Genet. Res., Camb. (2014), vol. 96, e009. © Cambridge University Press 2014
doi:10.1017/S0016672314000111

Organization for rare diseases India (ORDI) – addressing the challenges and opportunities for the Indian rare diseases' community

HARSHA KARUR RAJASIMHA[1]*, PRASANNAKUMAR BASAYYA SHIROL[1], PREVEEN RAMAMOORTHY[1], MADHURI HEGDE[1], SANGEETA BARDE[1], VIJAY CHANDRU[1], M. E. RAVINANDAN[1], RAMANI RAMCHANDRAN[2], KASTURI HALDAR[3], JIMMY C. LIN[4], IMRAN A. BABAR[4], KATTA M. GIRISHA[5], SUDHA SRINIVASAN[6], DURAISWAMY NAVANEETHAM[7], RAJANI BATTU[8], RAJASHREE DEVARAKONDA[9], USHA KINI[10], KINNIMULKI VIJAYACHANDRA[11] AND ISHWAR C. VERMA[12]

[1]*Organization for Rare Diseases India, No 10, 4th Main Road, # 2 (Ground Floor), Jaladarshini Layout, Bangalore – 560054 India*
[2]*Developmental Vascular Biology Program and Zebrafish Drug Screening Core, The Medical College of Wisconsin, 8915 W. Connell Ave, Milwaukee, WI 53226, USA*
[3]*Center for Rare and Neglected Diseases, University of Notre Dame, Notre Dame, IN 46556, USA*
[4]*Rare Genomics Institute, 4100 Forest Park Ave, Suite 204, St. Louis, MO, 63108, USA*
[5]*Department of Medical Genetics, Kasturba Medical College, Manipal University, Manipal, India*
[6]*Centre for Human Genetics, Biotech Park, Electronics City (Phase I), Bangalore 560 100, India*
[7]*Foundation for Research on Rare Diseases and Disorders, C252, Kandasamy Salai, Periyar Nagar, Chennai 600082, India*
[8]*Narayana Nethralaya, #121/C, Chord Road, 1st 'R' Block, Rajajinagar, Bangalore – 560 010, India*
[9]*Voisin Consulting Private Limited, #1, Hara House, 2nd Floor, Gutte Anjaneya Temple Road, Hosur Main Road, Wilson Garden, Bangalore – 560027, India*
[10]*Department of Pathology, St. John's Medical College and Hospital, Bangalore – 560034 India*
[11]*Ixora Biosciences Pvt Ltd, Institute of Bioinformatics and Applied Biotechnology, Biotech Park, Electronic City Phase-1, Bangalore – 560100, India*
[12]*Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi – 110060 India*

(*Received 19 June 2014; accepted 25 June 2014*)

Summary

In order to address the unmet needs and create opportunities that benefit patients with rare disease in India, a group of volunteers created a not-for-profit organization named Organization for Rare Diseases India (ORDI; www.ordindia.org). ORDI plans to represent the collective voice and advocate the needs of patients with rare diseases and other stakeholders in India. The ORDI team members come from diverse backgrounds such as genetics, molecular diagnostics, drug development, bioinformatics, communications, information technology, patient advocacy and public service. ORDI builds on the lessons learned from numerous similar organizations in the USA, European Union and disease-specific rare disease foundations in India. In this review, we provide a background on the landscape of rare diseases and the organizations that are active in this area globally and in India. We discuss the unique challenges in tackling rare diseases in India, and highlight the unmet needs of the key stakeholders of rare diseases. Finally, we define the vision, mission, goals and objectives of ORDI, identify the key developments in the health care context in India and welcome community feedback and comments on our approach.

Introduction to rare diseases

By definition, a rare disease occurs infrequently in a population, but there is no universal definition. There are three elements to the definition as used in various countries – the total number of persons having the disease, its prevalence and non-availability of treatment for the disorder. This definition was introduced to identify disorders that are neglected by health professionals. A formal definition helps a nation to identify diseases that require financial incentives for discovery and development of drugs and biologics, so as to encourage product development as well as funding for basic and clinical research on those diseases. Many countries define 'rare' or 'orphan' diseases as those affecting less than a specific number of persons in the populations. For example, in the USA, it is defined strictly according to its prevalence, specifically

* Corresponding author: E-mail: harsha@ordindia.org

'any disease or condition that affects less than 200,000 persons' (Shire Human Genetic Technologies, 2013). In Japan, the number is 50,000 persons, in Korea 20,000, in Taiwan 10,000, and in Australia 2000 (Lavandeira, 2002; Tang, 2013). The World Health Organization (WHO) has suggested that a rare disease should be defined as one with a frequency of less than 6·5–10 per 10,000 persons (Song, 2012), although, some experts feel this is rather high (Aronson, 2006). Stated as the prevalence per 10,000, the number used in the USA is 7·5, in Europe 5, in Japan 4, in South Korea 4, Australia 1·1 and Taiwan 1·0 (Song, 2012). In China, a rare disorder is defined as one that affects less than 1/500,000 persons, or one that has a neonatal morbidity of less than 1/10,000 (Song, 2012; Ma *et al.*, 2011). Thus, a country should define a rare disease in the context of its own population, health care system and resources. India, like many developing countries, currently has no standard definition. Considering the large population of India, we suggest the threshold for a disease to be defined as rare to be 1 in 5000. This would include diseases that have a higher prevalence, but do not have definitive therapy. Although this definition may suggest that the number of affected patients is small, it is important to note that when taken together, the number of patients living with a rare disease in India is over 70 million (Verma, 2000). By contrast, about 30 million Americans (Shire Human Genetic Technologies, 2013), and about 29 million persons in the EU are affected with rare disorders (Nogales, 2004).

