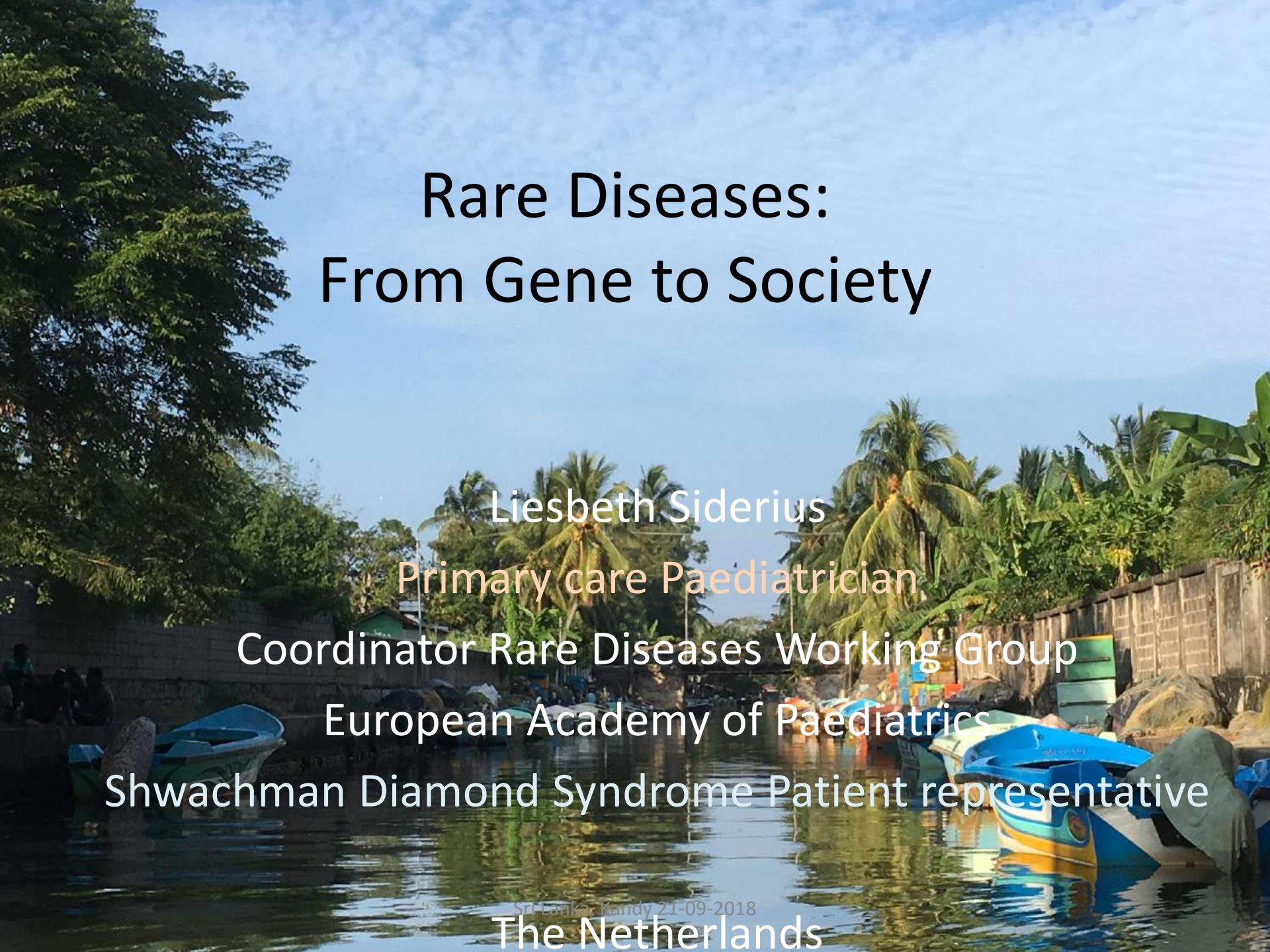


Rare Diseases: From Gene to Society

Liesbeth Siderius

Primary care Paediatrician

Coordinator Rare Diseases Working Group

European Academy of Paediatrics

Shwachman Diamond Syndrome Patient representative

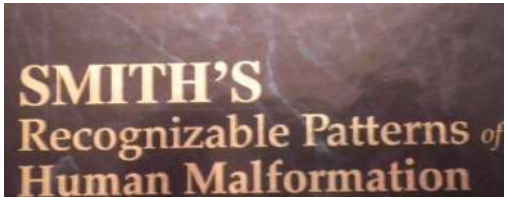
Sri Lanka, Kandy 21-09-2018

The Netherlands

Diagnosis First

Cornelia de Lange Syndrome 1: 10.000 - 1: 30.000
Severe developmental delay with characteristic features

1981
Chromosome
Abnormality
??

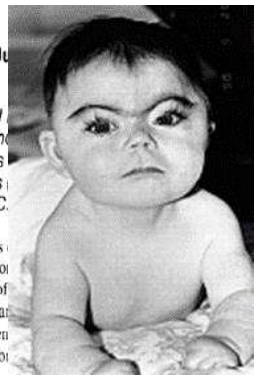


Prometaphase Chromosomes in Five Patients With the Brachmann-de Lange Syndrome

Elizabeth J. Breslau, Christine Disteche, Ju
and Pat Cooper

Departments of Pathology, Pediatrics and
ton and Children's Orthopedic Hospital an
Washington (E.J.B., C.D., J.G.H.); Genetics
Department of Social and Health Services
ics Program, Walla Walla, Washington (P.C.

