

Rett syndrome and the role of national parent associations within a European context

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ORIGINAL ARTICLE

Rett syndrome and the role of national parent associations within a European context

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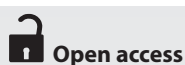
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Abstract

Rett syndrome (RTT) is a rare neurodevelopmental disorder arising from a genetic mutation on the X chromosome. In recent years there has been an increasing focus in Europe on developing links, both within and between countries, between researchers, clinicians, therapists, individuals with RTT and their families or caregivers in order to maximise approaches towards treatment and long-term-management of the disorder. This paper seeks to place RTT, especially the support of families living with RTT, in a European context. It explores the important role played by both the national Rett parent associations and the Rett expertise centres that exist in many of the Member States of the European Union and places the contribution of both within the context of European policy on rare diseases.

Key words

Rett syndrome, parent associations, centres of expertise, European Union, European policy, rare diseases, rare disease registries.

Introduction

Rett syndrome (RTT) is a rare neurodevelopmental disorder thought to affect 1 in 9,000-15,000 live female births [1-4]. This is due to a genetic mutation on the X chromosome which is most commonly found in the MECP2 gene [5-8] although other variants have been identified. The severity of the clinical presentation varies according to the specific mutation [9-14]. Typically, however, the syndrome is characterised by seemingly-normal development in the early months of life following which there is a noticeable regression of skills, beginning between 6 and 18 months of age [15]. A cascade of evolving clinical features has been delineated according to a series of stages [16, 17]. Individuals with RTT demonstrate a loss of motor and communication skills [18, 19], in large part due to the influence of dyspraxia which affects their ability to make purposeful movements; additional concomitant features generally include severe breathing abnormalities, epilepsy and scoliosis [20]. It is a severe, lifelong disorder which impacts greatly on quality of life and leads to a shortened life expectancy [21-24].

In 2007 Bird and colleagues first demonstrated that the symptoms of RTT could be reversed in mice [25]. Since then much research has been devoted to both the treatment and potential cure of RTT [26-29] as well as the development of more functional therapies which seek to enhance the participation and quality of life of individuals living with this rare disorder [30-37].

Both the literature and the number of clinicians worldwide with specialist knowledge and skills relating to this population are small but increasing, as is the number of multidisciplinary centres specialising in the care and management of individuals with RTT and their families. At the present time, however, there is huge variability in knowledge and expertise between countries and huge variability in clinical practices both between and within countries. There are few national and no internationally-agreed models for the delivery of clinical services to this population; neither are there international guidelines for the overall clinical management of the syndrome although these have been proposed for individual aspects, such as scoliosis [38] and growth and nutrition [39].

Within this global context, there is a growing recognition of the need to strengthen collaborations within and between professional and parent groups at both European and international levels, and it is clear that Rett parent associations can provide a valuable role in disseminating and sharing information and training, and in supporting both families and professionals. Rett Syndrome Europe (RSE, <http://www.rettsyndrome.eu/association-rse/europe/>) has formed as an umbrella organisation for the European parent associations and, as a member of EURORDIS (the European Rare Diseases Organisation, <http://www.eurordis.org/>), also makes a vital contribution to the debate on European policy in relation to rare diseases. Likewise, in recent years, professionals (researchers, clinicians and therapists) from a number of expert centres across Europe have come together to form ESRRRA, the European Scientific Rett Research Association (<http://www.europeanscientificrettresearchassociation.eu/>), a collaborative European platform for research focusing on RTT. Beyond Europe, international organisations such as rettsyndrome.org (<https://www.rettsyndrome.org/>) similarly give invaluable impetus to harnessing and stimulating developments in knowledge and expertise and promoting a sense of community between families and professionals within this relatively small field.

This paper offers an overview of the situation relating to RTT in countries within the European Union (EU) and European Economic Area (EEA) as of 2015.

