Introduction
Diagnostic criteria of a disorder are its defining features, reflecting in many instances the etiology, pathophysiology, and evolution. This is the case of Rett syndrome (RTT), with a history of diagnostic criteria tracing the trajectory of our knowledge on the disorder. Our current view is that RTT is a neurodevelopmental disorder, and not a degenerative one, despite its temporal dynamics that includes periods of loss of function and, in many individuals, decline in abilities after childhood. During the 50 years since the initial description of RTT (Rett 1966), there has been an extraordinary gain in knowledge and awareness despite the relatively low prevalence of the disorder (Kaufmann et al. 2016; Percy 2016; Leonard et al. 2017). A major milestone was reached in 1999, with the report of the association between the majority of cases of RTT and mutations in \textit{MECP2} (Amir et al. 1999), the gene encoding the transcriptional regulator methyl-CpG-binding protein 2 (MeCP2) (Kaufmann et al. 2005). Despite this major achievement, the diagnosis of RTT remains a clinical one due to the imperfect correlation between genotype and phenotype (Neul et al. 2010). Identification of other genes as closely associated with some variations in RTT’s clinical presentation (Neul et al. 2010; Olson et al. 2015; Sajan et al. 2017), as well as the report of a wide variety of neuropsychiatric symptomatology in individuals with \textit{MECP2} mutations (Suter et al. 2014; Lombardi et al. 2015), have increased the complexity of the diagnostic criteria and classification of the disorder. The following sections cover key issues related to RTT’s diagnosis, classification, and evolution. Detailed information about symptomatology and genetic testing is provided in the respective chapters.

Overview of the clinical features of Rett syndrome
RTT is a complex, primarily neurological disorder. Its complexity derives from its wide range of neurological, behavioral, and systemic impairments and their dynamic evolution. Although developmental delay is usually the earliest abnormal feature in RTT, developmental regression (i.e. loss of acquired skills) is the defining feature (Hagberg et al. 1983, 1985, 2002; The Rett Syndrome Diagnostic Criteria Work Group 1988; Kerr et al. 2001a; Neul et al. 2010). The current diagnostic criteria specify and require the loss of expressive language and fine motor (i.e. hand) skills (Neul et al. 2010). Impairment in ambulation, another major diagnostic criterion, could also include the loss of this function (Foley et al. 2011). Decline in neurological function led to the label of dementia in the initial English literature description.
of the disorder (Hagberg et al. 1983); however, the course of RTT is not progressive and irreversible. Indeed, variable and usually incomplete recovery of lost abilities is also a characteristic feature of the disorder (Neul et al. 2014). While standard medical histories reveal relatively typical development during the first 6 months of life (Neul et al. 2010), research studies using more sensitive methods demonstrate that deviation from typical trajectory may be present earlier (Marschik et al. 2013).

In addition to abnormal developmental trajectories of motor and language function, presence of hand stereotypies is a hallmark feature of RTT (Carter et al. 2010) and, as such, it is included in the core diagnostic criteria (Neul et al. 2010). As in other neurodevelopmental disorders, the prevalence of seizures is high and, as for most features of RTT, their frequency and severity are quite variable (Nissenkorn et al. 2015; Tarquinio et al. 2017). Autistic behavior was one of the first identified features of RTT, highlighted in Hagberg and colleagues’ (1983) publication. Nonetheless, severe autistic features are not clearly present in every affected individual and, if identified, they tend to be restricted to the period of regression (Mount et al. 2003; Kaufmann et al. 2012). On the other hand, other behavioral abnormalities such as anxiety and mood instability seem to be common and present throughout the individual’s life (Mount et al. 2002a, b; Anderson et al. 2014; Barnes et al. 2015; Cianfaglione et al. 2015). At present, inappropriate laughing/screaming spells is the only behavior considered a supportive diagnostic criterion for atypical RTT. A variety of other neurological features are highly prevalent and a cause of concern in RTT. These include breathing abnormalities and bruxism mainly when awake, peripheral autonomic (vasomotor) disturbances, sleep problems, diminished response to pain, and abnormal muscle tone; all of these features are also included as supportive diagnostic criteria for atypical RTT (Neul et al. 2010).

In addition to the neurological and behavioral features listed above, systemic abnormalities are almost invariably present in RTT with the consequent substantial impact on functioning and quality of life. Some of these systemic features appear to be the result of primary neurological abnormalities, such as orthopedic problems secondary to abnormal muscle tone (e.g. scoliosis, kyphosis, contractures, and foot deformities). Other manifestations seem to represent autonomic nervous system abnormalities. Examples of these include gastroesophageal reflux, constipation, and cardiac rhythm disturbances (e.g. long QT interval) (McCaughey et al. 2011; Motil et al. 2012; Baikie et al. 2014). The role of MeCP2 in non-neurological function is exemplified by the high prevalence of osteopenia/osteoporosis in RTT (Jefferson et al. 2016). Indeed, MeCP2 seems to be involved in bone turnover (Blue et al. 2015; Ross et al. 2016), although nutritional status, decreased mobility, and use of antiseizure medications could also play a role in the development of abnormal bone density in individuals with RTT.