The exact number of rare diseases is not known, but is estimated to be around 7000–8000 worldwide (Global Genes. RARE Facts and Statistics). With the rapid advances in genomic technologies in the last decade, the number is increasing steadily each year with new diseases and associated genes being discovered. About 80% of rare diseases are genetic in origin, many of which are thought to be monogenic (Global Genes. RARE Facts and Statistics). Rare diseases also include rare inherited cancers, autoimmune diseases, congenital malformations and infectious diseases amongst others. All rare diseases taken together affect about 6–8% of the world's population. About half of the rare diseases affect children causing significant social and economic burden, while the other half manifest in adulthood. Some examples of rare diseases include hemangiomas (Haggstrom, 2006), Hirschsprung disease (Butler Tjaden & Trainor, 2013), Gaucher disease (Rosenbloom & Weinreb, 2013), cystic fibrosis (Ehre, 2014), muscular dystrophies (Mercuri & Muntoni, 2013) and Pompe disease (Ausems *et al.*, 1999).

Treatments for rare diseases

According to a *Thomson Reuters* report (http://thomsonreuters.com/business-unit/science/subsector/pdf/the-economic-power-of-orphan-drugs.pdf), the global market for 'orphan drugs' (drugs that are meant to treat rare medical conditions) accounted for more than $50 billion in 2011. A majority of these diseases lack proper treatment options. A key challenge associated with rare diseases globally is the inability of the medical system to properly diagnose these diseases in a timely manner, leading to a delay in therapy. Early diagnosis is essential for proper disease management. The newborn screening program in the USA covers about 31 metabolic disorders, which, when detected in the neonatal period, can be treated to prevent disability. An example of this is phenylketonuria (PKU), which can be managed nutritionally to save the child from the devastating effects of PKU. Recently, a drug called 'Kuvan' was launched for the BH4 responsive version of PKU (BIOMARIN Pharmaceuticals; http://www.bmrn.com), which precludes the need for expensive dietary therapy. The average time to diagnose most rare diseases in the USA is about 7 years (Shire Human Genetic Technologies, 2013), causing significant anxiety and financial hardship to the families let alone increasing the morbidity in patients. In developing countries, the time to diagnosis is even longer. Even after proper diagnosis, there is little hope for cure. Only around 400 FDA approved 'orphan drugs' are available on the US market, and ~100 drugs approved by the European Medicines Agency (EMA) are available in the EU (Orphanet, 1997). Together, these approved drugs cover only about 11 million patients suffering from rare diseases leaving a majority of patients with no treatment options. Even where treatment is available, the cost is often prohibitive due to high development costs, fewer patients and lack of competition (Nogales, 2004). This is true for the enzyme replacement therapies (ERT) that have been approved for mucopolysaccharidosis types I, II, IV-A and VI, Gaucher disease, Fabry disease and others. The prohibitive costs limit their use to very few patients in India and other low resource countries. Charitable programs started for lysosomal storage disorders by companies like Genzyme, and on a smaller scale by Shire Human Genetic Technologies, are praiseworthy, and provide hope to some patients. These programs have also helped raise awareness among physicians, and stimulated them to make early and precise diagnosis. In India, enzyme therapies are provided either by the Pharma companies under their charitable programs, or by employers in India who are committed to giving 'free' health care to their employees and their dependents. A few associations of families of patients with rare disorders are also trying to persuade the government to cover the cost of therapies. Among the success stories in India is the case of providing Factor VIII to patients with hemophilia A and chelating agents to patients with thalassemia major. In an interesting development a plea was filed in the

Delhi High Court by the father of a 7 year old child suffering from Gaucher disease after being denied treatment by the All India Institute of Medical Sciences (AIIMS), New Delhi, for want of funds. He had lost four children with Gaucher disease. Justice Manmohan, remarking that 'health is not a luxury', and 'should not be the sole possession of a privileged few', asked the Delhi government to discharge its constitutional obligation and provide the child with ERT at AIIMS, free of cost, when required (Provide free treatment to Gaucher disease patient: High Court. News story at: http://www.newkerala.com/news/2014/fullnews-40628.html#.U22oX2xZrVI).

Global organizations devoted to rare diseases

Numerous organizations across the globe are tackling the challenge of rare diseases head on. The names of some such organizations, with URL addresses, are given below in alphabetical order:

- CORD: Canadian Organization for Rare Disorders (http://www.raredisorders.ca)
- EURORDIS: European Organization of Rare Diseases (http://EURORDIS.org)
- GARD: Genetic and Rare Diseases Information Center (https://rarediseases.info.nih.gov/GARD/)
- HMDSN: Hirschsprung's and Motility Disorders Support Network (http://www.hirschsprungs.info)
- INOD: In Need Of Diagnosis (http://www.inod.org)
- IRDiRC: International Rare Disease Research Consortium (www.irdirc.org)
- Jain Foundation (http://www.jain-foundation.org/)
- Madisons Foundation (http://www.madisonsfoundation.org/)
- NORD: National Organization for Rare Disorders (http://rarediseases.org)
- ORDR: Office of Rare Diseases Research (http://rarediseases.info.nih.gov)
- Orphanet (http://www.orpha.net)
- RARE – Rare disease, Advocacy, Research, Education (http://globalgenes.org/leadership)
- Rare Genomics Institute (RGI, USA) (http://raregenomics.org)
- Rare Health Exchange (http://rarehealthexchange.org)
- SWAN: Syndromes Without a Name (http://www.undiagnosed-usa.org)
- Vascular Birthmarks Foundation (http://birthmark.org)

ORDI will extend the work of these existing organizations in rare diseases, and collaborate at the international level, to advance the common objective of finding solutions to the problems of rare diseases and advocate for these patients. ORDI has partnered with RGI USA to institute a process for recruiting patients and their families with undiagnosed diseases (suspected to be familial) into exome-sequencing programs to identify potential causal mutations. ORDI is in discussion with other prominent international organizations to explore opportunities for collaboration and is already mutually cross-referenced with several of them.

