological studies to determine the prevalence, cause, and clinical significance of the syndrome have been conducted over the last 100 years. DS has been estimated to occur in ~1 in 732 infants in the United States, although there is some evidence that variability in prevalence of estimates exist among racial/ethnic groups. Progress has been made in characterizing the specific types of chromosome errors that lead to DS and in identifying associated factors that increase the risk of chromosome 21 malsegregation, i.e., advanced maternal age and recombination. Studies to examine the variability of the presence of specific DS-associated birth defects and medical conditions provide evidence for genetic and environmental modifiers. Here, we provide a brief survey of studies that address the current state of the field and suggest gaps in research that can soon be filled with new multidisciplinary approaches and technological advances. © 2007 Wiley-Liss, Inc.

Key Words: nondisjunction; trisomy 21; maternal age; recombination; congenital heart defects

INTRODUCTION

Epidemiology is the study of the patterns and causes of health-related traits in defined populations. Results from such studies form a foundation for interventional medicine. For Down syndrome (DS), such epidemiological studies began in the mid 1800s when several physicians described groups of patients, who had mental retardation and short stature along with specific facial characteristics, including oblique eye fissures, epicanthal folds, flat nasal bridge, and protruding tongue [Esquirol, 1838; Séguin, 1846, 1856; Down, 1866]. J. Langdon Down, for whom DS was named, contributed significantly to the epidemiology of this syndrome by emphasizing that this set of clinical findings constituted a distinct entity, and affected individuals could be distinguished from the heterogeneous group of all those with intellectual disabilities. In an excellent review of the history of DS, Rynders and Pueschel [1982] continue the story of the recognition of DS through the late 1800s and early 1900s.

Once DS was recognized as a separate entity, it became possible to identify associated determinants. The first to be linked to DS was increased parental age at the birth of the infant with DS [e.g., Van der Scheer, 1927; Thurston and Jenkins, 1931]. Shortly thereafter, Penrose demonstrated clearly that advanced maternal age, not paternal age or birth order, was the key determining factor for DS [Penrose, 1933, 1934]. He also suggested that very young mothers have an increased chance of an infant with DS. In 1954, Penrose further suggested that there could be different causes of DS based on the observation that about one-third of cases in his series were not associated with maternal age [Penrose, 1954]. For example, he observed that, in families with two affected siblings, the mean maternal age was lower when compared with the general sample of infants with DS. With significant insight, he suggested several plausible causes of DS: genetic susceptibility, unbalanced chromosomes caused by translocation, and factors associated with fluctuating endocrine disturbance.

With the advent of karyotyping, the etiology of DS was identified in 1959 as the presence of an extra chromosome 21 [Book et al., 1959; Ford et al., 1959; Jacobs et al., 1959; Lejeune, 1959]. It is now estimated that ~95% of individuals with DS have an extra chromosome 21 as a result of meiotic nondisjunction, or the abnormal segregation of chromosomes during gamete formation. Of the remaining 5%, less than 1% is due to somatic mosaicism and the rest to chromosome 21 translocations. Interestingly, in 1964, Penrose proposed that the maternal age-dependent cases of DS could be due to meiotic nondisjunction, but succinctly stated that "The traditional explanation that the ovum becomes abnormal with age is unhelpful unless some attempt is made to link the supposed deterioration with the observed distribution curve."

Thus, by the early 1960s, the syndrome hallmarks were described, the cytogenetic causes identified, and the most significant risk factor determined, namely maternal age. DS or trisomy 21, is now one of the most intensively studied human aneuploid conditions. This review will focus attention on the current literature related to two distinct, but related, areas of the epidemiology of DS. First, we will review the prevalence of DS and its associated risk factors. We will focus on meiotic nondisjunction of chromosome 21, the most common cause of DS. Second, we will review studies of the prevalence of DS-associated birth defects and disorders. As each topic is worthy of an entire journal, we will concentrate on a few exemplary studies to illustrate the progress made in

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the field and to outline potential genetic epidemiological study designs capable of uncovering the biological mechanisms underlying chromosome 21 nondisjunction and its clinical consequences. For this reason, we will not provide an extensive review of the many significant reports in the older literature, but will focus on surveying the current field.

