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VIEWPOINT

Down Syndrome: Let's Work Together to End the Stereotypes

Mario Motta[1], Amita Singhal[2], Angela B Hoyos[3], Abhay Lodha[4], Colin Michie[5], Michael Zemlin[6], Jargalsaikhan Badarch[7], Adrianna Frydrysiak-Brzozowska[8], Md Mozibur Rahman[9], Aimen E Ben Ayad[10,11], Surekha Ramachandran[12], Seema Thakur[13], Waldemar A Carlo[14], Ola D Saugstad[15], Kei Lui[16], Akhil Maheshwari[2,17,18], on behalf of the Global Newborn Society Down Syndrome Foundation

Abstract

Each year, we observe the 21st day of March as our World Down Syndrome Day. The goal is to raise public awareness of Down syndrome (DS) and encourage all member states, relevant organizations of the UN system, all member states, other international organizations, non-governmental organizations, and the private sector to join this effort. The epidemiology of DS is complex. The incidence of DS is estimated to be somewhere between 1 in 1,000 and 1 in 1,200 live births worldwide, but there may well be some temporal, racial/ethnic, and geographical variability in the prevalence of DS. Most infants with DS have an extra copy of chromosome 21, which occurs due to the failure of chromosome 21 to separate during gametogenesis. However, a minority with the same phenotype may have a Robertsonian translocation, an isochromosome, or a ring chromosome. Increasing information suggests that many of the most frequently seen phenotypic features may be rooted in sequential variability in only one band, the 21q22. The characteristic facial appearance, cardiac anomalies such as the endocardial cushion defect, neurodevelopmental delay, and many dermatoglyphic changes could result from a small region including the genes for superoxide dismutase in the region 21q22.1, the amyloid precursor protein mapping in 21q11.2-21.05, and six probes for single-copy sequences: D21S46 in 21q11.2-21.05, D21S47 and SF57 in 21q22.1-22.3, and D21S39, D21S42, and D21S43 in 21q22.3. Speaking from this medical perspective, we need to understand the pathophysiology of DS to meet their healthcare needs. If we could do so, we could make a small change in this world.

Keywords: Age-standardized rate, Down syndrome international network, Infant, Isochromosome, Neonate, Newborn, Ring chromosome, Robertsonian translocation, Sociodemographic characteristics, United Nations General Assembly.

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Key Points

- Each year, we mark March 21st as the World Down Syndrome Day to raise public awareness of DS.
- The incidence of DS is estimated to be somewhere between 1 in 1,000 and 1 in 1,200 live births worldwide; it is seen in people of all races and economic levels.
- Down syndrome is a complex genetic disorder; most cases involve the failure of chromosome 21 to separate during gametogenesis. However, some cases may show a Robertsonian translocation, an isochromosome, or a ring chromosome.
- As we are beginning to understand the genetics of DS, most of the phenotypic features of this condition seem to arise in the chromosomal region 21q22.
- Each time we lose an infant, we lose, and entire life and its potential. The World Down Syndrome Day 2024 was yet another reminder. Let's work together, and we might be able to make a difference.

Introduction

In December 2011, the United Nations (UN) General Assembly decided that starting in 2012, 21st March would be our World Down Syndrome Day (A/RES/66/149).[1] The goal was to raise public awareness of Down syndrome (DS) and encourage all member states, relevant organizations of the UN system, other international organizations, non-governmental organizations, and the private sector to participate in this effort. The DS International Network hosted the 13th World Down Syndrome Day Conference at the UN headquarters on 21 and 22 March 2024 in New York.[2] In this article, authors from all the 6 majorly-populated continents joined together to share their understanding and viewpoints. DS affects all humanity, and we need to act together.

