DS-Connect

A Promising Tool to Improve Lives and Engage Down Syndrome Communities Worldwide

Emmanuel K. Peprah*, Melissa A. Parisi†, Lisa Kaeser‡, Sujata Bardhan†, MaryLou Oster-Granite†, Yvonne T. Maddox§

Bethesda, MD, USA

Down syndrome (DS) is the most common genetic cause of intellectual and developmental disabilities in the United States with an estimated birth prevalence of 1:691 births; however, worldwide estimates of the number of individuals with intellectual and developmental disabilities, including DS, remain speculative. Little is known about the global health impact of DS, such as heart defects, gastrointestinal malformations, and other medical and behavioral issues. Further research is needed to develop the next generation of novel therapies and compounds aimed at improving cognition, reducing dementia, and mitigating other manifestations of DS. To address these challenges, the National Institutes of Health has created the first web-based, voluntary registry and data resource called DS-Connect: *The Down Syndrome Registry* to collect demographic and health information about individuals with DS.

Over the past several decades, families affected by both rare and common conditions have come to appreciate the value of systematic registries to document the natural history of the condition and to provide opportunities to participate in ongoing medical and social science research. Although Down syndrome (DS) is the most common genetic cause of intellectual and developmental disabilities (IDD) in the United States, worldwide estimates of the number of individuals with IDD such as DS remain speculative at best (Figure 1 [1–20]). Furthermore, little is known about the global impact of the other non-IDD manifestations of DS that are caused by having 3 copies of chromosome 21, such as heart defects, gastrointestinal malformations, and the other medical and behavioral issues.

In the last 40 years, substantial research has occurred to better elucidate the molecular underpinnings of DS and the resulting clinical consequences [21]. Specialized medical interventions (e.g., pediatric heart surgery and antibiotics) have improved early survival and longevity for many people with DS in the United States and Europe [8,22,23]. A wide spectrum of biomedical and educational research has led to the development of specialized medical and educational programs that have arguably had a profound and positive impact on the quality of life for people with DS and their families [24–26]. However, many challenges still remain. Adults with DS are hospitalized more often than the general population and for longer durations [27]. Approximately 50% of those with DS have some form of congenital heart disease, with atrioventricular septal defects constituting a significant proportion. Moreover, a high prevalence of celiac disease and autoimmune conditions was observed in older individuals. Also, those with DS in their 30s and 40s are known to be at significant risk for the early onset of Alzheimer disease, perhaps due to the triplicate copy of the beta-amyloid precursor protein on chromosome 21. These phenotypic presentations of DS are under intense investigation by researchers using various tools including animal models (e.g., trisomic mice) in hopes of developing novel therapies to ameliorate those impairments. However, mice are not equivalent to humans, and most testing paradigms do not capture the complexities of human cognition and behavior [28]. Moreover, many treatments effective in improving working memory in mice have not translated to humans [29], and relatively few cognition-enhancing pharmaceutical therapies have been tested in humans. The U.S. National Institutes of Health (NIH) have recognized the need to promote research that can benefit individuals with DS by informing the development of novel therapies and compounds to improve cognition, reduce dementia, and mitigate the other manifestations of DS.

DS-CONNECT: THE DOWN SYNDROME REGISTRY

To address these challenges, the NIH has created the first web-based, voluntary registry and data resource for DS called DS-Connect: *The Down Syndrome Registry* (http://DSConnect.nih.gov) to collect demographic and health information about individuals with DS. Since the launch of the registry in September 2013, >3,099 participants registered, mostly in the United States. All of the information in this secure registry is entered by an individual with DS or a family member after an online consent process and can be updated periodically. Notably, the deidentified, aggregate data can be viewed by registry

The authors report no relationships that could be construed as a conflict of interest.

From the *Center for Translation Research and Implementation Science, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA; †Intellectual and Developmental Disabilities Branch, Eunice Shriver Kennedy National Institute for Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA; ‡Office of Legislation and Public Policy, Eunice Shriver Kennedy National Institute for Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA; and the §National Institute on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD, USA. Correspondence: E. K. Peprah (peprahek@mail.nih.gov).