European Rett syndrome conferences

In 2009 the first European Rett Syndrome Congress was held in Milan, Italy. This was an important milestone in bringing together researchers, scientists, educators, therapists and families to explore aspects relating to then-current research and treatment of RTT. The value of such a pan-European format was recognised and a second European conference followed in Edinburgh in 2010. In 2013 this model was again repeated with the third European Rett Syndrome Conference (ERSCM2013). Entitled 'Research Update and Preventive Management', this three-day conference was held in Maastricht, The Netherlands, and attracted 340 participants from 31 countries, representing 19 Member States of the EU, two EEA States, and ten other countries. The wishes and needs of parents, as expressed by the Rett parent associations and Rett syndrome foundations, were central to the development of the programme. The conference proved to be an exciting and stimulating opportunity for the sharing and dissemination of information concerning the latest developments in scientific and medical research and therapies, with separate seminar streams offered for researchers and scientists and for therapists and families, in addition to shared sessions open to all.

During the 'parent track' there was a particular emphasis on fostering opportunities for networking and information exchange between the national Rett parent associations; sessions at both the beginning and end of

the conference were devoted to the European parent associations sharing information on their countries whilst RSE also held its annual General Assembly during the conference. At the close of the conference the organising committee and RSE signed a joint statement declaring their support for the European Union policy on rare diseases and defining more precisely the wishes of the European parent organisations in relation to the care and cure of RTT.

Of the 21 EU and EEA Member States present at the conference, 18 parent associations offered a presentation during the conference. In addition, presentations were given by the Israeli and Russian Rett parent associations. Each country was asked to set the scene by providing some basic national population statistics as well as statistics for RTT in that country, as far as available. Information on any Rett expertise centres or specialists in the field, together with an outline of the aims, activities and wishes of the parent association and/or foundation (if one existed) was also requested. The slides from these presentations can be accessed through the website of the Dutch Rett parent association (NRSV, <http://www.rett.nl/>).

Key information relating to the Rett parent associations in the EU and EEA Member States is shown in Table 1, whilst Table 2 provides an overview of centres of expertise and/or main hospitals providing diagnosis and medical care/advice and/or conducting research into RTT. The information contained within the tables is as presented by the national parent associations during ERSCM2013, supplemented by information taken from the websites of the national parent associations and/or email contact with parent representatives/medical consultants from each of the countries (up to September 2015). Additional and/or updated information on the current situation in each country (including details of parent association activities) can be accessed via the website addresses listed in the tables.

The fourth European Congress on Rett Syndrome took place in Rome, Italy, during the last weekend of October, 2015.

Comparisons across Europe

As of 2015 between five and ten European countries have (to varying degrees) either a national Rett expertise centre or specialised multidisciplinary Rett clinics, some of which are embedded within centres for rare diseases. A number of experts and researchers from these centres collaborate through ESRRRA, as described above. Several countries have one or more hospitals providing a diagnostic service and/or one or more medical experts offering advice and clinical management of the syndrome, whilst other European countries have no experts in RTT and rely on services aimed at general disabilities (for further details see Table 2). In these cases the role of the national parent association, where one exists, is especially crucial in supporting families and professionals alike.

Table 1. EU & EEA Member States information: national population and Rett statistics (known and estimated), and parent association details