Indian organizations devoted to rare diseases

Verma reviewed the burden of rare genetic diseases in India in 2000 and subsequently in 2002 and 2004 (Verma & Bijarnia, 2002; Verma, 2000, 2004). Although there has been improvement in the ability to reduce this burden over the years, still the services are inadequate and much remains to be done. Some of the organizations and resources for patients with rare diseases in India are listed below:

- ARDSI – Alzheimers and Related Disorders Society Of India (http://www.alzheimer.org.in)
- Birth Defects Registry of India (http://www.fcrf.org.in/bdri_abus.asp)
- Down Syndrome Federation India (http://downsyndrome.in/)
- Fragile X Society – India (www.fragilex.org)
- Genetic Alliance (http://www.geneticalliance.org)
- Hemophilia Federation (http://www.hemophilia.in/)
- Indian RETT Syndrome Foundation (www.rettsyndrome.in)
- Indian Association of Muscular Dystrophy (www.iamd.in)
- Indian Prader-Willi Syndrome Association (http://pwsindia.hpage.com)
- IPSPI – Indian Patients Society for Primary Immunodeficiency (www.ipspiindia.org)
- LSDSS – Lysosomal Storage Disorders Support Society (www.lsdss.org)
- MERD – Metabolic Errors and Rare Diseases (http://merdindia.com)
- Muscular Dystrophy Association India (http://mdindia.org/)
- Muscular Dystrophy Foundation India (http://www.mdfindia.org)
- Muskaan (intellectually disabled) (http://muskaan-delhi.com/)
- National Thalassemia Welfare Society (http://www.thalassemiaindia.org/)
- Pompe Foundation (http://pompeindia.org/)
- Rare Diseases India (http://www.rarediseasesindia.org)
- Retina India (http://www.retinaindia.org)
- Sjogren's India (http://www.sjogrensindia.org)
- Thalassemics India (www.thalassemicsindia.org)

These organizations render yeomen services to the patient community. Internationally, umbrella organizations such as NORD, EuroRDIS, Genetic Alliance and Global Genes RARE have played key roles in

engaging with stakeholders primarily in the USA and Europe. In India, an organization that can unite all rare disease stakeholders under a single umbrella, and speak in a single voice for them does not exist. The lack of such an umbrella organization has reduced the effectiveness of the above mentioned organizations as much of their resources are directed towards common causes such as raising general public awareness about rare diseases. As a result, progress in assisting patients with rare diseases is slow, leaving many patients hapless. The need for an umbrella organization that can provide a common framework for these disease-specific organizations to function effectively and to focus on their mission is clear. Such an organization could provide generic patient registries compliant with regulatory requirements in India, develop and maintain a comprehensive information portal about rare diseases, create and maintain a sample biorepository for use by Indian rare disease researchers in approved translational research studies, interface with international resources, broadcast best practices, raise public awareness about rare diseases, host national and international conferences and other events to engage key stakeholders, and create an ecosystem of incentives to accelerate research, development and delivery of affordable diagnostics and treatment options for patients with rare diseases. Bringing the various associations under one organization will give it greater leeway to lobby with the government, international agencies and philanthropists for help and support. It is ORDI's objective to fill these gaps. It must be stated that getting these different organizations in India to work under one umbrella organization would not be an easy task. In this context, the response from Indian organizations, since the launch of ORDI on 18 February 2014 in Delhi, has been most encouraging. The ORDI's nationwide rare disease telephone helpline receives on average, 3–4 enquiries every day. A total of 13 Indian organizations have already joined, as they are convinced that joint effort will be more rewarding than their individual efforts.

History of rare diseases in India

Extensive haplotyping studies have predicted that most present day Indian populations are descendants of ancestors who migrated out of Africa to the Indian continent about 65,000 years ago (Tamang *et al.*, 2012) Evidence suggests that today's Indian population is an admixture of two genetically divergent ancient populations, referred to as the Ancestral North Indians (ANI), who are genetically close to Middle East, Central Asian and European populations, and the Ancestral South Indians (ASI), who are less so (Reich *et al.*, 2009). This study estimated that ANI ancestry ranges from 39–71% among the various current Indian populations, with pure ASI groups represented by the indigenous Andaman Islanders (Reich *et al.*, 2009). Consanguineous marriages take place preferentially in many communities, while in other ethnic groups, endogamous marriages have occurred over long period of time. As a result, the frequencies of founder and common mutations are likely to be relatively higher in the Indian subpopulations. Rough estimates show that more than 56 million individuals in India are likely to be affected by single gene disorders (monogenic disorders) (Global Genes. RARE Facts and Statistics). With the lack of awareness in the general population about genetic disorders, and scarcity of specialized medical professionals and affordable genetic tests, the burden from these disorders is growing rapidly. This is, in part, due to the absence of a properly functioning social health care system in India, where the health professionals, including doctors and nurses, are not given enough exposure to medical genetics, molecular biology and rare disorders in their curriculum. There is also insufficient encouragement by the government for individual health insurance. Consequently, most of the population, especially in rural areas, does not opt for prenatal testing, predictive genetic diagnosis or timely genetic counseling with some families having more than one affected individual. The WHO has stressed the need for prevention, early diagnosis and management of genetic disorders in developing countries, and has issued detailed guidelines (http://www.doh.gov.za/docs/policy/humangenetics.pdf).