[1]Department of Neonatology and Neonatal Intensive Care, AUSL di Bologna, Italy

[2]GNS Down Syndrome Foundation, Delhi, India

[3]Department of Neonatology, El Bosque University, Bogota, DC, Colombia

[4]Department of Pediatrics, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[5]Deputy Lead, School of Medicine at the University of Central Lancashire, Preston, United Kingdom

[6]Klinik für Allgemeine Pädiatrie und Neonatologie, Universitätsklinikum des Saarlandes, Homburg, Germany (Department of General Pediatrics and Neonatology, Saarland University Hospital, Homburg, Germany)

[7]Department of Obstetrics and Gynecology, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

[8]Akademia Mazowiecka w Płocku, Collegium Medicum, Wydział Nauk o Zdrowiu, Płock, Poland (The Masovian University in Płock, Collegium Medicum, Faculty of Health Sciences, Płock, Poland)

[9]Department of Neonatology, Institute of Child and Mother Health, Matuail, Dhaka, Bangladesh

[10]Tawam Hospital, Al Ain, United Arab Emirates

[11]Panlibyan Neonatal Association

[12]Down Syndrome Federation of India, Chennai, Tamil Nadu, India

[13]Department of Genetics, Fortis Hospital, Shalimar Bagh, New Delhi, India

[14]Department of Neonatology/Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama, United States of America

[15]Department of Pediatric Research, University of Oslo, Norway; Department of Neonatology, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, Illinois, United States

[16]Department of Newborn Care, Royal Hospital for Women, Randwick, NSW, Australia

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The epidemiology of DS is complex.[3] The incidence of DS is estimated to be somewhere between 1 in 1,000 and 1 in 1,200 live births worldwide.[4] Each year, approximately 3,000–5,000 infants are born with this chromosome disorder.[1] The risk increases with maternal age (1 in 1,250 for a 25-year-old mother, 1 in 1,000 at age 31, 1 in 400 at age 35, and about 1 in 100 at age 40).[5,6] However, 75–80% of babies with DS are born to women under age 35 years.[7]

There may be some temporal, racial/ethnic, and geographical variability in the prevalence of DS.[3,8] In the past 30 years, the incidence/prevalence of DS, both overall and age-standardized, have shown both temporal and regional variance.[9] The prevalence has increased for both sexes in nearly all social-demographic index regions; the highest age-standardized incidence was noted in Brunei Darussalam, Ireland, and Haiti.[8,9] Georgia showed the highest increase in age-standardized rate, whereas Serbia has shown a decline in these numbers. The mortality has decreased gradually over the last two decades.[9]

In biological terms, nearly 96% of all persons with DS have an extra copy of chromosome 21 (Fig. 1), which occurs due to the failure of these chromosomes to separate during gametogenesis.[10] This results in an extra chromosome in all the cells of the body. Understanding the genetic pathogenesis of DS has been challenging because there are >200 protein-coding genes on chromosome 21, which can directly and indirectly affect homeostasis in cells, tissues, organs, and systems.[11] Furthermore, genetic alterations other than a canonical chromosomal 21 trisomy have also been identified in 3–4% of infants with DS. Many of these infants may have a Robertsonian translocation (Fig. 2), an isochromosome, or a ring chromosome.[12] The Robertsonian, or the translocation DS, is an unbalanced anomaly where the infant has three copies of the long arm of chromosome 21 instead of two.[13] As known, chromosome 21 is an acrocentric chromosome where the centromere is not central and is located near the end of the chromosome.[14] An isochromosome is a structural abnormality in a chromosome that causes the arms to mirror each other; a chromosome has two copies of either the long arm or the short arm.[15] The ring chromosome 21 is a rare abnormality in which the ends of chromosome 21 join and form a ring.[13] Finally, 1–2% of infants with DS are the so-called "mosaics", where some, not all, cells show a chromosome 21 trisomy.[16]

Overall, the phenotypic features cannot be used to predict the exact type of the above-mentioned genotypic abnormalities seen in DS. Still, infants with a ring chromosome 21 may have fewer distinctive features associated with DS. Some of these individuals develop normally and may be diagnosed only when tested due to infertility, multiple miscarriages, or when they have a child with DS phenotype.[17] However, others can have developmental delay and/or medical problems due to their having extra or missing genetic material on the ring.[18] This subset may present with short stature, microcephaly, seizures, neurodevelopmental delay, immunodeficiency, and other birth defects. Some males may have

[17]Department of Neonatology/Pediatrics, Louisiana State University – Shreveport, Louisiana, United States of America