We analyzed the prometaphase chromosomes
of sibs) with the Brachmann-de Lange syndro
significant chromosome abnormality in any of
tinct entities can be distinguished on clinical a
and the dup(3q) syndrome. We still recommen
tients with BDLS and BDLS-like manifestatio



2003 DNA mutation

NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome

Michael J Bamshad[2] & Tom Strachan[1]

Cornelia de Lange syndrome (CdLS) is a multiple malformation disorder characterized by dysmorphic facial features, mental retardation, growth delay and limb reduction defects[1,2]. We indentified and characterized a new gene, *NIPBL*, that is mutated in individuals with CdLS and determined its structure and the structures of mouse, rat and zebrafish homologs. We named its protein product delangin. Vertebrate delangins have substantial homology to orthologs in flies, worms, plants and fungi, including Scc2-type sister chromatid cohesion proteins, and *D. melanogaster* Nipped-B. We propose that perturbed delangin function may inappropriately activate *DLX* genes, thereby contributing to the proximodistal limb patterning defects in CdLS. Genome analyses typically identify individual delangin or Nipped-B-like orthologs in diploid animal and plant genomes. The evolution of an ancestral sister chromatid cohesion protein to acquire an additional role in developmental gene regulation suggests that there are parallels between CdLS and Roberts syndrome.

The multisystem nature of the CdLS phenotype suggests that it is caused by a microdeletion or microduplication affecting several genes or by a single gene that regulates various target genes. A high-density BAC microarray comparative genome hybridization screen found no evidence for a consistent pattern of microdeletion or microduplication[3]. Because CdLS is rare and most cases are sporadic, genome-wide linkage screens are problematic. As an alternative, we analyzed chromosomal breakpoints associated with CdLS, focusing first on three classical cases with *de novo* balanced translocations, including the previously described translocations t(3;17)(q26.3;q23.1)[4] and t(14;21)(q32;q11)[5]. We first analyzed the 3q26.3 breakpoint because of

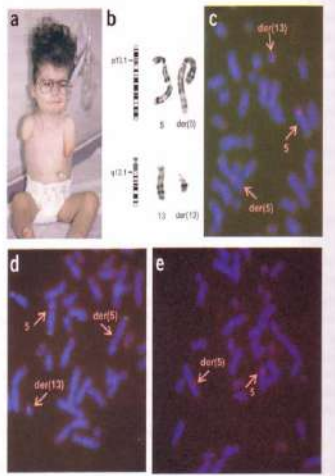


Figure 1 FISH mapping of a 5p13 translocation breakpoint in an individual with classical CdLS. (a) Individual with classical CdLS with characteristic limb and facial abnormalities (including an upturned triangular nose, long philtrum, thin upper lip, downturned corners of the mouth; see fuller description for individual P46 in Table 1). (b) Giemsa chromosome banding showing a balanced *de novo* t(5;13)(p13.1;q12.1) translocation. (c–e) Metaphase chromosome FISH with the breakpoint-spanning BAC clone CTD-2653m23 (c) and overlapping fosmid clones G248P84262B4 (d) and G248P8840C10 (e), all labeled with Spectrum Red. Labeled in green is a chromosome 5q telomere-specific probe. Arrows indicate the normal chromosome 5 and the der(5) t(5;13)(p13.1;q12.1) and der(13) t(5;13)(p13.1;q12.1) chromosomes. In occasional metaphases a weak G248P84262B4 signal can be detected on the der(5) chromosome as well as a strong signal on the der(13). The combined data suggest that the most likely location for the breakpoint is close to the proximal end of the region of overlap for inserts of G248P84262B4 and G248P8840C10 (Fig. 2a).

Abandoned

2014 - 2018

Georgia has become one of the first ex-Soviet republics to abolish state orphanages in favour of foster care.

But disabled children continue to be marginalised and face the prospect of life-long isolation from society.

www.bbc.com/news/world-europe-25575094

Sickle cell disease
1.1% of couples worldwide are at risk for having children with a haemoglobin disorder
WHO: Africa majority of children with the most severe form of the disease die before the age of 5, usually from an infection or severe blood loss

World Health Organization

WHO, 7 December 2010

Fact sheet N°172

- A collaborative management approach at primary health care level with patients, their families and other health care actors is a must to effectively prevent many major contributors to the burden of disease.