Country ^a	Population ^b	Birth rate per 1,000 population ^b	Estimated number of girls born per year with RTT ^c	Number of families/individuals known to have RTT (approximate in some cases) ^{d,e}	Parent association name & website
Austria	8.22 million	8.76	2.3-3.9	102 ^d	<i>Österreichische Rett-Syndrom Gesellschaft (ÖRSG)</i> Founded 1996 www.rett-syndrom.at Member of <i>Pro-Rare Austria</i>
Belgium	10.45 million	9.99	3.4-5.7	80 ^d	<i>Belgische Rett Syndroom Vereniging (BRSV)</i> Founded 1988 www.rettsyndrome.be
Bulgaria	6.92 million	8.92	2.0-3.3	No information available	No Rett parent association registered with RSE
Croatia	4.47 million	9.49	1.4-2.3	29 ^e	No Rett parent association registered with RSE
Cyprus	1.17 million (Republic & Northern Cyprus)	11.44	0.4-0.7	Several ^d (clinical rather than molecular diagnosis)	No Rett parent association registered with RSE <i>Pancyprian Association for Rare Genetic Disorders ('Unique Smiles')</i> offers support to families via Facebook
Czech Republic	10.63 million	9.79	3.4-5.6	50 ^d (unofficial)	<i>Rett Community Association</i> Founded 2004 www.rett-cz.com/cz Member of CAVO, <i>Czech Association of Rare Diseases</i>
Denmark	5.57 million	10.22	1.8-3.1	123 ^d	<i>Landsforeningen Rett Syndrom</i> Founded 1988 www.rett.dk Member of <i>Rare Diseases Denmark</i>
Estonia	1.26 million	10.29	0.4-0.7	No information available	No Rett parent association registered with RSE
Finland	5.27 million	10.35	1.8-3.0	60 ^d (unofficial)	<i>Rett ry – Rett Finland (formerly Autistien ja Rett-henkilöiden Tuki ry, AURE ry)</i> Founded 1989 www.aure.fi
France	66.26 million	12.49	26.9-44.9	523 ^d	<i>Association Française du Syndrome de Rett (AFSR)</i> Founded 1988 https://afsr.fr
Germany	82 million	8.42	22.1-36.8	623 ^d	<i>Elternhilfe für Kinder mit Rett-Syndrom in Deutschland e.V.</i> Founded 1987 www.rett.de
Greece	11 million	8.8	3.1-5.1	No information available	<i>Άγγελοι γης ('Angels on Earth')</i> Founded 2011 www.rettgreece.gr Member of <i>Panhellenic Association of Rare Diseases</i>
Hungary	9.92 million	9.26	3.0-5.0	80 ^d	<i>Magyar Rett Szindróma Alapítvány</i> Founded 1995 www.rettszindroma.hu Member of <i>RIROSZ, National Association of Rare Diseases</i>
Iceland	317,350	13.09	0.14-0.23	2 ^d (verified through DNA analysis)	<i>Gudrun's Rett Syndrome Research Trust</i> Founded 2012 http://rettenglaryolasite.com
Ireland	4.83 million	15.18	2.5-4.1	No information available	<i>The Rett Syndrome Association of Ireland</i> Founded 2003 http://rettsyndrome.ie
Italy	61.68 million	8.84	17.7-29.4	660 ^e	<i>Associazione Italiana Rett (AIRETT)</i> Founded 1990 www.airett.it
Latvia	2.17 million	9.79	0.7-1.2	No information available	No Rett parent association registered with RSE
Lithuania	3.51 million	9.36	1.1-1.8	No information available	No Rett parent association registered with RSE <i>Lietuvos autizmo asociacija "Lietaus vaikai" (Lithuania Autism Association)</i> offers support to families Founded 2013 www.lietausvaikai.lt

(Continues)

Table 1. (Continued)

Country ^a	Population ^b	Birth rate per 1,000 population ^b	Estimated number of girls born per year with RTT ^c	Number of families/individuals known to have RTT (approximate in some cases) ^{d,e}	Parent association name & website
Luxembourg	521,000	11.75	0.2-0.3	No information available	No Rett parent association registered with RSE <i>Autisme Luxembourg asbl</i> offers support to families Founded 1981 http://www.autisme.lu <i>ALAN – Rare Diseases Luxembourg</i> also supports families Founded 1998, rare disease included from 2005 http://www.alan.lu
Malta	412,655	10.24	0.1-0.2	4 ^d	No Rett parent association registered with RSE
Netherlands	16.88 million	10.83	5.9-9.9	175 ^d	<i>Nederlands Rett Syndroom Vereniging (NRSV)</i> Founded 2008 www.rett.nl <i>Stichting Terre - Dutch Rett Syndrome Foundation</i> Founded 2008 www.stichtingterre.nl
Norway	5.15 million	12.09	2.01-3.36	130 ^d	<i>Norsk Forening for Rett Syndrom</i> Founded 1987 www.rettmynd.no
Poland	38.35 million	9.77	12.1-20.2	70 ^d	<i>Ogólnopolskie Stowarzyszenie Pomocy Osobom Z Zespołem Retta (OSPOzZR)</i> Founded 1997 http://rettsyndrome.pl
Portugal	10.81 million	9.42	3.3-5.5	No information available	<i>Associação Nacional de Pais e Amigos Rett (ANPAR)</i> Founded 2002 http://anpar.planetaclix.pt
Romania	21.73 million	9.27	6.5-10.9	16 ^e	<i>Asociația "Un inger pentru ingeri" ("An angel for the angels")</i> Founded 2013 www.asociaiauningerpentruingeri.ro
Slovakia	5.44 million	10.01	1.8-2.9	30 ^d	<i>Rett Slovakia (Nadacia pre pomoc ľuďom postihnutým Rettovým syndrómom-Slovensko)</i> Founded 2002 No website
Slovenia	1.99 million	8.54	0.6-0.9	No information available	<i>Tihi angeli ("Quiet angels")</i> - not currently active
Spain	47.74 million	9.88	15.2- 25.3	426 ^e	<i>Asociación Española de Síndrome de Rett</i> Founded 1992 www.rett.es <i>Asociación Catalana del Síndrome de Rett</i> www.rettcatalana.es Members of the <i>Spanish Federation of Rare Diseases</i>
Sweden	9.72 million	11.92	3.8-6.3	250 ^d	<i>Rett syndrom i Sverige (RSIS)</i> Founded 1997 www.rsis.se
UK	63.74 million	12.22	25.3-42.2	255 ^e	<i>Rett UK</i> Founded 1985 http://www.rettuk.org Member of <i>Rett Disorders Alliance of the UK</i> Founded 2015 Includes: <i>Rett UK, Reverse Rett, Cure Rett, Reverse MECP2, FOXP1 UK, CDKL5 UK, Rett Education UK</i>

