Short Communication

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Rett Syndrome as a Rare Disease: A European Perspective

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Rett Syndrome

Rett syndrome (RTT) is a rare neurodevelopmental disorder, which predominantly affects females. It results from a genetic mutation on the X chromosome, several forms of which have been identified, the most common occurring in the *MECP2* gene. Severity varies according to the specific mutation. The syndrome is typically characterised by seemingly normal development in the first months of life followed by a regression in skills that begins between 6 and 18 months of age. Individuals with RTT demonstrate a loss of motor and communication skills; they may develop severe breathing abnormalities, epilepsy and scoliosis. It is a severe, lifelong disorder, generally resulting in a shortened life expectancy.

Diagnostic Process

Rapid advances in DNA analysis, especially in 'next-generation sequencing' technology are significantly improving the diagnosis of rare Mendelian disorders, including those underlying various forms of severe intellectual disability (ID) [1, 2]. At present, over 500 genes are linked to ID, but these are likely to represent <50% of all genes involved. For this reason, several research groups have applied family-based diagnostic exome and, more recently, genome sequencing as an unbiased diagnostic approach for individuals with severe, unexplained ID. Their results confirm the hypothesis that 'de novo' mutations are the most important cause of severe ID. De novo mutations have also been reported to play an important role in related disorders such as autism, epilepsy and schizophrenia [3].

In less than 10 years, the advantages offered by such advances in diagnostic techniques and knowledge have become clear. Shifting from array-based comparative genomic hybridization (array CGH) to whole genome sequencing (WGS) was shown in 2014 by Gilissen et al. [2] to increase the diagnostic yield for individuals with severe ID, especially if used as a first-tier test. This is beneficial to the detection and, ultimately, treatment of so-called rare disorders, including RTT (fig. 1).

In the majority of individuals with RTT, mutations in the X-linked *MECP2* gene have been identified as the likely cause. Yet, even for the analysis of the *MECP2* gene, WGS may still offer advantages. In one individual, Gilissen et al. [2] identified a de novo CNV (Copy Number

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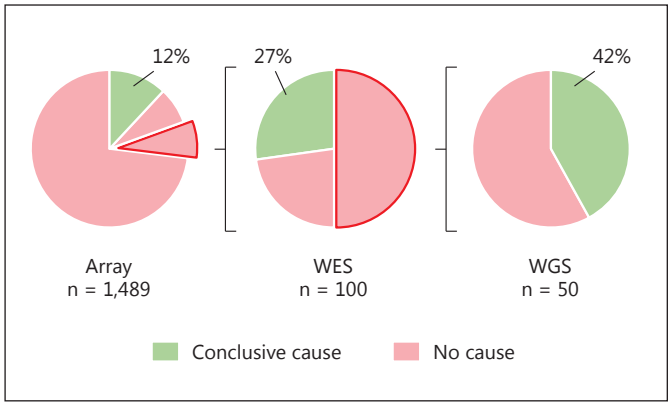

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Fig. 1. Diagnostic yield for patients with severe ID (IQ <50), specified by technology: genomic microarrays, WES (whole exome sequencing) and WGS. Percentages indicate the patients in whom a conclusive cause was identified using the specified technique. Brackets indicate the group of patients in whom no genetic cause was identified and whose DNA was subsequently analysed using the next technology. Reprinted with the permission of *Nature*.

Variation; an intra-exonic deletion) in exon 4 of the *MECP2* gene. This deletion had not been detected previously even though a clinical suspicion of RTT had indicated both Sanger sequencing and MLPA (Multiplex Ligation-dependent Probe Amplification) screening, both of which proved negative in this case. This observation in a single individual confirms the power of WGS. Alongside the promise of potential benefit, however, the clinical implementation of genomic sequencing opens up a whole debate about how to interpret causality of (rare) sequence variants, how to act upon 'incidental findings' and how to share results among researchers and clinicians as well as how to communicate these findings to the affected individuals and their families.

Rare Disease European Reference Networks and Centres of Expertise

In addition to genetic or molecular advances in recent years, there have been a number of important developments in Europe in relation to rare disorders. The 2005 Report of the High Level Group on Health Services and Medical Care [4] was fundamental in introducing the concepts of cross-border healthcare and of European networks of centres of reference, both of which have special relevance to rare disorders. Since then, these ideas have been further developed through the work of the European Commission's Rare Diseases Task Force (RDTF) and the European Union Committee of Experts on Rare Diseases (EUCERD).

In 2011, provisions for the development of 'European reference networks' (ERNs) were written into Article 12 of the Cross-Border Healthcare Directive (Directive 2011/24/EU) [5], where a specific reference is made to rare diseases. Article 13 also refers to the important relationship between ERNs, rare diseases and the availability of treatment across borders. Integral to the concept of ERNs is the intention that national, multidisciplinary 'centres of expertise for rare diseases' (CEs for RD) will be identified by Member States (MS) and their knowledge and expertise shared within the structure of ERNs. Quality criteria for such CEs were also specified by EUCERD in 2011 [6]. Both the European dimension of CEs and their function as 'key elements of the future ERNs' is stressed (p. 8).