GLOBAL HEART
Published by Elsevier Ltd. on behalf of World Heart Federation (Geneva).
VOL. 10, NO. 4, 2015
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2015.04.001

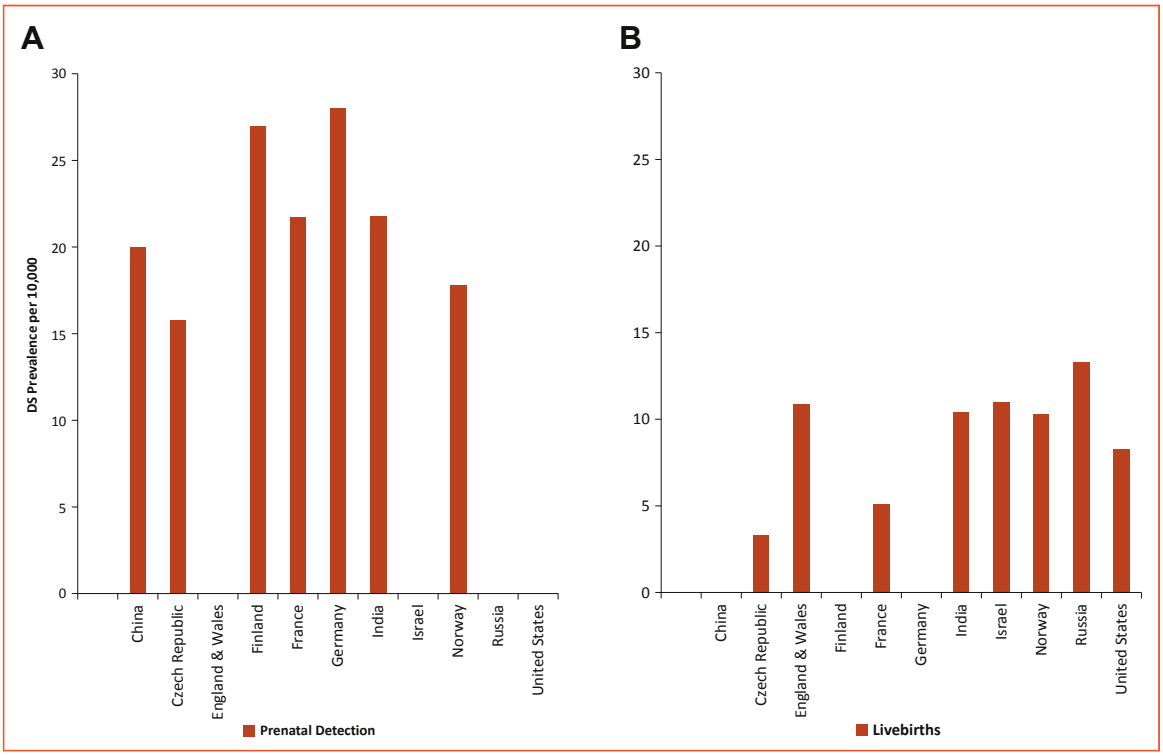

FIGURE 1. Estimated global prevalence of Down syndrome based on prenatal diagnosis/detection (A) and live births (B) per 10,000 in 11 countries. (A) Data were not available for England and Wales, Israel, Russia, and the United States. (B) Data were not available for China, Finland, and Germany. China: The overall incidence was 1 of 520 [2]. Czech Republic: The total incidence including prenatal diagnostics was 1.58 to 22.2, but the total incidence per 10,000 births reported was 3.3 to 6.5 [3]. England and Wales: In the United Kingdom, the prevalence was found to be 1 of 917 [4]. Finland: The prevalence was found to be 1 of 370 [5]. France: In France, numbers vary from an expected live birth prevalence of 1 of 460 to a termination-related decrease in live born prevalence to be 1 of 1,960 [6,7]; also the total prevalence of DS increased to 1 of 549 between 1993 and 2004, but the prevalence of DS births remained stable at 1 of 1,205 [8]. Germany: Among singleton pregnancies, the prevalence was 1 of 356 [9]. India: Reports show a prevalence during pregnancy to be 1 of 451; whereas in a maternity hospital in Kuala Lumpar, the incidence of live births was 1 of 959, and in a tertiary referral center, 1 of 800 [10—12]. Israel: Israel has a national program for the prevention of DS; however, a majority of DS infants, ~1 of 1,000, are born alive [13]. In 1997, the actual incidence rate was 1 of 909, whereas the true incidence rate was 23.2 [14]. Norway: One study involving paternal age found a weak estimated effect and an incidence of 1 of 971; another was 1 of 560; and a third study found a rate of 1 of 500 among 288,213 births and terminations during 2001 to 2005 [15-17]. Russia: Prevalence in Leningrad between 1982 and 1989 was 1 of 752 with a doubling of risk between ages 30 to 34 rather than 35 to 39. In Altai Republic, it was 1 of 1,075 [18,19]. United States: A current estimate of prevalence is 1 of 1,209 [20].