Additional information on each country (including details of parent association activities) can be accessed via the parent association websites as listed in this table or via the website of *Rett Syndrome Europe* (<http://www.rettysyndrome.eu/association-rse/europe/>). In addition, the slides which were presented by national parent associations during the 'Country Updates' sessions of ERSCM2013 can be accessed via: <http://www.rett.nl>

^aCountries are arranged in alphabetical order. Liechtenstein is not included.

^bCountry population as of mid-2014, annual crude birth rate, and sex ratio at birth are all taken from: <http://www.indexmundi.com/europe.html>.

^cAdjusted per country according to sex ratio at birth (varying between 1.04-1.07 male(s)/female) and calculated to show upper and lower potential limits taking into account an estimated incidence of Rett syndrome as 1 per 9,000-15,000 live female births.

^dNumbers of 'known' individuals/families as reported by the national parent associations.

^eNumbers of individuals registered on the Rett Database Network as of September 2015 (shown where numbers of 'known' individuals were not available through the parent association), see: <https://www.rettbasenetwork.org/>.

Table 2. Overview of centres of expertise and hospitals providing diagnosis, medical care and advice for Rett syndrome in EU & EEA Member States

Country ^a	Overview of experts and/or expertise centres
Austria	Expertise centre for RTT: under development Diagnosis and medical care/advice: Departments of Medical Genetics and Paediatric and Adolescent Neurology, Medical University of Vienna, in cooperation with other specialists/clinics Research: Medical University of Graz
Belgium	Diagnosis, medical care/advice: Centre for Developmental Disabilities, University Hospital, Leuven follows up all rare diseases and disorders with developmental delay, other University Hospitals across Belgium offer support for epilepsy, scoliosis, nutrition Second opinions/medical care/advice: Rett Expertise Centre Maastricht (Netherlands) may be consulted
Bulgaria	Diagnosis, medical care/advice: Paediatric Neurology Clinic of St Nahum Hospital in Sofia
Croatia	Diagnosis – Institute Rudjer Boskovic and the Children's Hospital Zagreb Medical care/advice – Centre of Expertise for Congenital Disorders at the Children's Hospital, Zagreb, and Neuropaediatric Departments of the Clinical Hospitals in Zagreb, Split, Osijek and Rijeka
Cyprus	Diagnosis, medical care/advice, research – Makarios Children's Hospital and Cyprus Institute of Neurology and Genetics
Czech Republic	Diagnosis, medical/paramedical care and advice – University Hospital of Motol, Prague A few schools/day care centres offer education and consultancy specific to RTT
Denmark	Expertise centre for RTT – Danish Centre for Rett Syndrome (part of the Kennedy Centre at Glostrup) http://www.kennedy.dk Diagnosis, medical/paramedical care, advice, research – multidisciplinary team in Glostrup, in cooperation with local hospitals
Estonia	Diagnosis and medical care/advice – consultant at Tartu University Hospital, Children's Clinic
Finland	Diagnosis - Child neurology departments at university hospitals across Finland (rare disease expertise centres will be established at all university hospitals, currently available at Helsinki University Central Hospital and in Turku) Medical care/advice – child neurologist with a special interest in RTT at Children's Hospital of Helsinki, basic health care provided by hospitals across Finland, Government-funded therapy provided weekly according to each individual's personal rehabilitation plan
France	Expertise centre for RTT – due to open at Necker Enfants Malades in Paris in 2015 Diagnosis, medical/paramedical care, advice, research – a range of experts/teams at various hospitals across France, e.g. hospitals in Paris, Marseille, Douai, Nancy, Tours, Barr, Bordeaux, Dijon
Germany	Diagnosis, medical care/advice – clinics in Kassel, Göttingen and Langen-Depstedt
Greece	Diagnosis, medical care/advice – several doctors across Greece have an interest in RTT
Hungary	Diagnosis and research – Rett Centre/Medical Genetics, University of Pécs <i>PART</i> and <i>DROP</i> programmes for families (therapy and education) and professionals (professional development/training) arranged by parent association