More recently, in 2013, recommendations for Rare Disease ERNs (RD ERNs) were set out in greater detail by EUCERD [7]. RD ERNs are described as providing the 'framework for healthcare pathways for RD patients through a high level of integrated expertise' (p. 5) with nationally designated CEs as the 'core participants' (p. 5) working in 'collaboration with healthcare providers, laboratories, patients and individual experts within Member States and between Member States' (p. 2). The integral role of patient organisations is recognised in this. Despite the need for flexible structuring to accommodate differences between national healthcare systems and medical areas, certain core elements are prescribed. These include: the creation and use of disease registries; the development and sharing of good practice guidelines and common training and education tools, and the use of tele-expertise. Ultimately, it is suggested, patients will benefit from improvements in diagnosis, care and knowledge and the development of new therapies that can be facilitated through such exchange.

In order to add further substance to these recommendations, EUCERD also published recommendations for core indicators for national plans/strategies in relation to rare diseases in 2013 [8] as well as recommendations specific to RD patient registration and data collection [9]. The core indicators elaborate upon the Council of the European Union's 2009 recommendations[1] that MS develop their own action plans for rare diseases. Amongst other things, these recommendations support the requirement

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

for MS to create (or support) existing CEs for RDs, to participate in RD ERNs, to develop good practice guidelines for RDs and to build RD registries. The patient registration recommendations provide explicit details for MS on this latter topic.

In October 2014, EUCERD held a joint action workshop on the topic of RD ERNs and structural funding. The focus of the workshop was to review progress in MS to date. During the workshop, the heterogeneity of existing CEs and networks was addressed, and the idea of grouping RDs for future ERNs was agreed upon. In total, 25 clinical disease 'areas' were identified as a strategic starting point with one RD ERN per area, offering the 'concept of an EU system for RD ERNs within which all patients could find a home' [10] (p. 6). In this way, it was envisaged that variations between countries in size, population and medical models/approaches to RDs could be overcome.

European Rett Expertise Centres and Databases

In order for the RD ERNs to move from a paper-based concept to a working reality, and in preparation for the official call for ERNs expected in December 2015, it is important that CEs are established across Europe. The Rett Expertise Centre, Maastricht University Medical Centre, is one example of a recently-formed single-focus CE, hosted within the Governor Kremers Centre, which researches into other rare diseases such as Prader-Willi syndrome and Angelman syndrome. Based at the academic hospital and the University of Maastricht, the Rett Expertise Centre brings together specialists in fields such as genetics, (child) neurology, paediatrics, endocrinology, communication and orthopaedics. It has a particular interest in brainstem neurophysiology and offers inpatient facilities for, amongst others, orthopaedic surgery and cortico-bulbar assessment.

The Rett Expertise Centre Maastricht is a founding member of ESRRA, the European Scientific Rett Research Association [11], a collaborative European platform for research focusing on RTT.

At the time of writing, and according to information first shared by Rett parent associations during the third European Rett Syndrome Conference held in Maastricht in October 2013 (ERSCM 2013) [12], between five and ten European countries benefit to varying degrees from the services of a national Rett Expertise Centre or from specialised multidisciplinary Rett Clinics, some of which are housed within centres for rare diseases. Several European countries have one or more hospitals that can provide a diagnostic service, with one or two medical experts able to offer advice and clinical management specific to RTT. Other European countries have services for general disabilities, but no one specialised in RTT (for recent information on selected countries, see [13]). In these cases, the role of the national parent association, where one exists, is crucial in helping to raise awareness, disseminating information and knowledge, providing support for families and professionals and lobbying for change.

A number of European countries have some form of national database or registry for RTT, and/or may contribute to a larger European or international database such as InterRett or the Rett Networked Database. As of 2014, the Rett Networked Database contained information on just over 2,000 patients from 14 countries across Europe and further afield [14].

Implications for RTT of the European Policy of Rare Diseases

At the close of ERSCM 2013 in October 2013, the organising committee and *Rett Syndrome Europe* signed a joint statement declaring their support for the European Union policy on rare disorders and defining more precisely the wishes of the European parent organisations in relation to the care and cure of RTT. There is no doubt that the level and type of services and support offered to individuals and families with RTT across Europe are disparate and inequitable at all stages of the healthcare pathway, (pre)diagnosis onwards. A few MS are well served by knowledgeable and expert medical professionals and/or multidisciplinary expert centres, but a far greater number are not. Several countries have invested in a registry for RTT and contribute to a wider European or international database, but this is by no means a universal given and, with a rare disease, maximum benefit from sharing of data must surely be gained by all individuals/countries contributing to a shared registry. Parent organisations provide crucial information, advice, support and training for fellow parents and for professionals where they can. In some cases, they are in a position to fund research or even to support expert centres with funding. In other cases, the parent associations are run on a voluntary basis without dedicated funding and are limited in what they are able to offer.

For those families where expertise in RTT is minimal in their own country, European policy in relation to rare diseases offers hope for the future, in particular through the Cross-Border Directive and EUCERD recommenda-

tions for RD ERNs and for CEs. The Rett Expertise Centres that already exist, together with other skilled and knowledgeable teams and practitioners, are well placed for inclusion within the broader RD ERNs, which could operate both within and across MS. From the proposed ERN groupings, it would seem most logical to include Rett Expertise Centres, whether they are stand-alone centres or organised under an umbrella such as ESRRA, in group 5: 'Rare diseases of brain development and rare intellectual disabilities' [10] (table 1, p. 10). Coordinated RD ERNs, including RTT within their remit, would not only strengthen existing services for RTT but would also facilitate diagnosis, advice, support and treatments for individuals and families in countries that are currently under-resourced, as well as stimulating professional development and quality of care through the creation and sharing of clinical guidelines, models of best practice and training resources. Furthermore, referral of individuals for diagnosis and treatment between countries should be entirely possible.

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