participants as well as registered professionals; the professional portal was launched in fall 2014 and is open to interested researchers, clinicians, advocates, and industry representatives. One feature of the registry is that a researcher will be able to apply for assistance in recruiting subjects with DS for clinical studies; once the investigator's study is approved, the registry coordinator will contact eligible families to inform them of the study and invite them to contact the researcher directly to participate in the research. This provides a targeted mechanism to recruit individuals with specific manifestations for clinical trials via DS-Connect while maintaining participant confidentiality, because scientists and researchers will never have direct access to the registrants. DS-Connect will also be an essential tool for obtaining self-reported medical information from individuals and families throughout the lifespan of affected individuals, which can create a better understanding of the natural history of DS and hence, enable the design of better therapeutic interventions and treatments tailored to different phases of development. The information in DS-Connect could also be used to comprehend disparities in health outcomes for those with DS both within the United States and internationally. Participation by a global cohort of individuals in DS-Connect could

facilitate longitudinal studies of many aspects of DS and enrich geographic and racial/ethnicity data, while promoting clinical research that will improve the health and quality of life for individuals with DS.

In addition, the NIH is addressing ongoing challenges in DS research by engaging in continued dialogue with the broader DS community. The NIH published the first national research agenda for DS, the NIH Research Plan on Down Syndrome, in 2007, after inviting comments from researchers, clinicians, advocates, and families across the United States [30]. In 2011, the NIH brought together national and international DS organizations in the creation of a public-private partnership, aptly named the Down Syndrome Consortium, with the goal of advancing DS research. Consortium members and other interested parties provided rich commentary on the NIH Research Plan on Down Syndrome, which led to an updated research agenda. This current plan addresses needs articulated by the DS research community in 5 major areas: pathophysiology of Down syndrome and disease progression; screening, diagnosis, and functional measures of Down syndrome-related conditions; treatment and management; Down syndrome and aging; and research infrastructure. This updated plan outlines priority areas and can be used as a roadmap to support promising DS research in the future [31].

CONCLUSIONS

By tapping into the collective voice of individuals and families using DS-Connect, the global DS community, researchers and caregivers will improve our understanding of this condition throughout the lifespan of affected individuals and enhance research participation globally. Along with a clear research agenda as articulated in the 2014 NIH Research Plan on Down Syndrome [31], NIH is working to create the tools and resources to support a global research effort to improve the quality of life for those with DS; furthermore, the success with this approach could galvanize research across all IDD and other rare genetic diseases, and thus help improve the lives of a broad range of affected individuals worldwide.

ACKNOWLEDGMENT

The authors would like to thank Vesna Kutlesic for providing significant discussions in regard to shaping the manuscript.