Iceland	Expertise centre for RTT – State Diagnostic and Counselling Centre (SDCC) http://www.greining.is Diagnosis, medical care/advice – collaboration between SDCC, neurology department of the Children's Hospital, and Benefit Society for Children with Disabilities
Ireland	Diagnosis – National Centre for Medical Genetics, Dublin Medical care and advice – hospitals across Ireland offer general support, some families seek more specific assessment and advice from UK Rett clinics
Italy	Expertise centres for RTT – Genoa, Milan, Rome, Siena, Messina Diagnosis, medical care/advice, research – range of consultants and researchers at centres in Genoa, Milan, Rome, Siena, Messina Founding member of ESRRRA
Latvia	Diagnosis, medical care/advice – Children's Clinical University Hospital, Riga is the only hospital in Latvia that offers specialised multi-disciplinary treatment and care for rare diseases, the Medical Genetics Department provides genetic testing and counselling across all ages
Lithuania	Diagnosis – Coordinating Centre for Rare Paediatric Diseases, Children's Hospital Vilnius Medical care and advice – Child Development Centre, Vilnius and hospitals across Lithuania offer general support
Luxembourg	Diagnosis, medical care and advice – neurologist at Centre Hospitalier de Luxembourg, supported by experts in neighbouring countries e.g. Rett Expertise Centre Maastricht (Netherlands), CHU de Liège (Belgium)
Malta	Diagnosis, medical care/advice – included within Malta's National Care for Disabled Persons (KNPD) Education/therapy – <i>INSPIRE</i> Foundation offers holistic programmes and services to children and adults with various disabilities http://inspire.org.mt
Netherlands	Expertise centre for RTT – Rett Expertise Centre Maastricht, national reference centre recognised by the Dutch government http://gkc.daily-cms.com/pages/Rett_syndroom Diagnosis, medical care/advice, research – multidisciplinary team in Maastricht in cooperation with other (University) Hospitals and local teams Founding member of ESRRRA

(Continues)

Table 2. (Continued)

Country ^a	Overview of experts and/or expertise centres
Norway	Expertise centre for RTT – Frambu Resource Centre for Rare Disorders (national resource centre for people with rare disorders and disabilities) http://www.frambu.no/rettps-syndrom Diagnosis, medical care/advice and research – multidisciplinary team at Frambu
Poland	Diagnosis – Medical Universities in Bialystok, Warsaw, Krakow Medical care/advice – provided by centres for general disabilities (e.g. cerebral palsy, autism) with a (small) number of medical specialists who have an interest in RTT based in University Medical Centres across Poland
Portugal	Diagnosis, medical care/advice – Paediatric neurology departments of Hospital de Santo Antonio, Porto (also provides second opinions) and hospitals in Coimbra and Lisbon
Romania	Diagnosis – Carol Davila University of Medicine, Bucharest or hospitals in other countries e.g. Bulgaria, Hungary, Spain Medical care/advice – Paediatric Neurology Department of Carol Davila University manages seizures, hyperventilation problems, kinetic and psychotherapy programmes, other hospitals across Romania offer general support
Slovakia	Diagnosis – Comenius University Hospital in Bratislava or via University Hospital of Motol, Prague (Czech Republic) Medical care/advice – hospitals across Slovakia offer general support
Slovenia	Diagnosis, medical care/advice – Department of Child, Adolescent and Developmental Neurology, University Children’s Hospital, Ljubljana sees all cases of RTT and organises further therapies through local hospitals/teams
Spain	Expert centre for RTT – Hospital Sant Joan de Deu in Barcelona Diagnosis, medical care/advice and research – child neurologists and local teams at hospitals across Spain, in cooperation with Sant Joan de Deu
Sweden	Expertise centre for RTT – Swedish Rett Centre in Östersund www.rettcenter.se Diagnosis, medical care/advice and research – multidisciplinary team at Östersund, in cooperation with other hospitals/local teams Founding member of ESRRRA See also – Ågrenska, National Competence Centre for Rare Diseases http://www.agrenska.se
UK	Expertise centres for RTT: under development Diagnosis, medical care/advice and research – specialist multidisciplinary RTT clinics in London, Manchester, Nottingham and Cardiff, in cooperation with local hospitals/teams Founding member of ESRRRA