Over a decade since the completion of the Human Genome Project, awareness about genetic disorders among physicians as well as the general population of India is still lacking. As a result, early and affordable diagnostic tests, even where available, are not widely prescribed. To remedy this, a few accredited and reputed educational institutions, hospitals and laboratories across the country have initiated genetic diagnostic services covering selected disorders. A directory of accredited genetic testing service centers in India compiled in 2007 (Singh *et al.*, 2010) showed that there were 47 such centers offering genetic services, including cytogenetic (40 centers), biochemical (26 centers) and molecular diagnosis (26 centers), along with genetic counseling. A current directory of genetic centers and services is now available online http://www.geneticsindia.org. This is supported by the Indian Council of Medical Research (ICMR). It has listed 649 disorders, 66 genetic centers and 35 prenatal diagnostic centers. Another ten genetic counseling centers are known to the authors that are not yet listed on the website. It has also started listing the parent support groups for various diseases in India. The number and distribution of these centers are abysmally small to serve the massive Indian rare disease community. Many of the centers need to upgrade

capabilities to include recent advances such as next-generation sequencing (NGS)-based molecular diagnosis of rare diseases. Most of the genetic centers offer targeted tests that involve screening for common mutations, although in recent years, many centers provide sequencing of entire disease-associated genes. A number of private companies have set up NGS technologies, harnessing the excellent bioinformatics resources available in India. They are providing molecular diagnosis based on NGS of disease gene panels at a fraction of the cost of these tests abroad, making them affordable to the Indian population. However, some samples are still sent abroad for genetic testing. International laboratories (Quest, Centogene, BGI China and Core Diagnostics) have also set up offices in India. Some Indian national laboratories such as SRL Labs and Lal Path Labs also offer advanced medical and genetic tests. Therefore, an extensive network of collection centers has spread all over India. This enables every person, even in small remote towns, to provide samples for advanced genetic and biochemical tests. This has tremendously improved the diagnostic abilities for genetic tests in the country.

Education and genetic counseling (GC) are critical necessities to help patients and physicians deal with rare diseases. GC is needed at various levels such as prior to genetic testing, post-testing, prenatal diagnosis and family planning particularly in consanguineous marriages. GC needs to be made an integral part of all genetic testing centers in India. This has been realized by the private genetic laboratories and they have appointed genetic counselors on their staff. There are at least three institutions offering courses in GC for non-medical personnel. There is a move by one of the authors of this paper to initiate a GC course under the Indira Gandhi Open University. ORDI will provide expertise for this venture by enlisting experts from the USA to assist the faculty in India. This will, to some extent, fill the gap of qualified genetic counselors in India.

The burden of providing care for an individual affected by rare disease is not easy to meet in India due to lack of infrastructure. Therefore, determining carrier status for genetic diseases can help individuals make decisions about prenatal testing when both partners are carriers of a particular disease. In urban areas at least, most obstetricians screen for common infections and thalassemia. After that, the family history guides the screening strategy. Carrier testing for genetic diseases using NGS of a panel of genes is being offered by one company now, while others are in the process of validating such tests. A number of institutions, both in the public and private domains, provide GC to patients.

The National Board of Examinations, with support from the Department of Biotechnology, Government of India, is due to start a national postgraduate course in Medical Genetics and Genomics. The Medical Council of India (MCI) has expanded the curriculum for medical students to include genetics and molecular biology (Vision Document 2015: http://www.mciindia.org/tools/announcement/MCI_booklet.pdf). What is still woefully inadequate is the number of medical genetics departments in the country. To meet the shortage of medical doctors and to ensure that rural populations are better served, the Ministry of Health and Family Welfare, Government of India, pushed for a 3 year B. Sc. course in Community Medicine to be imparted to doctors in Ayurveda and other indigenous systems of medicine. The course has been approved by the MCI (Sinha, 2012). The number of seats in medical courses, at both the graduate as well as the postgraduate level has increased by 1·5 to 2 times in a short time span. Kapoor *et al.* (2013) reviewed the challenges and opportunities for newborn screening (NBS) in India and recommended widespread implementation of the NBS program across the country starting with the metro cities. At least six private laboratories offer newborn screening through tandem mass spectrometry and gas chromatography mass spectrometry at a nominal fee. Many private hospitals have instituted NBS programs. Some states like Gujarat, Chandigarh, Delhi, Maharashtra, Kerala, Goa and Tamil Nadu, have started pilot NBS programs, and it is expected that these will be further extended to cover larger populations in the near future.

India-specific challenges in the management of rare diseases

India faces numerous challenges in awareness, public perceptions, diagnosis, treatment and public policy on rare diseases. Some of the most significant ones are listed below.

Lack of awareness

There is significant lack of awareness about rare diseases among the lay public, and unfortunately even among physicians in India. The health care training and education system in India are more focused on training physicians and health care personnel to treat common diseases such as infectious diseases, diabetes mellitus, cardiovascular disease and common cancers. This has led to a pronounced dearth of trained physicians and health care personnel to care for patients with rare diseases.

Lack of infrastructure

Inadequate training and facilities to properly diagnose rare diseases in a timely manner is another disadvantage. If it takes an average of 7 years to diagnose a rare disease in developed nations like the USA (Shire Human Genetic Technologies, 2013) the average time

to diagnose is likely to be greater in developing countries (Christianson & Modell, 2004). It is unclear as to the average time that it may take to diagnose a rare disease in India. There is lack of adequate statistics and data on incidence as well as prevalence of rare diseases in India. A systematic catalogue of the different rare diseases in India does not exist. The availability of such basic information is essential for use by policy makers, physicians, scientists, drug or device manufacturers, patients and the community at large.