Essential elements for action

- **Support a paradigm shift towards integrated, preventive health care**
- **Promote financing systems and policies that support prevention in health care**
- **Equip patients with needed information, motivation, and skills in prevention and self-management**
- **Make prevention an element of every health care interaction**

Rare **D**iseases Global Action

EURORDIS, Vienna, May 2018

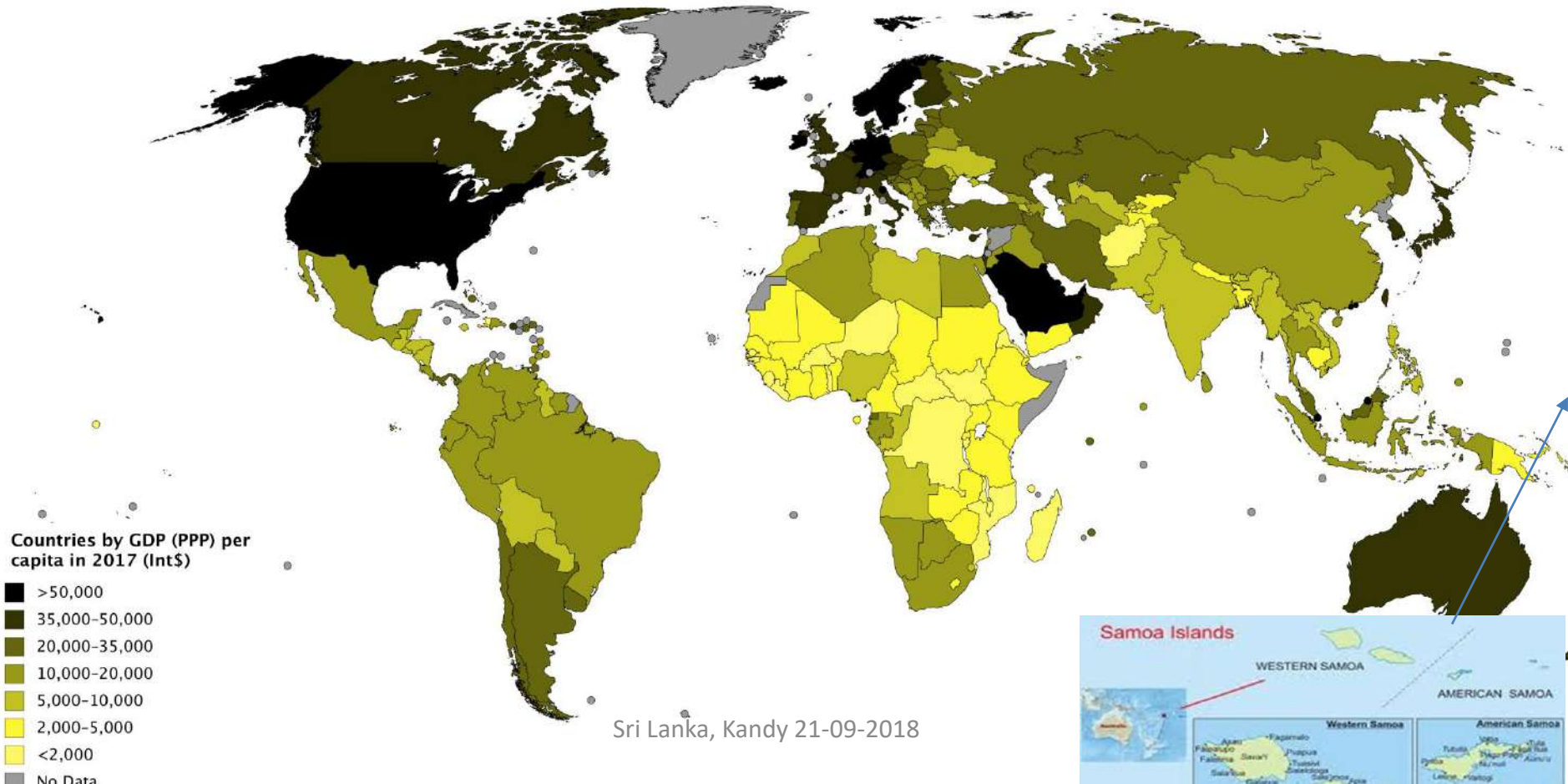
European Conference on Rare Diseases & Orphan Products

- RD as a Collective Health and Social issue
- RD Universal Health Coverage
- Access to Diagnostics
- Access to Medicines / fair pricing
- Inclusion in the Non- Communicable Disease agenda
- RD in the Sustainable Development Goals

Bruck Syndrome 1: 1.000.000 world wide; bone fractures, limited movement, high incidence Samoa Islands

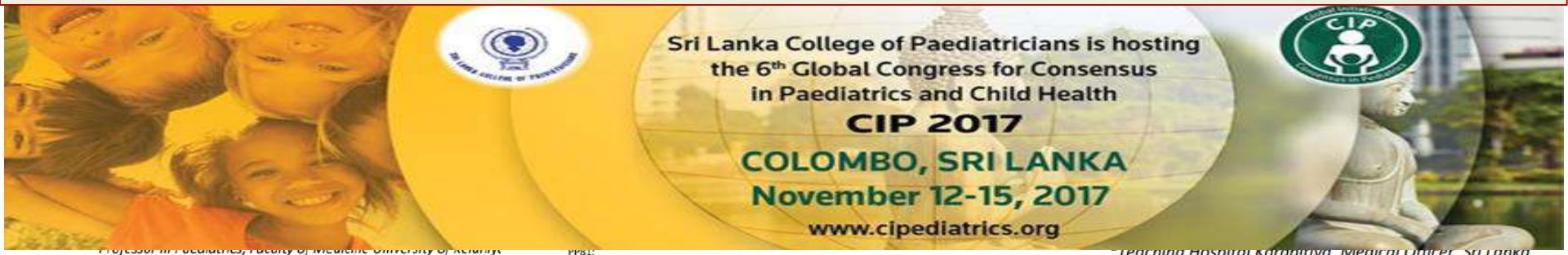
Gross Domestic Product per Capita in Purchasing Power Parity per capita

estimated by IMF for year 2017



Sri Lanka, Kandy 21-09-2018

Brugada syndrome 5-50 : 10.000; higher in south east Asia, recognizable through ECG abnormality