PREVALENCE OF DS

Reliable prevalence estimates form the basis for determining the resources needed for health care and education, as well as for basic science and public health research. Examination of differences in prevalence among populations or over time helps to identify potential risk factors as well as to evaluate public health interventions. The design of studies to estimate the prevalence of DS must be clearly stated to interpret the results. For example, studies can focus on birth prevalence or they can also include spontaneous and elective abortions. The former would be more effective for studying the clinical features of DS, such as heart and gastrointestinal defects, and for estimating healthcare needs, whereas the latter would be more suitable for providing information about possible exposures associated with chromosome nondisjunction.

The report by Canfield et al. [2006] provides a recent example of a large study to obtain an estimate of the birth prevalence of DS in the U.S. They obtained data from 11 birth surveillance systems that used active-case finding methods. All pregnancy outcomes, including live births, fetal deaths, spontaneous and induced abortions, and all gestational ages were eligible. However, each active surveillance system varied in their case inclusion criteria with respect to pregnancy outcome, gestational age and the ability to ascertain prenatally diagnosed cases from specialized sources. The estimated maternal age-adjusted prevalence of DS based on the surveillance of ~22% of the live births in the U.S. was 13.65 [95% confidence intervals (CI): 13.22–14.09] per 10,000 live births, or 1/732. This suggests that ~5,400 of the ~4 million infants born each year in the U.S. have DS.

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CHROMOSOME 21 NONDISJUNCTION IN OOCYTES: A MAJOR CAUSE OF DS

As emphasized by Penrose in the early 1900s, the ability to identify the biological mechanisms and associated risk factors for DS is greatly enhanced in studies that focus on a specific type of error. Soon after the chromosomal basis of DS became known in 1959, cytogenetic techniques allowed investigators to distinguish the underlying types of chromosome errors: (1) standard trisomy 21, (2) translocations, and (3) mosaicism (one normal cell line and one trisomic cell line). The identification and application of chromosome heteromorphisms and DNA polymorphisms led to the ability to define further the etiology of standard trisomy 21
by categorizing nondisjunction errors by parental origin (maternal and paternal) and type of error [meiosis I (MI), meiosis II (MII) and mitotic]. To date, the largest study to categorize these nondisjunctional errors is the National Down Syndrome Project (NDSP), a population-based study conducted from 2000 to 2005 at six national sites representing ~11% of annual births in the United States [Freeman et al., 2007]. Data analysis is in progress on the 907 cases (infants with DS) and 977 controls (infants without DS) enrolled in the NDSP.

Based on results from the NDSP (Table 1) and other population-based series [e.g., Mikkelsen et al., 1995; Gomez et al., 2000], over 90% of nondisjunction errors leading to trisomy 21 occur in the oocyte and the majority of those occur during MI. Because of space limitations, we will only review maternal nondisjunction errors as most work has been done in this area. A recent review [Sherman et al., 2005] provides an overview of our limited knowledge of paternal nondisjunction and its associated risk factors.

**Advanced Maternal Age is Restricted to Maternal Nondisjunction Errors**

The most important risk factor associated with DS is advanced maternal age. The impact of this factor is significant given the trend for women to delay childbirth [e.g., Dolk et al., 2005]. Investigators have thoroughly documented that advanced maternal age as a risk factor for DS is restricted to nondisjunction errors that occur in the oocyte [e.g., Antonarakis et al., 1992; Ballesta et al., 1999; Muller et al., 2000; Sherman et al., 2005]. That is, advanced maternal age is not observed among mothers whose offspring received the extra chromosome 21 as a result of: (1) a nondisjunction error in spermatogenesis (paternal errors [Petersen et al., 1993; Yoon et al., 1996; Sherman et al., 2005]), (2) a postzygotic mitotic error (e.g., Antonarakis et al., 1993; Sherman et al., 2005), or (3) a translocation (inherited or de novo) [Hook, 1983].