Prohibitive costs

A majority of patients with rare diseases in India cannot afford the high costs of treatments even when available. Most orphan drugs are not curative but palliative, and need to be administered regularly. These drugs are highly expensive and inaccessible to the majority of the Indian population affected by rare diseases.

Cultural influences

The incidence of rare diseases is believed to be higher in India compared to western countries due to practice of consanguineous marriages in many communities. Social stigmas for disabled individuals and patients with rare diseases continue to be a societal challenge that can only be addressed with education and awareness.

Government initiatives

There seems to be no official policy on rare diseases in India. There is no specific push for research and development in the field of rare diseases in India, although the programs by funding agencies like the ICMR, Department of Science and Technology (DST), Council of Scientific and Industrial Research (CSIR) as well as the Department of Biotechnology (DBT) are noteworthy. The Government should encourage and fund Indian academic research laboratories as well as pharmaceutical and biotechnology industries to take up scientific research work leading to the development of diagnostics and drugs for rare diseases. ORDI would persuade and assist the government to (i) enact an act similar to the Orphan Drugs Act (ODA) of USA, and (ii) create a fund to support work related to rare disease research, education and treatment by institutions that are prepared to take up this work. The Government has already started funding such work in a small way but we believe that a lot more needs to be done. A national plan for rare disease research needs to be developed.

Funding

The lack of significant public funding for rare disease research is another critical impediment in creating the much needed momentum for education, diagnosis and treatment of rare diseases in India.

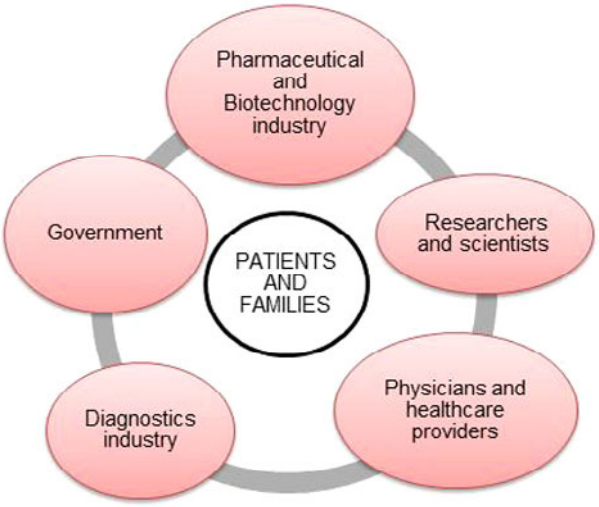

Fig. 1. Key stakeholders of rare diseases in India.

The rare disease stakeholders in India

Fig. 1 depicts the key stakeholders of rare diseases in India. The patients and their families are the most important stakeholders as they experience the disease first hand. The other important stakeholders such as physicians, health care providers, researchers, diagnostic laboratories, biotechnology and pharmaceutical companies, government, regulatory bodies, non-profit patient organizations and health insurance companies have a significant impact on the rare disease patients and their families.

Patients and families

Patients with rare diseases and their families need quick and easy access to information about affordable diagnosis and treatment options. A single portal for such information would serve the purpose and is urgently needed. The ORDI has already provided such a portal and receives many enquiries every day. The existing parent support groups also play an important role in providing such information, and in providing a forum for parents of children with specific diseases to exchange experiences.

Physicians and health care providers

Indian doctors need access to more clinical training, research and education on rare diseases. In addition, they need access to state-of-the-art diagnostic tests, information on clinical trials and currently available drugs for rare diseases in India. ORDI could help organize workshops to meet this need. The ratio of doctors to patients in India continues to be

significantly lower compared to those in developed countries and compared to the ratio recommended by WHO. Training in medical genetics needs to be scaled up urgently across the country.

Scientists and researchers

Indian scientists need access to rare disease patient registries and biorepositories to advance science and understanding of these diseases in order to translate research findings into diagnostic tests and therapeutics. Biorepositories that house patient samples and associated clinical, genomic, transcriptomic, proteomic and metabolomic data will be the main catalysts of therapeutic and diagnostic solutions for rare diseases. Defective genetic pathways contribute to a great extent to the pathogenesis of rare diseases (Global Genes. RARE Facts and Statistics). Molecular diagnostic technologies such as NGS offer great opportunities to sequence the genome or targeted regions of a patient's DNA at an affordable cost to identify mutations that may be associated with a disease. There is a need and immediate opportunity to accelerate the identification of as yet unknown critical genes involved in rare diseases. To establish a strong association between a mutation and disease, a large number of patient samples are often required. Dalal *et al.* (2012) report on an Indian cohort study involving 35 progressive pseudorheumatoid dysplasia patients harboring mutations in the *WISP3* gene. Such studies will clearly benefit the populations in the Indian subcontinent. Inherited disease-causing mutations could be detected by comparing DNA sequencing data from the trio (patient and parents). Being able to access patient samples could help identify associated mutations that could lead to drug targets and thereby therapies. Moreover, identification of rare disease genes and mutations can advance our overall understanding of underlying biological mechanisms of more common human diseases. For example, understanding the involution process in vascular tumors such as hemangiomas (Haggstrom *et al.*, 2006), a rare disease, will benefit the understanding of human solid tumor regression biology.