PP53:
Revesz Syndrome: Rare Variant of Dyskeratosis Congenita. A Case Report
Imalke Kankananarachchi[1], Nuwan Wickramasinghe[2], Sujeewa Am
Sadani Vithana[2], Thilina Madushanka[2]
[1]Paediatrics, Faculty Of Medicine University of Ruhuna, Sri Lanka
[2]University Paediatric Unit, Teaching Hospital Karapitiya, Sri Lanka

PP54:

PP78:
Oculo-Auricular- Vertebral (Oav) Spectrum Disorders: Experience From Sr
WMDAS Wanninayake[1], Romesh Gunasekera[2], Saman Yasawarder
Basnayake[4], Malka Jayathilake[5], DDC Nilini[6], Deepthi de Silva[7]
[1]Demonstrator, Department of Physiology, Faculty of Medicine, Ur
Kelaniya, Sri Lanka, [2]Consultant Plastic Surgeon, Lady Ridgway Hos
Colombo, Sri Lanka
[3]Consultant ENT Surgeon, Lady Ridgway Hospital, Colombo,
[4]Lady Ridgway Hospital, Colombo, Consultant Orthodontist,
[5]Speech and Language Therapist, Lady Ridgway Hospital, Co
[6]Research Assistant, Department of Chemistry, Faculty of Sci

PP81:
Partial 1Q Trisomy Syndrome Due Maternal T(1;4) Balance Translocation; A Case Report
R.J.M.K.A Jayasundara[1], M.D.C.J.P. Jayamanne[1], G.B.A.M. Rathnasiri[1], S. Mayoorathy[1], Ranmali Rodrigo[2]
[1]Colombo North Teaching Hospital, Registrar in Paediatrics, Sri Lanka
[2]Faculty of Medicine, University of Kelaniya, Consultant Neonatologist, Sri Lanka

PP82:
Pallister Killian Syndrome: Experience of Clinical Diagnosis and Molecular Confirmation in Sri Lankan Patients
Nirmani Ratnayake[2], DDC Nilini[1], Samantha Waidyanatha[3], Kumudu Weerasekera[2], Nicole de Leeuw[4], Deepthi de Silva[3]
[1]Department of Chemistry, Faculty of Science, University of Colombo, Research Assistant, Sri Lanka, [2]Department of Physiology, Faculty of Medicine, University of Kelaniya, Demonstrator, Sri Lanka, [3]Lady Ridgway Hospital, Consultant Pediatrician, Sri Lanka
[4]Department of Human Genetics, Radboud University Medical centre, Nijmegen, the Netherlands, Clinical Laboratory Geneticist, Netherlands
[5]Department of Physiology, Faculty of Medicine, University of Kelaniya,

PP105:
Oculocerebrorenal Syndrome of Lowe - A Case Report
Sadani Vithana[1], Imalke Kankananarachchi[1], Thilina Madusha
Wickramasinghe[1], Sujeewa Amarasena[1], Harshini Dharmawar
Rukshani
[1]professorial unit, Paediatrics, Teaching Hospital Karapitiya, S
[2]paediatric Nephrology, Teaching Hospital Karapitiya, Sri Lan

A Case Report
Randula Ranawaka[1], Nirmala Sirisena[2], Kavinda Dayasiri[3], Manoji Gamage[4],
[1]Department of Paediatrics, Faculty of Medicine, University of Colombo, Sri Lanka
[2]Human Genetics Unit, Faculty of Medicine, University of Colombo, Sri Lanka
[3]University Paediatric Unit, Lady Ridgeway Hospital for Children, Colombo, Sri Lanka
[4]Human Nutrition Unit, Lady Ridgeway Hospital for Children, Colombo, Sri Lanka
[5]Rare Kidney Stone Consortium/Dent Disease Program, Mayo Clinic Division of Nephrology and Hypertension, USA

PP65:
A Child with a Limp-A Presentation of Maccune Albright Synd
Gayan Sampath[1], Sadani Vithana[2], Charith Udagedara
Navoda Atapattu[3]
[1]Peadiatrics, Provincial General Hospital,Ratnapura, S
[2]Paediatrics, Teaching Hospital-Karapitiya, Sri Lanka
[3]Paediatrics, Lady Ridgeway Hospital for Children, Sri Lanka

PP66:
Are Sri Lankan Children with Congenital Adrenal Hyperplasia at Risk of Morbidity and Mortality in the Absence of Newborn Screening?