The information presented in this table is as reported by the national parent associations during ERSCM2013, with additional information taken from the websites of the national parent associations and/or representatives from the countries (as of September 2015). Further updates on the current situation in each country can be accessed through the website of the relevant parent association (addresses shown in Table 1), any of the websites listed in this table, or the website of *Rett Syndrome Europe* (<http://www.rettps-syndrom.eu/association-rse/europe/>).

^aCountries are arranged in alphabetical order. Liechtenstein is not included.

All of the European parent associations listed in Table 1 exist to offer support and networking opportunities for families of individuals with RTT. They also see that they have an important role in disseminating information and raising awareness of RTT, both in keeping families up to date with new advances in research and in increasing the knowledge of professionals in their countries. The majority of associations are volunteer-led by parents and other family members; a few of the larger organisations are able to fund administrative and, occasionally, support staff to bolster and extend the work of the parents. In some cases, they are also in a position to fund research or even to support centres of expertise with funding. All but one of the existing parent associations host websites as a medium for sharing information and most use social media such as Facebook as a support mechanism.

Furthermore, a number of countries benefit from Rett foundations or research trusts which may exist in place of or in addition to the national parent association. The focus of such organisations is to raise funds for and to promote basic and applied research in relation to the treatment and cure of RTT. For example: in the Nether-

lands, the Stichting Terre-Dutch Rett Syndrome Foundation and in Iceland, Gudrun’s Rett Syndrome Research Trust, whilst in the UK, the Rett Disorders Alliance of the UK was formed in July 2015, a collaboration of organisations working with and for the benefit of RTT and RTT-like disorders. This alliance comprises: Rett UK, Reverse Rett, Cure Rett, Reverse MECP2, FOXP1 UK, CDKL5 UK, and Rett Education UK. International collaborations are also evident. For example, Reverse Rett (formerly Rett Syndrome Research Trust UK) works in partnership with the US-based Rett Syndrome Research Trust and Cure Rett is in partnership with rettsyndrom.org in the US.

Databases and registries

Several European countries have some form of national database or registry specifically for RTT, for example, France, Italy, Portugal, Spain, UK¹. These and others also contribute to larg-

¹Some of these registries are listed on Orphanet: [http://www.orpha.net/consor/cgi-bin/ResearchTrials_RegistriesMaterials.php?lng=EN&type_list=researchtrials_search_simple_shd&data_id=91&Disease\(s\)/group%20of%20diseases=Rett-syndrom&search=ResearchTrials_RegistriesMaterials](http://www.orpha.net/consor/cgi-bin/ResearchTrials_RegistriesMaterials.php?lng=EN&type_list=researchtrials_search_simple_shd&data_id=91&Disease(s)/group%20of%20diseases=Rett-syndrom&search=ResearchTrials_RegistriesMaterials)

er European or international RTT databases, for example, the Rett Database Network (<https://www.rettbasenetwork.org>) and/or InterRett (<http://www.aussierett.org.au/>). As of September 2015, the Rett Database Network held information on just over 2,000 individuals from 14 countries across Europe and further afield.

In addition, a number of mutation databases exist, which, in the era of 'next generation sequencing' (NGS) [40] are invaluable in contributing to an understanding of the biology associated with rare diseases such as RTT [41]. One such database to which a number of European (and other) countries contribute is RettBase, a MECP2 variation database, initiated by John Christodoulou and colleagues (<http://mecp2.chw.edu.au/>) [42]. Recently, information from this database has been incorporated into LOVD 3.0 (Leiden (open) Source Variation Database, <http://www.lovd.nl/3.0/home>) [43], a locus-specific database which seeks to connect NGS-driven collections built upon whole exome - and whole genome sequencing, such as ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>) and EVS (<http://evs.gs.washington.edu/EVS/>), and global initiatives such as the Global Alliance for Genomics and Health (<http://genomicsandhealth.org>).