Intriguingly, advanced maternal age is a risk factor for both MI and MII maternal nondisjunction errors [e.g., Antonarakis et al., 1992; Yoon et al., 1996; Muller et al., 2000; Sherman et al., 2005]. The timeline for oogenesis compared with spermatogenesis points to possible error-prone stages of meioisis. Meiosis is initiated in oocytes during fetal life. After homologous chromosomes synapse and initiate recombination, meiosis arrests. MI resumes 10–50 years later in individual oocytes just prior to their ovulation. MII only extends over the 3–4-day ovulation period and is completed after fertilization. This timeline differs significantly from that in spermatogenesis, which begins at puberty and cells entering meiosis move from one stage to the other without delay.

Plausible explanations for maternal age-related nondisjunction in both MI and MII include, but are not limited to: (1) an accumulation of toxic effects of the environment during the arrested state of the oocyte, (2) a degradation of meiotic machinery over time while in the arrested state, leading to a suboptimal resumption of MI and MII, and/or (3) a change in ovarian functioning due to suboptimal hormonal signaling. Most likely, several processes are affected by advanced maternal age and thus more than one of the various hypotheses proposed to explain this effect will be correct. Several excellent reviews of hypotheses to explain the maternal age effect are available [e.g., Gaulden, 1992; Eichenlaub-Ritter, 1996] along with a recent review of hypotheses related to biological aging of the ovary [Warburton, 2005].

**Examining the Maternal Age Effect**

By far, advanced maternal age is the most significant risk factor for nondisjunction of chromosome 21. One potential way to understand the maternal age effect is to examine maternal health factors and environmental exposures in cases where the nondisjunction error occurred in the oocyte. Once a risk factor for nondisjunction is identified, it can be further evaluated in the context of biological aging to provide insight into the mechanism causing the maternal age effect. For example, biological aging of the ovary is characterized by a decline in the total oocyte pool, a decline in the number of antral follicles maturing per cycle and in reproductive hormonal changes. A decrease in the number of maturing follicles has been hypothesized to decrease the probability that one of them will be at the precise stage necessary for optimal response to follicle stimulating hormone (FSH), the trigger for ovulation. In 1989, Warburton [1989] put forth the “limited oocyte pool” hypothesis suggesting that under these circumstances, the follicle selected for ovulation may be one whose oocyte is under- or overripe and thus more susceptible to chromosome malsegregation. In an excellent review, Warburton [2005] found inconsistent results among the studies that have examined the relationship between nondisjunction and biological aging of the ovary. For example, Freeman et al. [2000] found that mothers with a maternally-derived chromosome 21 nondisjunction error were more likely to have a reduced ovarian complement (congenital or surgical) compared with mothers of infants without DS (OR: 9.61; 95% CI: 1.18–46.3). Women with reduced ovarian complement have a smaller oocyte reserve and thus would “mimic” an older woman. However, this observation has not been confirmed. Other indirect evidence to support ovarian aging specifically for chromosome 21 nondisjunction was reported by van Montfrans et al. [1999]. They found higher levels of follicle-stimulating hormone (FSH), an indicator of decreased ovarian reserve, among women with an infant with DS compared with controls. A more recent case–control study compared maternal

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**Table 1. Origin of Trisomy 21**

<table>
<thead>
<tr>
<th>Origin</th>
<th>N</th>
<th>Proportion</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meiosis I (MI)</td>
<td>529</td>
<td>MI/(MI + MII) = 529/708</td>
<td>74.7%</td>
</tr>
<tr>
<td>Meiosis II (MII)</td>
<td>179</td>
<td>MII/(MI + MII) = 179/708</td>
<td>25.3%</td>
</tr>
<tr>
<td>Stage unknown</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Subtotal</strong></td>
<td>729</td>
<td>M/All = 729/782</td>
<td>93.2%</td>
</tr>
<tr>
<td>Paternal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meiosis I (PI)</td>
<td>13</td>
<td>PI/(PI + PII) = 13/31</td>
<td>41.9%</td>
</tr>
<tr>
<td>Meiosis II (PII)</td>
<td>18</td>
<td>PII/(PI + PII) = 18/31</td>
<td>58.1%</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>32</td>
<td>P/All = 32/782</td>
<td>4.1%</td>
</tr>
<tr>
<td>Mitotic</td>
<td>21</td>
<td>Mitotics/All = 21/782</td>
<td>2.7%</td>
</tr>
<tr>
<td><strong>Total informative cases (all)</strong></td>
<td>782</td>
<td></td>
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</tr>
</tbody>
</table>

Data taken from Freeman et al. (2007).