Pharmaceutical and biotechnology industries

The lack of an Orphan Drug Act type of legislation in India is hampering the development of indigenous development of drugs for rare diseases. While the opportunity for growth in the rare disease market is high from patients/providers' perspectives, industry faces mixed benefits and barriers. Orphan drugs are relatively non-profitable as rare diseases affect a small patient population, and usually are unaffordable to Indian patients as the drug cost per patient far exceeds the per capita income. Hence, the Indian pharma/biotech industry needs incentives for investing in research and development of orphan drugs. A stable and reliable regulatory environment conducive to investments in long-term R&D is also desired. If the Indian pharmaceutical companies take up manufacturing of products for rare disorders this would bring the cost down not only for the Indian market, but also for the whole world. An example is the manufacture and supply of anti-retroviral drugs by CIPLA, a pharmaceutical company in India that helped tremendously in controlling AIDS across the world. Some global pharma companies, such as Genzyme, have developed charitable access programs for orphan drugs in developing countries including India. The Gaucher initiative to provide Genzyme's first approved orphan drug (1999), called Cerezyme, is one such example. Such initiatives work with humanitarian organizations but a commitment from the Government of India to support the cause of rare diseases in the form of an ODA will clearly improve accessibility to orphan drugs. The policy to import orphan drugs into India also needs a fresh re-evaluation, as companies should be permitted to import free of duty.

Government of India

The support of the Indian government is critical to the success of health initiatives such as the one we are proposing for rare diseases. The government should play an active role in addressing the enormous health care challenges posed by rare diseases through various mechanisms such as public funding for research in orphan diseases, creating business friendly policies for pharmaceutical and biotech companies and developing a balanced regulatory framework that catalyses innovation and protects the safety of patients.

ORDI vision

Our vision is to make rare diseases as easily diagnosed and treated as common diseases are in India. Collection of epidemiologic data, catalysing research and facilitating creation of registries and biorepositories would be high on our agenda.

ORDI mission

We at ORDI aim to be the umbrella organization, uniting and providing a common forum for all individual disease-specific organizations in India. It will have branches in all the state capitals. It will collaborate with other parent support groups and help to initiate new parent groups for disorders that currently do not have one. It will obtain funds from corporate houses, pharmaceutical companies, private genetic laboratories and foundations both in India and abroad. It will formulate plans of action on various

topics involving rare disorders, such as epidemiology, natural history, mechanisms of disease and treatments. It will seek support for these plans from the Government of India – DST, ICMR, DBT, CSIR, other Government agencies, and philanthropists. Memberships will be available for parent support organizations, individual patients, various categories of health professionals, hospitals (both public and private), corporate houses and pharmaceutical companies for the following mission:

- Create awareness for rare diseases all over India using mass media, newspapers, television, social media, pamphlets and posters.
- Set up patient registries for the more prevalent 'rare disorders'.
- Represent the collective voice and concerns of over 70 million patients with rare diseases in India.
- Obtain concessions from the local governments (as health is a state subject in India) for travel, treatments and jobs.
- Work with the government of India to create an optimal business and regulatory environment for the diagnostics and drug development industry (pharmaceutical and biotechnology).
- Catalyse rapid development and delivery of affordable diagnostics and treatments for rare diseases in India through innovative collaborations and partnerships among stakeholders.
- Advocate investments in rare disease research, diagnostics and drug development.
- Work with the insurance regulatory agency to ensure non-discrimination in health insurance based on the genetic constitution of an individual.
- Organize national and international conferences in India on rare disorders to create awareness and promote research and development of therapies.
- Provide assistance for rare disease patients to the largest possible extent.
- Service a 24/7 rare disease helpline that has been launched to provide assistance to patients. A proposal by ORDI to develop this helpline into a comprehensive rare disease care coordination center is currently being reviewed by pharmaceutical companies in India.

Future perspectives

Although the challenges for rare diseases appear to be of Himalayan (pun intended) proportions, the advent of precision medicine, otherwise referred to as personalized medicine, offers hope in the diagnosis and treatment of rare diseases. Precision medicine is being applied in relatively common disorders such as cancer, immune diseases and infectious diseases. It is based on the premise that by stratifying patients with similar genomic, transcriptomic, proteomic and metabolic biomarker profiles, it is possible to direct specific therapies to achieve higher levels of efficacy and reduce drug toxicities. The 'blockbuster model' of pharmaceutical companies is no longer tenable in this scenario and hence they are already developing therapies for smaller patient populations with relatively common disorders such as cancer, immune diseases and infectious diseases. All of the recent epochal advances in drug development, diagnostics and regulatory paradigms are likely to have a beneficial impact in driving precision medicine into rare disease clinics across the world.

India has a high potential to cost-effectively develop and manufacture small molecule drugs, biologics and vaccines for rare diseases due to its inherent capabilities in drug and vaccine development and manufacturing (Smita, 2006; Chakma *et al.*, 2011). India is already considered as a global hub for vaccines as it supplies close to half of the world's childhood vaccines (Virk, 2010). In addition, the small molecule drug development and manufacturing capabilities of Indian pharmaceutical companies are well recognized, especially in the generic market segment (Genetic Engineering and Biotechnology News, 2006; Kale, 2012). The biosimilars (generic biologic drugs that are produced using recombinant DNA technology such as monoclonal antibodies, hormones and cytokine therapeutics) segment is likely to experience significant growth in India in the coming years with numerous biologics likely to go off patent adding to India's capabilities in the biologic manufacturing arena (Mukherjee, 2010).

The rapid growth and innovations in molecular diagnostics and bioinformatics globally are also likely to have a beneficial impact on precision diagnostics for rare diseases. The advent of NGS in the clinic has led to the application of multi-gene, exome and whole genome-based diagnostic tests. India's strength in information technology and bioinformatics will be highly beneficial in the development and democratization of precision diagnostics for rare diseases.