SN Seneviratne, HGU Sandakelum, WAAM Weerasinghe, WAPS Wickramarachchi, KSH de Silva
Department of Paediatrics, Faculty of Medicine, University of Colombo, Sri Lanka

180 Posters
36 Rare Diseases
24 from Sri Lanka

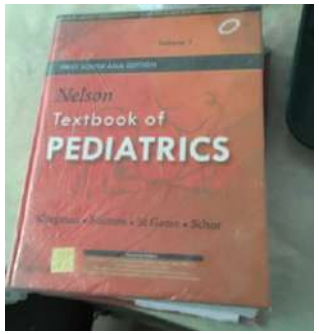
Navabalasooriyar Pratheep, Kavinda Dayasiri, Nalin Kitulwatte
Medical Intensive Care Unit, Lady Ridgeway Hospital for Children, Sri Lanka

PP50:
A Paediatric Case of Brugada Syndrome
Navabalasooriyar Pratheep, Kankananarachchi Imalke, Kitulwatte Nalin
Medical Intensivecare Unit, Lady Ridgeway Hospital for Children, Sri Lanka

Dyskeraotosis congenita X-linked recessive (OMIM 305000),
autosomal dominant (OMIM 127550), and autosomal recessive (OMIM 224230)

Rare Diseases Forum

- Well trained and **experienced paediatricians**
- Families have their own data and are co-managing
- Little access to diagnostic tests
- Little access to internet
- No facilities for electronic data collections



With limited resources :
accurate diagnosis !

Rare **D**iseases Paediatric Global Action

What can paediatricians do to improve health and wellbeing of children with a rare and disabling condition and their families?

RECOGNIZE

- strengthen primary paediatric care with sufficient knowledge
- advocate for access to proper diagnostics and treatment
- collect and share data
- support families

Turner syndrome : 50 per 100,000 liveborn females;
coarctation of the aorta and bicuspid aortic valve reduce life expectancy

Primary Health Care can meet 80-90% of an individual's needs over the course of their life http://www.who.int/primary-health/en

@WHO_Europe 7 sep. #PrimaryHealthCare has a strong focus on quality of care.

Quality health services, build trust in patients and encourage individuals to engage in their health and the health of their families. We cannot have Health For All without quality care.

Complex chromosome rearrangement ; developmental delay, behavioral problems, 'autism'

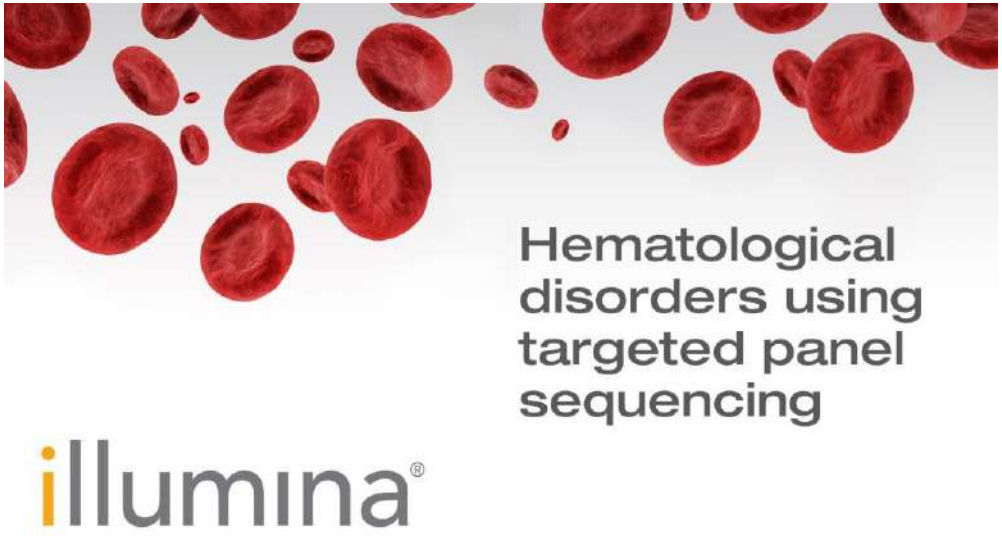
Rare **D**iseases Paediatric Global Action

What can paediatricians do to improve health and wellbeing of children with a rare and disabling condition and their families?

- strengthen primary paediatric care with sufficient knowledge
- advocate for access to proper diagnostics and treatment
- collect and share data
- support families

Fanconi anemia: 1:160.000; skin pigmentation, growth retardation, bone marrow failure

Next Generation Sequencing



Welcome to NGS

The massively parallel sequencing technology known as next-generation sequencing (NGS) has revolutionised the biological sciences. With its ultra-high throughput, scalability, and speed, NGS enables researchers to perform a wide variety of applications and study biological systems at a level never before possible.

https://www.illumina.com/science/technology/next-generation-sequencing.html

.

Fabry 1 : 40 - 60,000 males Fabrazyme X linked , pain skin pigmentations, Heart disease, stroke

Orphan Drugs: European Academy of Paediatrics position statement on the Paediatric Regulations and Rare diseases December 2017

Rare diseases should not be overlooked in discussing how to improve impact of Paediatric Regulation

Developers of medicines for rare paediatric diseases need to comply with both the Orphan and Paediatric Regulations. Decisions of the Orphan and Paediatric Committees should be aligned.