LOVD's capability to include phenotypic HPO-based information is also considered to be one of its strengths (<http://human-phenotype-ontology.github.io/about.html>).

Wishes and future aims of the European parent associations

In general terms, all parent associations express a wish for early diagnosis and better medical, therapeutic and care services, increased support for families and increased dissemination and application of evidence-based knowledge in order to improve quality of life for individuals with RTT and their families. All families ultimately hope for a 'cure' for RTT.

In more specific terms, they call for further research and funding for research into areas such as epilepsy, scoliosis, brainstem dysfunction, genetics and stem cell research. Several associations hope for increased recognition of the syndrome within the health insurance system and for increased funding to enable the buying or renting/loan of medical equipment and communication aids. There is also a desire expressed by all associations for collaboration with and between scientific researchers, increased contact and networking between national parent associations, collaboration between Rett expertise centres in different countries and the establishment of national centres of expertise in countries where they do not currently

exist. Furthermore, they advocate for the building up of pan-European specialist networks, linking medical experts and therapists within and between countries and facilitating the training and recruiting of specialists in countries where they are currently lacking.

European policy on rare diseases

Of particular relevance at the time of ERSCM2013 were the provisions for the creation of 'European reference networks' (ERNs) written into Articles 12 and 13 of the 2011 Cross-Border Healthcare Directive (Directive 2011/24/EU)², which built on earlier recommendations made by the Council of the European Union for Member States to develop their own national plans for rare diseases³. Quality criteria for 'Centres of Expertise for Rare Diseases' were also provided by the European Union Committee of Experts on Rare Diseases (EUCERD) in 2011⁴, following which core indicators for the aforementioned national plans/strategies⁵ and further recommendations for RD patient registration and data collection⁶ and for Rare Disease ERNs⁷ were released by EUCERD in 2013. Included in these recommendations was recognition of the integral role of patient/parent organisations.

It was in support of these policy developments, as well as to convey the more specific wishes of the Rett parent associations as outlined above, that the joint statement aimed at the Directorate General for Health and Consumers Affairs of the European Commission was signed at the end of the third European Rett Syndrome Conference in October 2013.

Following publication of the European Commission's Delegated Decision (2014/286/EU)⁸ and Implementing Decision (2014/287/EU)⁹ in March 2014, further clarification on the structure of RD ERNs was provided through a EUCERD joint action workshop set up to review progress in Member States in October 2014¹⁰. During this meeting, the suggested grouping of rare diseases within the new structure of ERNs was first promulgated and in June 2015 the final decision of the EC Expert Group on Rare Diseases¹¹

²See <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:en:PDF>

³Council Recommendation of June 8, 2009, on an action in the field of rare diseases (2009/C 151/02).

⁴See <http://www.EUCERD.eu/upload/file/EUCERDRecommendationCE.pdf>.

⁵See http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf

⁶See http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

⁷See http://www.eucerd.eu/?post_type=document&p=2207

⁸See http://ec.europa.eu/health/ern/docs/ern_delegateddecision_20140310_en.pdf

⁹See http://ec.europa.eu/health/ern/docs/ern_implementingdecision_20140310_en.pdf

¹⁰See http://www.eucerd.eu/wp-content/uploads/2015/02/WP8Workshop_ERN_2014.pdf

¹¹EUCERD's mandate ended in July 2013 and was replaced from 2014 by the EC

regarding “the grouping of RD into thematic networks and the necessity of a patient-centred approach to RD ERNs” (*Addendum*, p. 2) was published as an Addendum¹² to the EUCERD Recommendations of January 2013. According to these groupings RTT would most naturally seem to sit within an ERN for ‘Rare neurological diseases’ (*Addendum*, p. 8). A further account of recent developments in European policy and their implications for RTT can be found in Townend et al, 2015 [40] whilst a commentary on the challenges and opportunities to be offered by the development of ERNs can be found in Morciano et al, 2015 [44].