The government of India has a crucial leadership role to play in advancing progress in this area. We persuade the government agencies to sponsor various activities beginning with a national level assessment of the needs of various stakeholders in the rare diseases community. India can draw upon the model that the US government developed to support rare diseases. The US government funded rare disease community needs assessments on three occasions: first, in the 1970s, approximately 5 years prior to the enactment of ODA; second, in the 1980s about 5 years after the ODA and then as part of a Special Emphasis Panel on the Coordination of Rare Diseases Research in 1998. The surveys completed examined the needs and priorities of the patients/families, physicians and medical specialists, research investigators,

voluntary health organizations (patient advocacy groups), the pharmaceutical industry, and philanthropic foundations, regulatory agency (FDA), biomedical research agency (National Institutes of Health (NIH)) and other government agencies such as Health Resources and Services Administration (HRSA) and the Centers For Disease Control And Prevention (CDC). According to the office of rare disease research (ORDR) at the NIH, these surveys helped identify the needs and opportunities to implement specific recommendations provided by the stakeholders. In many cases, these recommendations even became part of the legislative initiatives such as the ODA in 1983 and then the Rare Disease Act of 2002. Innovative government funded programs such as the Rare Disease Clinical Research Network (RDCRN; http://rarediseasesnetwork.epi.usf.edu), have made significant positive impact to the overall cause of rare disease patients in the USA. We urge the government of India to similarly take a lead in initiating and funding such needs assessments formally, to pave the way towards developing a roadmap for tackling rare diseases in India.

Developments in India

In recent years, some significant developments have taken place that will change the future of health care in India. First, the launch of the Rasthtriya Bal Swasthya Karyakram (National Health Program for Children), on 6th February 2013 (Rashtriya Bal Swasthya Karyakram, 2013). It covers 270 million children starting from birth to 18 years of age, in a phased manner and moving towards the goal of Universal Health Coverage. This program screens for 30 health conditions among children including defects at birth, deficiencies and diseases, development disabilities and also helps manage these conditions. The following conditions have a significant genetic component and will be screened and managed: impairment of vision, hearing, neuro-motor system, delay of motor functions, cognition and language, autism and attention deficit hyperactivity disorder. Birth defects such as neural tube defects, Down syndrome, cleft lip and palate, club foot, developmental dysplasia of hip, congenital heart disease, congenital deafness and congenital cataracts will also be included. Second, is the significant lowering of the infant mortality rate (IMR) across India due to government initiatives in health care. The IMR is currently 42 per 1000 at the national level, 46 in the rural areas and 28 in the urban areas (Mukherjee, 2010). Many states have an IMR of less than 20. The WHO has recommended that genetic services should be established without fail in countries with an IMR of less than 50 (Sample Registration System Bulletin, 2013). Third, is the changing pattern of diseases in India from communicable and nutritional disorders to predominance of non-communicable disorders. Finally, an enlarging and expanding private health sector and genetic laboratory services are driving health care and public awareness for genetic disorders. These events are likely to effect a remarkable change in the care and cure of rare disorders in India. ORDI has its work cut out to play a major role in this transformation.

Contact us

Visit us online at www.ordindia.org. Email your comments and suggestions to contactus@ordindia.org. We have launched the first rare disease telephone helpline in India to guide patients with rare diseases through their journey by connecting them with experts and parent support groups: +91 8892 555 000.

Funding

No specific funding was available to the authors to carry out this work.

On 16 May 2013, the first broader brainstorming session was organized to gather feedback from various stakeholder groups in India. We received valuable suggestions from the diverse participants at this event hosted by Strand Life Sciences, Bengaluru, India, as well as offline from thought leaders in India and abroad. Individual team members have gathered feedback from a large number of relevant people via informal discussions, e-mails, the Facebook page and LinkedIn group discussions. Much of this feedback has defined the core principles of ORDI as a neutral, non-profit organization. The authors wish to thank all organizations and individuals for volunteering their time and sharing their perspectives during informal meetings, discussions, brainstorming sessions, and teleconference calls. Many of these organizations are listed in the body of this manuscript. In particular, we thank Dr Stephen C. Groft and Dr Rashmi Gopal-Srivastava at the NIH office of rare disease research for their guidance, support and contribution, based on 30+ years of experience in rare diseases in the USA and worldwide. Dr Rajat Agrawal from Retina India and Dr Linda Shannon-Rozell from vascular birthmarks foundation are among other organizations that offered detailed discussion and suggestions. We thank everyone who has contributed directly or indirectly to the formation of this important initiative.

References

Aronson, J. K. (2006). Editor's view – rare diseases and orphan drugs. *British Journal of Clinical Pharmacology* **61**, 243–245.

Ausems, M. G., Verbiest, J., Hermans, M. P., Kroos, M. A., Beemer, F. A., Wokke, J. H., Sandkuijl, L. A., Reuser, A. J. & van der Ploeg, A. T. (1999). Frequency of glycogen storage disease type II in the Netherlands: implications for diagnosis and genetic counseling. *European Journal Human Genetics* **7**, 713–716.

Butler Tjaden, N. E. & Trainor, P. A. (2013). The developmental etiology and pathogenesis of Hirschsprung disease. *Translational Research* **162**, 1–15.

Chakma, J., Masum, H., Perampaladas, K., Heys, J. & Singer, P. A. (2011) Indian Vaccine Innovation: the case of Shantha Biotechnics. *Globalization and Health* **7**, 9.

Christianson, A. & Modell, B. (2004). Medical genetics in developing countries. *Annual Review of Genomics and Human Genetics* **5**, 219–265.