To improve the availability of high quality medicines for use in children, transparency on development costs and agreement on maximum price, is warranted.

The price should match a considerable and measurable clinical benefit.

Retinoblastoma, 3.4 to 42.6 cases per million live births
eye tumor, screening in recognizable signs

Rare **D**iseases Paediatric Global Action

What can paediatricians do to improve health and wellbeing of children with a rare and disabling condition and their families?

- Strengthen primary pediatric care with sufficient knowledge
- Advocate for access to proper diagnostics and treatments
- Collect and share data
- Support families

Shwachman Diamond Syndrome 1:70.000, pancreatic insufficiency, neutropaenia , skeletal dysplasia, developmental delay

Stichting Shwachman syndroom Support Holland

European Patient Registry

Sri Lanka, Kandy 21-09-2018

Building the Rare Disease

knowledge and information ecosystem

Thalassemia, 3500 patients have been identified in Sri Lanka.

RareCare.World

thalassemia SEARCH

Find and share knowledge about

Rare diseases all over the world

ATC

- L01XX05 Hydroxycarbamide (Hydroxyurea) (1)
- V03AC01 Deferoxamine (1)
- V03AC02 Deferipron (1)
- V03AC03 Deferasirox (1)

ICD

- D57 Sickle-cell disorders (1)

ICPC Reference

- B78.01 Thalassemia (1)
- B87 Splenomegaly (1)

LOINC

- 718-7 Hemoglobin in blood (1)
- 20567-4 Ferritin in Serum or Plasma (1)
- 46740-7 Hemoglobin disorders newborn screen interpretation (1)
- 53857-9 Hemoglobin F (1)

OMIM

fractures or vertebral deformities. **Thalassemia** major or Beta **Thalassemia** ...
Rare Condition
Thalassemia major or Beta Thalassemia

Large spleen

Feature

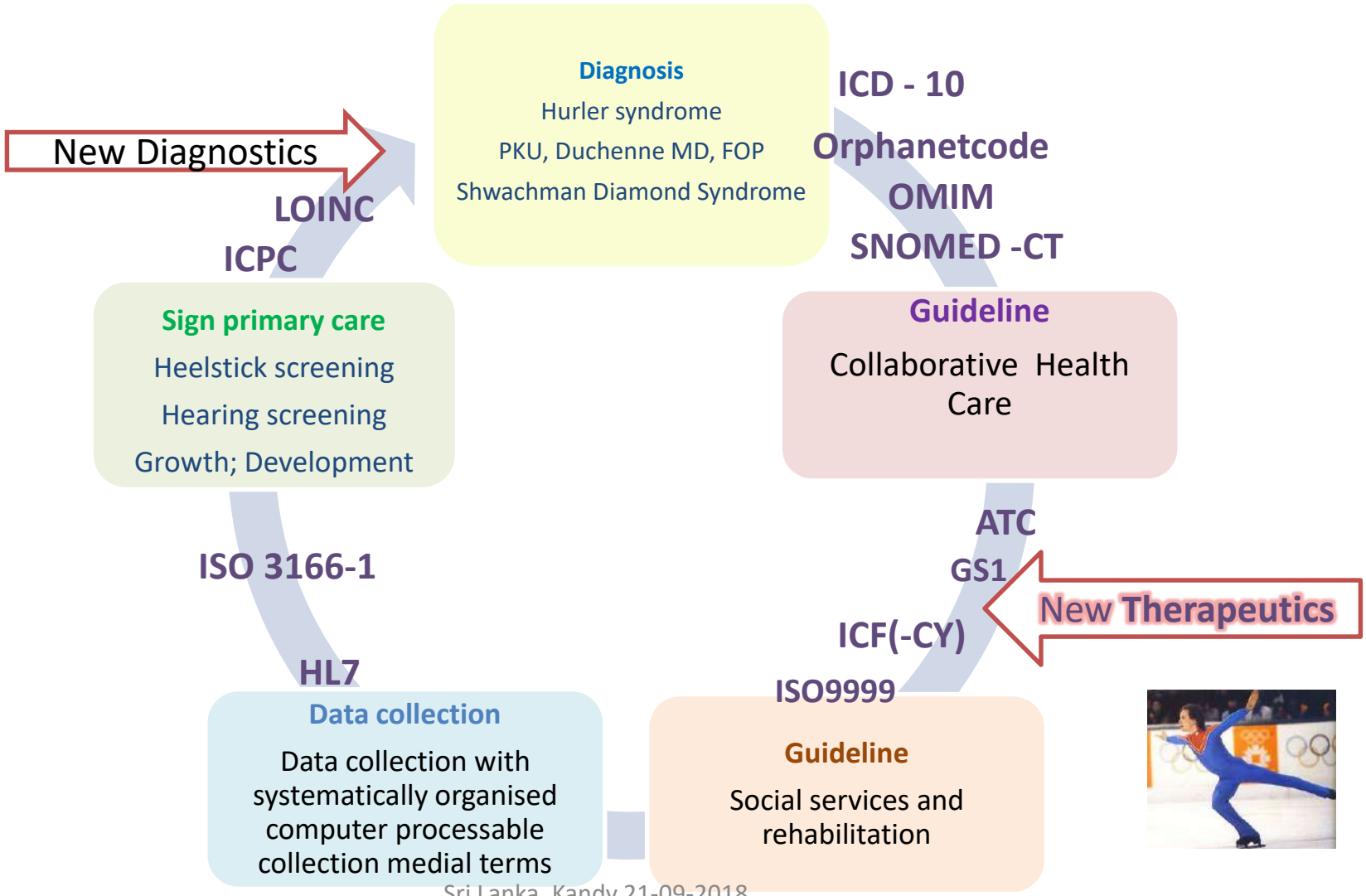
... costal margin. A large spleen is a feature of for example **Thalassemia** Infections Nieman Pick disease Gaucher disease Splenomegaly Splenomegaly in **thalassemia** **Thalassemia** major or Beta **Thalassemia** ...
Rare Condition
Thalassemia major or Beta Thalassemia
Symptom
Splenomegaly in thalassemia
Abnormality
Splenomegaly