Stage unknown = DNA markers in the centromeric region were not informative.
serum anti-mullerian hormone (AMH) levels, another marker for ovarian reserve. Although the sample size was limited, they did not find any differences in AMH levels during pregnancy between 25 women with a DS fetus and 125 women with an unaffected pregnancy [Seifé et al., 2007]. In a recent review, Warburton [2005] concluded that much of the evidence to date suggests that, if the processes of ovarian aging are related to chromosome nondisjunction, they probably involve factors other than those measured by oocyte or antral follicle pool size and reproductive hormone levels.

**Altered Recombination Patterns Along Chromosome 21 Play a Role in Maternal Nondisjunction**

Aside from maternal age, only one additional factor has been shown to be unequivocally associated with maternal nondisjunction, that is, altered recombination patterns. Warren et al. [1987] provided the first evidence to suggest that a proportion of maternal nondisjunction errors was associated with reduced recombination along chromosome 21. In addition to the absence of an exchange, the placement of an exchange along the nondisjoined chromosome is an important susceptibility factor for chromosome 21 segregation [Lamb et al., 2005a; Sherman et al., 2005]. Briefly, examination of recombination along the maternal nondisjoined chromosome 21 has suggested three susceptibility exchange patterns: (1) no exchange leads to an increased risk of MI errors, (2) a single telomeric exchange leads to an increased risk of MI errors, and (3) a pericentromeric exchange leads to an increased risk of MI errors [Lamb et al., 1996, 1997]. The association of maternal MI errors with a specific recombination pattern suggests that at least some proportion of MI errors are initiated in MI. We will simply use the designation “MII” to indicate this suggestion.

More recently, we have examined altered recombination patterns of maternal nondisjoined chromosomes 21 stratified by maternal age to gain insight into possible mechanisms of nondisjunction. The data on 400 maternal MI errors grouped by maternal ages <29 years, 29–34 years and >34 years have provided preliminary results suggesting there could be multiple causes of nondisjunction, some age dependent and others age independent [Lamb et al., 2005b]. In a young woman, meiotic machinery (spindle function, sister chromatid adhesie proteins, microtubule motor proteins, etc.) functions optimally and, as a result, can correctly segregate all but the most susceptible exchange configurations. For young women then, the most frequent risk factor for MI nondisjunction is the presence of a telomeric exchange. As a woman ages, her meiotic machinery is exposed to an accumulation of environmental and age-related insults, becoming less efficient/more error-prone. Suboptimal exchange patterns still increase susceptibility to nondisjunction, but now even homologous chromosomes with optimally placed exchanges are at risk. Over time, the proportion of nondisjunction due to normal exchange configurations increases as age-dependent risk factors exert their influence. As a result, the most prevalent exchange profile of nondisjoined oocytes shifts from susceptible to nonsusceptible patterns with increasing age of the oocyte.

If “MII” errors are initiated in MI, exchange patterns among maternal age groups with “MII” errors are predicted to be similar to those observed for MI errors. Preliminary data suggest that this is not the case (unpublished data). In our limited study sample (about 40 cases in each age group), the amount of recombination significantly decreased with increasing maternal age for “MII” errors (P < 0.01). For example, the mean age of women with an “MII” error and one observed recombinant was 32.8 years whereas the mean maternal age of those with two or more recombinants was 28.2 years. Moreover, the proportion of susceptible pericentromeric exchanges increased with age, the opposite pattern to that observed in MI. Whether these results are robust remains to be seen. If these results are confirmed, the apparent difference in MI- and “MII”-maternal age associated exchange patterns may provide clues to the nondisjunction mechanism and associated risk factors.