Dalal, A., Bhavani, G. S. L., Togarrati, P. P., Bierhals, T., Madhusudan, R., Nandineni, , Danda, S., Danda, D., Shah, H., Vijayan, S., Gowrishankar, K., Phadke, S. R., Bidchol, A. M., Rao, A. P., Nampoothiri, S., Kutsche, K. & Girisha, K. M. (2012). Analysis of the *WISP3* gene in Indian families with progressive pseudorheumatoid dysplasia. *American Journal of Medical Genetics Part A* **158A**, 2820–2828.

Ehre, C., Ridley, C. & Thornton, D. J. (2014). Cystic fibrosis: an inherited disease affecting mucin-producing organs. *International Journal of Biochemical Cell Biology* **2014**, pii: S1357–2725(14)00086–7. doi:10.1016/j.biocel.2014.03.011.

Genetic Engineering and Biotechnology News. (2006). Drug discovery and development in India: an untapped seam of outsourcing opportunities. Vol. 26, No. 3, 1 February (http://www.genengnews.com/gen-articles/drug-discovery-and-development-in-india/1314/). Accessed July 2014.

Global Genes. RARE Facts and Statistics (http://global-genes.org/rarefacts). Accessed March 2013.

Haggstrom, A. N., Drolet, B. A., Baselga, E., Chamlin, S. L., Garzon, M. C., Horii, K. A., Lucky, A. W., Mancini, A. J., Metry, D. W., Newell, B., Nopper, A. J. & Frieden, I. J. (2006). Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics* **118**, 882–887.

Kale, D. (2012). Innovative capability development in the Indian pharmaceutical industry. *International Journal of Innovation and Technology Management* **9**, 1250013.

Kapoor, S., Gupta, N. & Kabra, M. (2013). National newborn screening program – still a hype or a hope now? *Indian Pediatrics* **50**, 639–643.

Lavandeira, A. (2002). Orphan drugs: legal aspects, current situation. *Haemophilia* **8**, 194–198.

Ma, D., Li, D. G., Zhang, X. & He, L. (2011). The prevention and treatment on rare diseases in China: opportunities and challenges. *Chinese Journal of Evidence Based Pediatrics* **6**, 81–82. (in Chinese).

Mercuri, E. & Muntoni, F. (2013) Muscular dystrophy: new challenges and review of the current clinical trials. *Current Opinions in Pediatrics* **25**, 701–707.

Mukherjee, S. (2010). Pharmaceutical R&D: India at the crossroads. *Financial Chronicle* December 2010.

Nogales, E. A. (2004). Rare diseases: a new chapter in medicine. *Anales de la Real Academia Nacional de Medicina* **121**, 139–151; discussion 151–155. (in Spanish; Castilian).

Orphanet: an online database of rare diseases and orphan drugs. Copyright, INSERM 1997 (http://www.orpha.net). Accessed May 2014.

Rasthtriya Bal Swasthya Karyakram (2013). Child health screening and early intervention services under NRHM. Ministry of Health and Family Welfare, Government of India, February 2013 (http://www.unicef.org/india/7). Accessed July 2014.

Reich, D., Thangaraj, K., Patterson, N., Price, A. L. & Singh, L. (2009). Reconstructing Indian population history. *Nature* **461**, 489–494.

Rosenbloom, B. E. & Weinreb, N. J. (2013). Gaucher disease: a comprehensive review. *Critical Reviews in Oncogenesis* **18**, 163–175.

Sample Registration System Bulletin. (2013). Registrar General India, New Delhi. September **48**, 2 (http://tripura-anrhm.gov.in/pdf/SRS_BULLETIN_SEPETEMBER_2013.pdf). Accessed July 2014.

Shire Human Genetic Technologies (2013). Rare disease impact report (http://www.rarediseaseimpact.com). Accessed April 2014.

Singh, J. R., Singh, A. R. & Singh, A. R. (2007). Directory of Human Genetic Services in India 2007. *International Journal of Human Genetics* **10**, 187–192.

Sinha, K. (2012). Medical Council of India approves 3·5 years medical course. The Times of India, 24 September. (http://timesofindia.indiatimes.com/home/education/news/Medical-Council-of-India-approves-3-and-a-half-year-medical-course/articleshow/16523446.cms). Accessed July 2014.

Smita, S. (2006). Industrial development and innovation: some lessons from vaccine procurement. *World Development* **34**, 1742–1764.

Song, P., Gao, J., Inagaki, Y., Kokudo, N. & Tang, W. (2012). Rare diseases, orphan drugs, and their regulation in Asia: current status and future perspectives *Intractable and Rare Diseases Research* **1**, 3–9.

Tamang, R., Singh, L. & Thangaraj, K. (2012). Complex genetic origin of Indian populations and its implications. *Journal Bioscience* **37**, 911–919.

Tang, W. (2013) Editorial. Hopes for intractable and rare diseases research. *Intractable and Rare Diseases Research* **2**, 1–2.

Verma, I. C. & Bijarnia, S. (2002). The burden of genetic disorders in India, and a framework for community control. *Community Genetics* **5**, 192–196.

Verma, I. C. (2000). Burden of genetic disorders in India. *Indian Journal of Pediatrics* **67**, 893–898. Erratum in: *Indian Journal of Pediatrics* (2001). 68, 25.

Verma, I. C. (2004). Genetic disorders and medical genetics in India. In *Genetic Disorders of the Indian Subcontinent* (ed. D. Kumar), pp. 50–518. Dordrecht: Kluwer Academic Publishers.

Virk, PK (2010). India's future as a biologics manufacturing hub. *BioPharm International* **23**, 1.