Carrier screening thalassemia

Symptom

... Carrier screening **thalassemia** Related family members with elevated HbA2 In carrier screening for the classical beta-**thalassemia** trait, the hallmark is the presence of an ... 2 (α 2 δ 2). Another way of identifying people with **thalassemia** major is neonatal screening. Neonatal screening ...
Rare Condition
Thalassemia major or Beta Thalassemia
Disease
Hemoglobinopathies

Patient Informatiom	Primary Care	Diagnosis Collaborative care	Social Services
www.shwachman.nl	Growth retardation Recurrent infections (LOINC)	Guideline SDS (Orphanetcode; SNOMED, ATC e.a.)	Recurrent illness Fatigue, Short (ICF-CY; ISO 9999)



Fibrodyspalsia Ossificans Progressiva 1:2.000.000
No intramuscular vaccinations > muscle becomes bone

Rare **D**iseases Paediatric Global Action

What can paediatricians do to improve health and wellbeing of children with a rare and disabling condition and their families?

- strengthen primary paediatric care with sufficient knowledge
- advocate for access to proper diagnostics and treatments
- collect and share data
- support families

Anal atresia 1:5000, after operation parents daily wash the bowel, child will not easily be toilet trained if at all

Rare diseases seriously impact everyday life

7 in 10 patients & carers
reduced or stopped professional activity due to their or their family member's rare disease.

8 in 10 patients & carers
have difficulties completing daily tasks (household chores, preparing meals, shopping etc.)

2/3 of carers
spend more than 2 hours a day on disease-related tasks.

3 times more people
living with a rare disease and carers report being unhappy and depressed than the general population*

* Rare Barometer Voices sample compared to International Social Survey Programme, 2011

Rare Barometer Voices
A EURORDIS INITIATIVE

Rare Barometer Voices is a EURORDIS-Rare Diseases Europe online survey initiative. It brings together over 6,000 patients, carers and family members to make the voice of the rare disease community stronger. Results are shared with policy decision makers to bring about change for people living with a rare disease.

3,071 people responded to the survey.

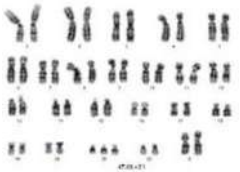
The survey was conducted in **23** languages across **42** countries

Thank you to all Rare Barometer Voices participants and partners!