REFERENCES

1. World Health Organization. World Bank. World Report on Disability. Geneva: World Health Organization; 2011.
2. Miao ZY, Liu X, Shi TK, Xu Y, Song QH, Tang SH. First trimester, second trimester, and integrated screening for Down's syndrome in China. J Med Screen 2012;19:68–71.
3. Sipek A Jr, Gregor V, Sipek A, Horacek J, Langhammer P. Recent results of prenatal diagnosis in the Czech Republic. Paper presented at: EUROCAT Registry Leaders Meeting; Budapest: 2012.
4. Irving CA, Chaudhari MP. Cardiovascular abnormalities in Down's syndrome: spectrum, management and survival over 22 years. Arch Dis Child 2012;97:326–30.
5. Marttala J, Yliniemi O, Gissler M, Nieminen P, Ryynanen M. Prevalence of Down's syndrome in a pregnant population in Finland. Acta Obstet Gynecol Scand 2010;89:715–7.
6. Rousseau T, Ferdynus C, Thauvin-Robinet C, Gouyon JB, Sagot P. Impact of maternal age distribution on the expected live birth prevalence of Down's syndrome in the metropolitan France between 1965 and 2008 [in French]. J Gynecol Obstet Biol Reprod (Paris) 2010;39:284–9.
7. Rousseau T, Amar E, Ferdynus C, Thauvin-Robinet C, Gouyon JB, Sagot P. Variations in the prevalence of Down's syndrome in the French population between 1978 and 2005 [in French]. J Gynecol Obstet Biol Reprod (Paris) 2010;39:290–6.
8. Cocchi G, Gualdi S, Bower C, et al. International trends of Down syndrome 1993—2004: births in relation to maternal age and terminations of pregnancies. Birth Defects Res A Clin Mol Teratol 2010; 88:474–9.
9. Luthgens K, Abele H, Alkier R, Hoopmann M, Kagan KO. Cross-validation of the first trimester screening algorithm of the FMF London on 38,700 pregnancies in Germany [in German]. Ultraschall Med 2011;32:367–72.
10. Kaur G, Srivastav J, Kaur A, et al. Maternal serum second trimester screening for chromosomal disorders and neural tube defects in a government hospital of North India. Prenat Diagn 2012;32:1192–6.
11. Hoe TS, Boo NY, Clyde MM. Incidence of Down's syndrome in a large Malaysian maternity hospital over an 18 month period. Singapore Med J 1989;30:246–8.
12. Noraihan MN, See MH, Raja R, Baskaran TP, Symonds EM. Audit of birth defects in 34,109 deliveries in a tertiary referral center. Med J Malaysia 2005;60:460–8.
13. Zlotogora JL, Haklai Z, Leventhal A. Utilization of prenatal diagnosis and termination of pregnancies for the prevention of Down syndrome in Israel. Isr Med Assoc J 2007;9:600–2.
14. Merrick J. Incidence and mortality of Down syndrome. Isr Med Assoc J 2000;2:25–6.
15. Kazaura MR, Lie RT. Down's syndrome and paternal age in Norway. Paediatr Perinat Epidemiol 2002;16:314–9.
16. Offerdal K, Blaas HG, Eik-Nes SH. Prenatal detection of trisomy 21 by second-trimester ultrasound examination and maternal age in a nonselected population of 49 314 births in Norway. Ultrasound Obstet Gynecol 2008;32:493–500.
17. Melve KK, Lie RT, Skjaerven R, et al. Registration of Down syndrome in the Medical Birth Registry of Norway: validity and time trends. Acta Obstet Gynecol Scand 2008;87:824–30.
18. Kovaleva NV, Butomo IV, Verlinskaia DK, Il'iashenko TN, Davidenkova EF. Increase in the incidence and risk of birth of children with Down's syndrome in Leningrad (1982—1989). Genetika 1994;30: 265–70 [in Russian].
19. Krikunova NI, Minaicheva LI, Nazarenko LP, et al. Epidemiology of congenital malformations in Gorno-Altaisk, Altai Republic, Russia. Genetika 2004;40:1138–44.
20. Presson AP, Partyka G, Jensen KM, et al. Current estimate of Down Syndrome population prevalence in the United States. J Pediatr 2013; 163:1163–8.
21. Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. Ment Retard Dev Disabil Res Rev 2007;13:221–7.
22. Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet 2002;359:1019–25.
23. Englund A, Jonsson B, Zander CS, Gustafsson J, Anneren G. Changes in mortality and causes of death in the Swedish Down syndrome population. Am J Med Genet A 2013;161A:642–9.
24. American Academy of Pediatrics Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics 1994;93:855–9.
25. Bull MJ. Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics 2011;128:393–6.
26. Esbensen AJ. Health conditions associated with aging and end of life of adults with Down syndrome. Int Rev Res Ment Retard 2010;39: 107–26.

27. Tenenbaum A, Chavkin M, Wexler ID, Korem M, Merrick J. Morbidity and hospitalization of adults with Down syndrome. Res Dev Disabil 2012;33:435–41.
28. Underwood E. Can Down syndrome be treated? Science 2014;343: 964–7.
29. Costa AC, Scott-McKean JJ. Prospects for improving brain function in individuals with Down syndrome. CNS Drugs 2013;27: 679–702.
30. National Institutes of Health. National Institutes of Health Research Plan on Down Syndrome. October 2007. Available at: https://www.nichd.nih.gov/publications/pubs/documents/dsresearchplan_2007.pdf. Accessed December 1, 2014.
31. National Institutes of Health. Down Syndrome Directions: The National Institutes of Health Research Plan on Down Syndrome. Available at: http://www.nichd.nih.gov/publications/pubs/documents/dsresearchplan_2014.pdf; 2014. Accessed December 1, 2014.