**Environmental Risk Factors for Chromosome 21 Nondisjunction**

A wealth of candidates for environmental risk factors has been identified in epidemiological studies of DS. Smoking at the time of pregnancy is an excellent example of the difficulties and limitations of such studies. Previously, a number of studies reported a nonsignificant negative association between maternal smoking around the time of conception and the risk for DS [e.g., Kline et al., 1983, 1993; Hook and Cross, 1985, 1988; Shiono et al., 1986; Chen et al., 1999]. One explanation for the negative association was that trisomic conceptuses were selectively lost prenatally among women who smoke [Hook and Cross, 1985; Kline et al., 1993]. However, other studies have concluded there is no association between DS and periconceptional smoking [e.g., Cuckle et al., 1990; Kallen, 1997; Tords and Christianson, 2000]. Yang et al. [1999] analyzed periconceptional smoking among women less than 35 years with maternal MI and “MII” errors separately and found an increased frequency of smoking among women with “MII” errors only (OR = 2.98; 95% CI = 1.01–8.87). The odds ratio for this group of women increased significantly if the interaction term of periconceptional smoking and oral contraceptive use was modeled (OR = 7.62; 95% CI = 1.63–35.6). The authors speculated that this combined risk factor may compromise the blood flow surrounding the developing follicle, depleting the follicular fluid of oxygen. This hypoxic environment may cause the meiotic machinery to malfunction. This speculation is similar to that proposed by Gaulden [1992] to explain maternal-age related nondisjunction. She suggested that the follicular microcirculation may be compromised in an aging ovary because of abnormal hormone signaling. Although the study of Yang et al. must be confirmed with a larger sample size, this example illustrates the potential of relating identified risk factors to the maternal age effect.

Other factors, such as alcohol [e.g., Kaufman, 1983], maternal irradiation [e.g., Uchida, 1979; Strigini et al., 1990; Padmanabhan et al., 2004], fertility drugs [e.g., Boue and Boue, 1973], oral contraceptives [e.g., Harlap et al., 1979; Yang et al., 1999], spermicides [e.g.,
Candidate Genes for Chromosome 21 Nondisjunction

Model organisms have been used to identify genes that are important in the proper segregation of chromosomes. Genes involved in the meiotic process (e.g., homolog pairing, assembly of the synaptonemal complex, chiasma formation, sister chromosome cohesion, meiotic spindle formation) may predispose an organism to chromosome nondisjunction. To date, a large study to investigate the association of variants in these genes with nondisjunction of human chromosome 21 has not been conducted.

Candidate gene studies of the folate pathway provide the best example of genetic epidemiological approaches being used to evaluate the association of genetic variants with nondisjunction. James et al. [1999] provided preliminary evidence that the 677C > T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene increased the chance of having a child with DS (OR = 2.6; 95% CI: 1.2–5.8). This polymorphism is associated with an elevation in plasma homocysteine and/or low folate status. The authors hypothesized that low folate status, whether due to dietary or genetic factors, could induce centromeric DNA hypomethylation and alterations in chromatin structure. Such alterations could adversely affect DNA–protein interactions required for centromeric cohesion and meiotic segregation. Later studies of the MTHFR 677C > T polymorphism, as well as several other allelic variants in the folate pathway, generated inconsistent results especially when genotypes were assessed without biomarkers of metabolic phenotype [e.g., Hobbs et al., 2000; O’Leary et al., 2002; Bosco et al., 2003]. James [2004a,b] provide an excellent review of these studies. Those who have examined blood homocysteine levels, a broad-spectrum indicator of nutritional and/or genetic impairment in folate/B12 metabolism, have documented a significantly higher level among the mothers of children with DS compared with control mothers. Several recent studies have focused on the interaction among genes in the folate pathway and continue to find intriguing correlations [e.g., Coppede et al., 2006; Martinez-Frias et al., 2006; Scala et al., 2006, 2007]. Clearly, this story needs to be pursued. Future studies should focus on gene–gene and gene–nutrition interactions in the folate pathway using large sample sizes, appropriate controls and genetic epidemiological methods that adjust for possible confounding due to population substructure.

Studies from model organisms make it clear that a wide variety of genetic and environmental disturbances can affect aneuploidy levels. Large population–based studies that separate individuals with DS by type of nondisjunction error will increase the power to identify risk factors that have remained elusive.