www.eurordis.org/content/contribute-rare-barometer-programme

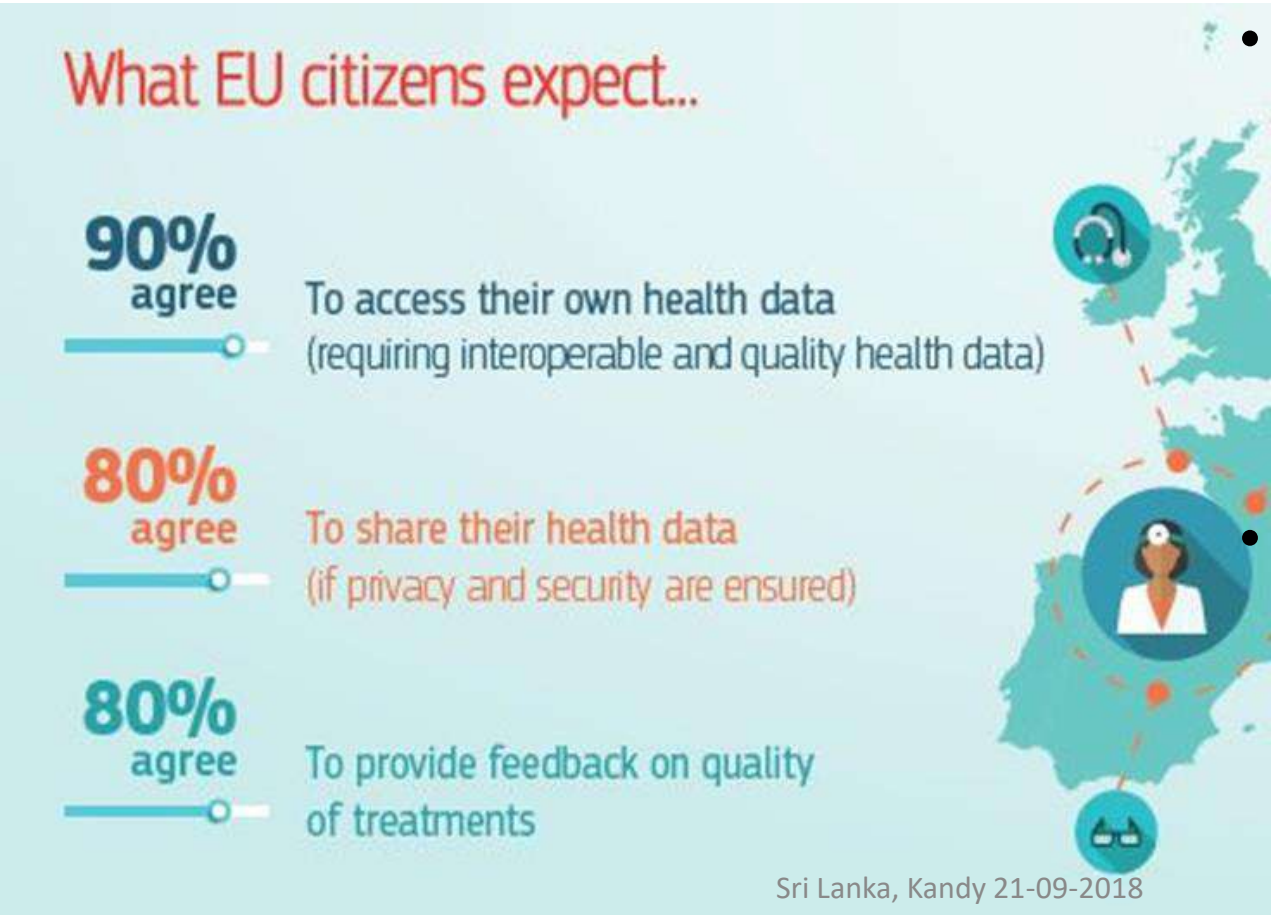
For more information visit **eurordis.org/voices** or email **rare.barometer@eurordis.org**

Down Syndrome 1:1000
International Guidelines



@EU_Health
25 April 2018

- EU_Health
- Citizens' expectations on digital health: access to their own data, privacy & security and the ability **to give feedback on treatment**.
- Data in the EU: Commission steps up efforts to increase availability and boost **health care data sharing**



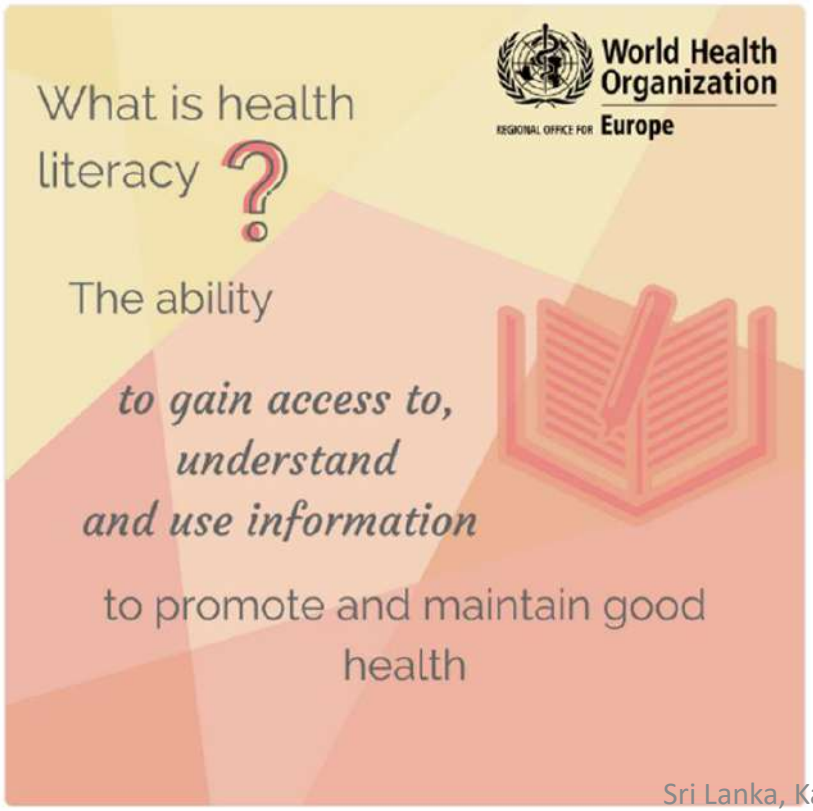
Familial Hypercholesterolaemia1:250, diet and medicine will prolong life expectancy, patient organisation developped and app https://fheurope.org/about-fh/familial-hypercholesterolaemia/

@WHO_Europe 30 August 2018

Q: What is health literacy?

communities. #HealthForAll

Tweet vertalen



07:09 - 30 aug. 2018

Sri Lanka, Kandy 21-09-2018

Rare becomes Common
Patient-Centered
Universal health coverage