Discussion

The European Commission’s policy on rare diseases provides significant political leverage within the Member States of the EU in the quest to raise awareness, to promote research and develop a stronger knowledge base, and to provide more equitable, higher quality services and support for individuals and families affected by rare disorders like RTT. On its own it is unlikely that any rare disorder would be high on the agenda of a national government. The European Commission’s inclusion of rare diseases within Articles 12 and 13 of the Cross-Border Directive and the subsequent recommendations of EUCERD are, however, clear signals that minority health groups cannot and should not be ignored. Furthermore, pan-European collaboration between stakeholders – parents, professionals (clinicians, therapists, educators), researchers – is recognised as an integral and fundamental requirement. Within this context umbrella organisations such as ESRRA, as a collaboration of professionals and researchers, and RSE, as a collaboration of parents associations, have important roles to play whilst European (as well as international) conferences offer valuable opportunities for these groups to come together to engage in discussion and dissemination of latest research, treatment and management techniques. A commitment by all EU countries to the sharing of clinical data through pan-European (and/or international) registries/databases for rare diseases such as RTT is also a vital step in the collaborative endeavour.

There have been a number of attempts to construct (genetic) databases in relation to RTT, at country-based, European and international levels [42-43, 45-47]. Where these do exist they prove valuable sources of data for research purposes [21, 23, 24, 48-50]. At present, however, most countries are unable to report definitive figures for numbers of individuals diagnosed with RTT in their country. In part this is due to the fact that some individuals are diagnosed on the basis of clinical symptoms alone and some are diagnosed following genetic analysis. Even in the case

of genetic analysis there are a number of possible mutations and the accuracy of diagnosis may depend upon the test(s) that are performed. In any case, it is clear from studies which suggest the likely incidence and prevalence rates of RTT that there are large numbers of undiagnosed individuals in every country, even when services are relatively well-coordinated and the syndrome is well-known amongst the professional community. In the near future, however, the application of new molecular techniques such as whole exome- and whole genome sequencing, especially if applied to new-born bloodspot screening, may lead to the detection of MECP2 mutations even before the characteristic clinical features of Rett syndrome appear (<http://www.genomes2people.org/babyseqproject/>). Of course, the blanket application of such screening should only be considered if the early findings of the pilots are clinically actionable.

The reversal of the symptoms of RTT in mice has excited interest amongst families such that the ultimate goal in the minds of most families, and hence, most associations, is to find the ‘cure’. Some of the larger parent associations are in a position to contribute funding towards basic research in this area as well as being in a stronger position to lobby politically within their own countries for recognition of the syndrome. Families and associations are realistic, however, and recognise that a cure will not be forthcoming immediately. Thus they aim for a better quality of life for their children (of whatever age) in the here and now. This translates into parent associations acting as support networks for families, sharing knowledge and information, offering training where they are in a position to do so and pushing for the creation of centres of expertise and networks of knowledgeable and specialised professionals wherever possible. Few of the parent associations receive state funding and rely on fund-raising, donations and grants. The level to which this can be achieved naturally varies between countries, leading to disparities in services and support between countries. National parent associations gain strength in banding together to form a strong European network (as seen, for example, in RSE), both for lobbying purposes at a European level and as a practical way for countries to offer support to each other. The declaration signed by RSE and the conference organising committee on the final day of ERSCM2013 gave a clear signal that parents across Europe are united in their determination to see the ambitions of the European Commission policy on rare diseases, as well as their own specific wishes in relation to the treatment and cure of RTT, realised.

A co-ordinated European Reference Network for ‘Rare neurological diseases’, which includes RTT within its remit, will strengthen existing services for RTT, facilitate diagnosis, advice and support for individuals and families in countries which are currently under-resourced, and will allow for the referral of individuals between countries in order to seek diagnosis and treatment. In addition, the model established by the first four European Rett Syndrome Con-

Expert Group on Rare Diseases. The final meeting of the EUCERD Joint Action was on 15th September 2015.

¹²See http://ec.europa.eu/health/rare_diseases/docs/20150610_erns_eucerdaddendum_en.pdf

ferences, bringing together professionals and families to share updates on the most recent developments in research, treatment and management of RTT, has set an invaluable precedent which should be continued. Such pan-European collaborations can only be to the benefit of individuals with RTT and their families.

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