DS-ASSOCIATED BIRTH DEFECTS AND DISORDERS

Almost universally, individuals with DS have characteristic facial features, mental retardation, and hypotonia. However, other birth defects and medical disorders that are relatively frequent among individuals with DS compared with the general population are not present in all individuals with an extra chromosome 21. For example, congenital heart defects (CHDs) occur in about 50% of individuals with DS and digestive abnormalities occur in about 10%. Two important epidemiological questions are: (1) among those with DS, what is the prevalence of a specific phenotypic outcome and is it increased or decreased compared with those without DS and (2) are there associated risk factors that explain the reduced penetrance and variable expression of such traits? There are few studies that have addressed these significant questions using population–based strategies [e.g., Fabia and Drolette, 1970; Stoll et al., 1990; Kallen et al., 1996; Freeman et al., 1998; Torfs and Christianson, 1998].

One example of a recent population–based study that examined both questions is that conducted by Torfs and Christianson [1998, 1999]. They studied 2,894 confirmed cases of DS collected through the California Birth Defects Monitoring Program (CBDMP) between 1983 and 1993. They compared the frequency of specific birth defects among infants with DS to the distribution in close to 2.5 million newborn infants from the same population. They cataloged 61 major birth defect known to be uniformly ascertained through the CBDMP, i.e., those that were readily noted in an infant through age one or those that require early action. Forty-five defects were significantly more common in DS. For example, the chance for atrioventricular septal defects (AVSD, or sometimes called atrioventricular canal) was increased 1,000-fold over that for infants without DS. Other cardiac defects were also increased, including atrial septal defects (ASD), ventricular septal defects (VSD), and defects of cardiac valves. Gastrointestinal defects were about 20 times more common in infants with DS. Duodenal atresia and annular pancreas had the highest risk ratios (265 and 430, respectively). Intriguingly, most defects of the primary developmental field and midline defects were either not significantly associated or not observed in infants with DS (e.g., anencephaly, spina bifida, encephalocele, and diaphragmatic hernia). Subsequently, they conducted a case/control study based on 687 infants with DS to identify factors that might contribute to DS–associated birth defects [Torfs and Christianson, 1999]. They compared demographic information, pregnancy and medical histories, and use of tobacco, alcohol, and coffee among mothers of infants with and with specific birth defects. Taking CHD and tobacco use as an example, smoking was found to be associated with CHD (OR = 2.0; 95% CI: 1.2–3.2)
and specifically, with AVSD, ASD, and tetralogy of Fallot. Maternal race, age, parity, income, and education did not confound the association. Others have examined smoking and DS-associated CHD and have not found a significant association; however, comparison of studies is difficult as sample sizes were smaller, the timeframe of tobacco use differed (prior to conception versus during the first trimester), and the diagnostic methods used to identify and categorized CHD were older [e.g., Khouby and Erickson, 1992; Fixler and Threlkeld, 1998]. Nevertheless, the combined results suggest smoking plays only a small role, if any, in explaining the variation in heart development among those with DS, as the frequency of periconceptional smoking is low and the association modest.

Irrespective, the earlier studies illustrate sound epidemiological approaches to identify genetic or environmental modifying factors for DS-associated birth defects and medical conditions. Not only will such studies provide insight into the etiology of, say abnormal heart development or Alzheimer disease, in the context of trisomy 21, but may also contribute to the understanding of these conditions in general.

SUMMARY

DS is one of the most intensely studied genetic syndromes because of its frequency in our population and its medical significance. Epidemiology tools, clinical diagnostic technology, molecular and bioinformatic tools have advanced considerably over the last 150 years since DS was recognized as a specific entity. Although progress has been made toward understanding the causes of DS and the associated risk factors, much work needs to be done. Large racially and ethnically diverse population-based studies need to be conducted to evaluate risk factors for each type of nondisjunction error and to explore potential interventions. Ideally, such studies would continue throughout the lifespan of individuals with DS to determine the prevalence of and risk factors for medical conditions known to be associated with trisomy 21. Such studies are key to understanding the medical impact of trisomy 21 and to developing resources to ensure that individuals with DS reach their potential in our society.

REFERENCES


