Down Syndrome in India—Diagnosis, Screening, and Prenatal Diagnosis

Ishwar C. Verma, MBBS, FRCP*,
Meena Lall, PhD, Ratna Dua Puri, MD, DM

KEYWORDS

- Down syndrome • Cytogenetic studies • Folate metabolism
- Screening and prenatal diagnosis • Noninvasive prenatal diagnosis
- Future therapies

KEY POINTS

- Down syndrome (DS) is the most common genetic cause of mental retardation.
- Clinical manifestations are variable, and children have psychomotor impairment, multiple malformations, and medical conditions.
- Confirmation of the diagnosis is by karyotype analysis. The cytogenetic abnormality can be classified into pure trisomy 21, translocation, or mosaicism.
- Risk of recurrence depends on the primary cytogenetic abnormality in the proband.
- Prenatal screening is by biochemical and ultrasound markers in the first and second trimester. Definitive prenatal diagnosis is by analysis of fetal chromosomes in fetal chorionic villi, amniocytes, or cord blood.
- A noninvasive test for trisomy 21 in maternal blood has been developed by massively parallel shotgun sequencing.
- Therapeutic studies in Ts65Dn mice suggest an exciting prospect of improvement of learning ability and memory deficits.

INTRODUCTION

Down syndrome (DS) is the most common genetic cause of mental retardation around the world and is one of the best studied. John Langdon Down described the phenotype of the syndrome named after him in 1866. However, as is usual in medicine, the physical characteristics of Down syndrome had been described 20 years earlier by Esquirol and also Sequin. Lejeune and colleagues reported in 1959 that Down syndrome is caused by trisomy of chromosome 21, starting the chapter of cytogenetic disorders.[1] Chromosome 21 was sequenced in 2000 by Hattori and

The authors have nothing to disclose.
Center of Medical Genetics, Sir Ganga Ram Hospital, Rajender Nagar, New Delhi, India 110060
* Corresponding author.
E-mail address: icverma@yahoo.com

Clin Lab Med 32 (2012) 231–248
http://dx.doi.org/10.1016/j.cll.2012.04.010 **labmed.theclinics.com**

colleagues.[2] It is estimated that chromosome 21 encodes approximately160 "classical" protein-coding annotated genes, 5 microRNAs, and more than 350 genes of unassigned function.[3] The recent advances in genomics have led to a better understanding of the consequences of dosage imbalance attributable to trisomy 21. The recent evidence-based therapeutic approaches to ameliorate the harmful effects of trisomy 21 effects on brain structure and function in animal models are very encouraging and hold great promise for human application.[4]

EPIDEMIOLOGY

The incidence of trisomy 21 is influenced by maternal age and differs between populations.[5,6] Canfield and colleagues[7] estimated maternal age-adjusted prevalence of DS based on the surveillance of 22% of live births in the United States to be 1 in 732 live births. However, estimation of the frequency of DS depends on whether maternal age, gestational timing of diagnosis, and case loss caused by prenatal diagnosis and termination of pregnancy are taken into account.[8] Therefore, although the number of fetuses conceived with DS has increased in recent years as the mean age of pregnant women has increased in the United States, the number of terminated pregnancies with DS has also increased, so that the current prevalence is likely to have decreased to about 1 in 1000. On the other hand, extremely high frequencies have been recorded in the Middle Eastern countries, varying from 18 to 3.5 per 1000.[6] The reasons for this are that conceptions continue until women are in their late 40s, and abortion is not allowed. Murthy and coworkers[6] observed that 20% of the mothers in the United Arab Emirates (UAE) belonging to the younger age group of 17 to 25 years had a child with DS compared with 9.75% of the mothers in this age group belonging to non-UAE nations, suggesting the presence of some possible predisposing factor.

In India, meta-analysis of the earlier data on a study of 75,103 live births, with 82 cases of DS gave a frequency of 1 in 916.[9] In a 3-center study of 94,600 births that specifically investigated DS, 1 per 1150 births was affected.[9] In this study, the diagnosis of DS was confirmed by cytogenetic analysis. However, these data pertain to 1993 to 1997. The authors estimated the frequency of DS, based on the data provided by Baird and coworkers[10] from Vancouver and the maternal age distribution at birth in 2010 in Delhi,[11] to be 1 in 1200. The picture is muddied by widespread ultrasound studies during pregnancy, biochemical screening, amniotic fluid studies, and abortion of affected fetuses. However, in India, only 2% to 5 % of women at delivery are more than 35 years in age, which is much lower than that observed in the West or the Middle East.[11]

CLINICAL PRESENTATION

Children with DS have cognitive and psychomotor impairment, multiple malformations and medical conditions. The manifestations are varied, and all features may not be present in every affected child. The diagnosis is particularly difficult at birth, as the child often keeps the eyes closed, and the common diagnostic sign of upward slant of the palpebral fissures is not observed. However, presence of moderately severe hypotonia is more characteristic, and fewer cases would be missed if attention is paid to this sign. Additional features that are helpful in diagnosis at birth are increased skin at the nape of the neck, brachycephaly, flat midfacies with depressed bridge of nose, epicanthic folds, dysmorphic and small ears, protruding tongue, small fifth finger with clinodactyly, Simian crease, and deep vertical groove on the plantar surface of the foot between the first and second toes. The developmental retardation is difficult to