[18]Banaras Hindu University Institute of Eminence, Varanasi, India

All the authors are members of the Global Newborn Society (GNS)

Corresponding Author: Mario Motta, Department of Neonatology and Neonatal Intensive Care, AUSL di Bologna, Italy, Phone: +39 0516478563, e-mail: mario.motta@ausl.bologna.it

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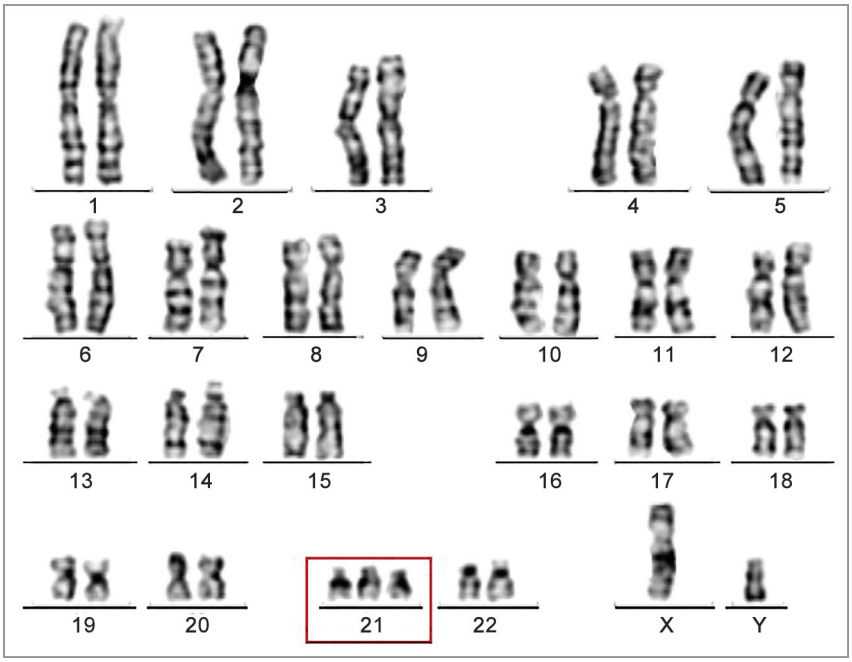
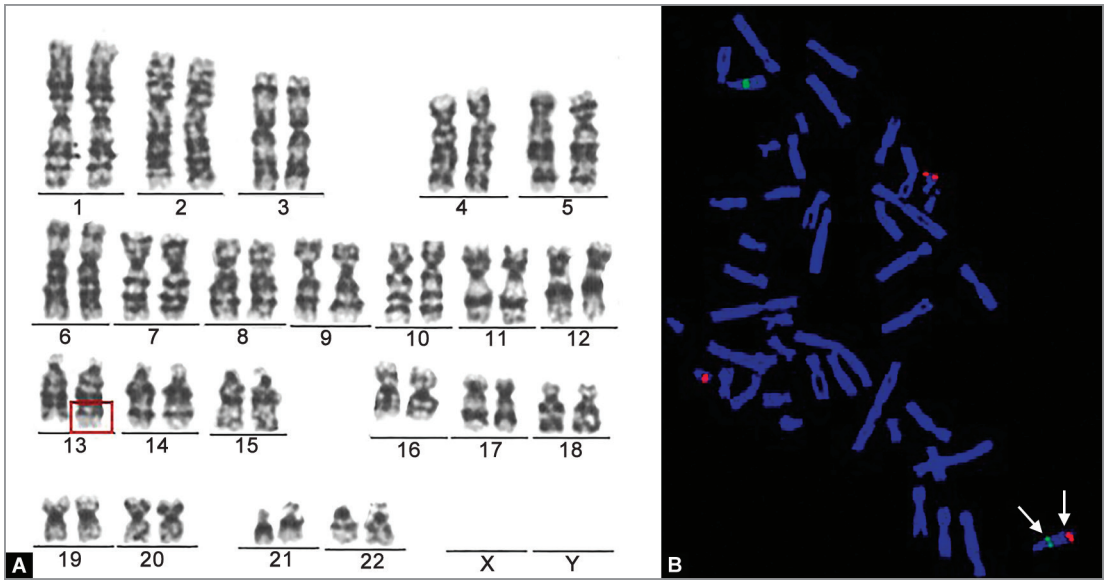


Fig. 1: Karyotyping on cells isolated from venous blood. GTG staining/banding; resolution 400×. The infant had trisomy 21 (as marked by the rectangle)



Figs 2A and B: (A) Karyotype: 46,_ _, add (13) (q133).ish der (13) [t(13;21) (q33;q21.3)] (D21S259+, D21S341+, D21S342+). There was a cryptic translocation between chromosomes 13 and 21, which was not easily detectable on cytogenetic analysis; (B) In the fluorescence *in situ* hybridization (FISH) image (right), the two chromosomes 13 showed a green-appearing signal for 13qter. Chromosomes 21 were identified by the orange-red signals. Interestingly, one of chromosome 13 (right lower corner) also showed a red-orange signal suggestive of a partial trisomy (translocation) of chromosome 21. These findings were identified in the karyotype (left; red rectangle). The other chromosome 13 did not show such a signal. This cryptic chromosome arrangement appears to be unbalanced with a partial trisomy 21 and partial monosomy 13. One of the parents was likely a carrier of this chromosome 13;21 translocation

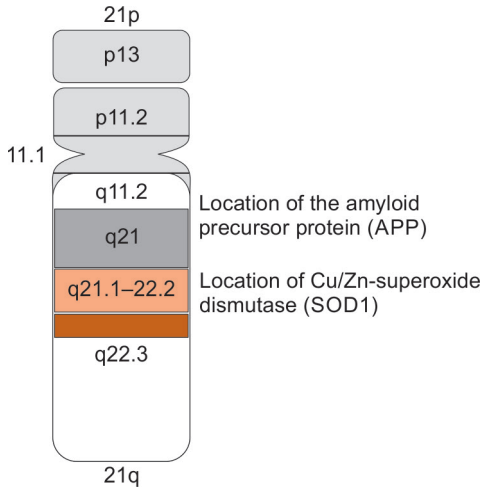


Fig. 3: Schematic diagram showing the major bands in chromosome 21

delayed puberty.[19,20] The ring chromosome 21 may be inherited from a parent, typically the mother, or it may occur sporadically.[19] Similarly, infants who are mosaics for DS may also have fewer clinical features that are typically seen in DS.[13]

The DS phenotype has been traditionally ascribed to the presence of an extra chromosome 21.[21] However, newer molecular and cytogenetic analyses suggest that many diagnostic features such as facial appearance, cardiac anomalies such as the endocardial cushion defect, neurodevelopmental delay, and dermatoglyphic changes could be rooted in a relatively small region of this chromosome. The gene for the Cu/Zn-superoxide dismutase (SOD1; Fig. 3) is located in 21q22.1, the amyloid precursor protein (APP) in 21q11.2-21.05, and six probes for single-copy sequences bind in a narrow, contiguous region: D21S46 in 21q11.2-21.05, D21S47 and SF57 in 21q22.1-22.3, and D21S39, D21S42, and D21S43 in 21q22.3.[22–25] All sequences located in 21q22.3 were present in three copies in the affected individuals, whereas those located proximal to this region were present in only two copies. Cytogenetic analysis with R and G banding of prometaphase preparations and *in situ* hybridization revealed a translocation of the region from very distal 21q22.1 to 21qter to chromosome 4q.[26] The deletion of chromosome band 4q35 is another important genotypic change. The variability in the DS phenotype may result from the variability of gene expression of transcription factors that are encoded both on chromosome 21 and also elsewhere in the genome, copy number polymorphisms, the function of conserved non-genic regions, microRNA activities, RNA editing, and perhaps DNA methylation.[27]

Healthcare providers need to understand the pathophysiology of DS in greater detail to meet the healthcare needs of these children.[28] If we can gain in our ability to understand, predict, detect, counsel, convince, track, mitigate, follow, and eventually ameliorate or correct even some of the DS-related morbidities, we could make a small change in this world.[29–31] For individuals with DS to achieve optimal quality of life, they definitely need parental and family care but can also use medical guidance and inclusive community-based support systems.[1,32] It's time we end the stereotypes–we all need to come together, bring information, and share our experiences.[31,33] Every baby counts-each time we lose an infant, we lose an entire life and its potential.[34] The World Down Syndrome Day 2024 was yet another reminder.[35] Let's work together.[36]

Here are some organizations that provide information and support for families with a child with DS:

- ACT Down Syndrome Association (Australia).
- Asociacion Guatemalteca para el Sindrome de Down (Guatemala).
- Asociacion Sindrome de Down de la Republica Argentina.
- Asociacion Sindrome de Down de Baleares (Spain).

- Association du Syndrome de Down de Down De L'estrie (Canada).
- Association Francaise pour la recherche sur la Trisomie 21 (France).
- Associazione Italiana Persone Down (Italy).
- Canadian Down Syndrome Society.
- Center for Disease Control and Prevention: Facts about Down Syndrome.
- Csupaszívek Társasága (Hungary).
- Down España (Spain).
- Downs forening en hovedstaden (Denmark).
- Down's Heart Group (UK).
- Down Syndrome Affiliates in Action.
- Down Syndrome Albania.
- Down Syndrome Australia.
- Down's Syndrome Association (Russia).
- Down Syndrome Association (Singapore).
- Down Syndrome Association of Minnesota.
- Down's Syndrome Association of Nepal.
- Down Syndrome Association of Nigeria.
- Down Syndrome Association of NT (Australia).
- Down Syndrome Association of Greece.
- Down Syndrome Association of Hamilton (Canada).
- Downs Syndrome Norge (Norway).
- Down Syndrome Association of Toronto (Canada).
- Down's Syndrome Association of Uganda.
- Down Syndrome Diagnosis Network.
- Down Syndrome Education International (UK).
- Down Syndrome International.
- Down Syndrome Foundation.
- Down Syndrome NSW (Australia).
- Down-Syndrome Netzwerk Deutschland e.V. (Germany).
- Down-Syndrome Österreich (Austria).
- Down Syndrome Resource Foundation.
- Down Syndrome Federation of India.
- Down Syndrome Ireland.
- Down Syndrome Queensland (Australia).
- Down Syndrome Research Foundation (Canada).
- Down Syndrome South Australia.
- Down Syndrome South Africa.
- Down Syndrome Tasmania (Australia).
- Downsyndroom Vlaanderen (Belgium).
- Down Syndrome Victoria (Australia).
- Down Syndrome WA (Australia).
- DSIJ (Japan).
- Edmonton Down Syndrome Society (Canada).
- Familias Extraordinarias (Mexico).
- FRUTOS (Ecuador).
- Fundação Síndrome de Down (Brazil).
- Fundacion Sindrome de Down del Caribe (Colombia).
- Fundacio Catalana Sindrome de Down (Spain).
- Fundación Iberoamericana Down 21 (Spain).
- Genetics Home Reference: Down Syndrome.
- Global Down Syndrome Foundation.
- German Down Syndrome InfoCenter (Germany).
- Gulf Kids (Saudia Arabia).
- Hong Kong Down Syndrome Association.
- Insieme 21 (Switzerland).
- International Down Syndrome Coalition.
- International Mosaic Down Syndrome Association.
- Jack's Basket.
- Japan Down Syndrome Society.
- Kids Health: Down Syndrome.
- La Asociacion Venezolana para el Sindrome de Down (Venezuela).
- Landsforeningen Downs Syndrome (Denmark).
- Laufclub Down-Syndrome Marathonstaffel e.V. (Germany).
- Libyan Down Syndrome Association.
- National Down Syndrome Congress.
- National Association for Down Syndrome.
- New Zealand Down Syndrome Association.
- Norsk Nettverk for Down Syndrome (Norway).
- National Down Syndrome Society.
- Sindrom Down Romania.
- Stowarzyszenie Rodzin i Opiekunów Osób (Poland).
- Türkiye Down Syndrome Association (Turkey).
- Ups and Downs Calgary Down Syndrome Association (Canada).
- UBE "Down Syndrome" (Ukraine).
- UAE Down Syndrome Association.

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