Finally, RTT is a growth disorder. Deceleration of head growth after the neonatal period, which results in average head circumference reduction of 20–25%, was recognized in the first descriptions of RTT (Nomura et al. 1984) and incorporated into its diagnostic criteria (The Rett Syndrome Diagnostic Criteria Work Group 1988). Nevertheless, growth disturbances are more global and include weight, height, and hand and feet size (Tarquinio et al. 2012). The latter abnormality is most likely to be also influenced by peripheral vascular
abnormalities. Orthopedic and growth abnormalities are included among the supportive diagnostic criteria for atypical RTT (Neul et al. 2010).

In summary, RTT is a complex neurodevelopmental disorder with a wide range of manifestations and high variability in clinical severity. Chapter 2 presents an overview of RTT in the context of the Natural History of the disorder. Other chapters in the Clinical section of the book cover in detail specific features of RTT and their management. The subsequent sections address how the intricate clinical picture of RTT has led to the current diagnostic criteria and how these may evolve in the next decades.

Evolution of diagnostic criteria
The history of the diagnostic criteria of RTT is illustrative of our evolving perspectives about the disorder. Initial descriptions already reported elements of current diagnostic criteria, such as developmental regression involving language and hand use, gait abnormalities (apraxia, ataxia) as well as hand stereotypies, but also included autistic behavior, acquired microcephaly, vasomotor disturbances, and seizures (Rett 1966; Hagberg et al. 1983). Efforts at developing formal clinical criteria ‘for research purposes’ began shortly after that. In 1985, Hagberg and colleagues published inclusion and exclusion criteria that began with the recognition of the almost exclusive female presentation of the disorder. Some concepts that emerged at this time and extended until recently included a typical pre- and perinatal period, typical head circumference at birth followed by early deceleration of head growth, and exclusion of individuals with perinatally acquired brain impairment. For the first time, loss of communication abilities and purposeful hand use along with gait abnormalities were required for the diagnosis (Hagberg et al. 1985). The 1988 revision of criteria did not introduce major conceptual changes, but relabeled the inclusion criteria as necessary diagnostic criteria and expanded the exclusion criteria. The only noticeable difference was the delineation of supportive criteria representing common but not obligatory features that could assist in the diagnosis (The Rett Syndrome Diagnostic Criteria Work Group 1988). Two more updates, one focused on case reporting and genetic testing (Kerr et al. 2001a) and the other a formal revision of diagnostic criteria (Hagberg et al. 2002) attempted to address the recent identification of MECP2 mutations in a substantial proportion of patients with RTT. The 2002 criteria continued to emphasize that the diagnosis of RTT is clinical and made minor changes to the criteria (e.g. delayed psychomotor development as an option under necessary criteria) for the common cases, termed classic or typical. A unique contribution of this publication was the acknowledgement of uncommon presentations, termed variants or atypical. It refined early attempts at delineating this type of RTT (Hagberg and Skjeldal 1994) by defining combinations of six main and 11 supportive criteria (Hagberg et al. 2002). The 2010 revision or current criteria built upon these valuable initial efforts, attempted to increase reliability and provide empirical evidence of its adequacy (Neul et al. 2010; Percy et al. 2010).

Current diagnostic criteria of Rett syndrome
As mentioned above, the diagnosis of RTT continues to be clinical and based on consensus statements. Despite the changes in criteria over the years (Hagberg et al. 1983, 1985, 2002;
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The Rett Syndrome Diagnostic Criteria Work Group 1988; Neul et al. 2010), many concepts have remained. The first is that developmental regression is a key feature, required (i.e. obligatory) in the current diagnostic criteria. The second is that there is a broad range of clinical severity that results in some individuals not displaying all the core features of RTT. Thus, two main clinical presentations are recognized: typical or classic, displaying all the core features; and atypical or variant, presenting some but not all the key features of the disorder. The current criteria, published in 2010 (Neul et al. 2010), is a simplified version of the previous one (Hagberg et al. 2002) and, in contrast to earlier diagnostic revisions, it was validated on a large cohort (Percy et al. 2010). It retains the concepts of necessary and supportive criteria, which are helpful for delineating all forms of RTT from other neurodevelopmental disorders. Its simplified scheme intended to facilitate a broader application, beyond neurologists and other specialists.

**Typical Rett Syndrome**

The diagnosis of typical RTT requires the common necessary criterion, presence of regression, plus four main criteria derived from the natural history of most individuals with the disorder: (1) regression of purposeful hand use; (2) regression of spoken language; (3) gait abnormalities; and (4) hand stereotypies (Neul et al. 2010; Table 1.1). Because the course of RTT is dynamic, including stabilization and potentially partial recovery of skills after the period of regression, a careful developmental history needs to be obtained.

With our increasing knowledge of the evolution of RTT, it has become clear that postnatal deceleration in head growth is not found in all individuals with typical course (Tarquinio et al. 2012). Therefore, this is no longer a necessary criterion. Nevertheless, as stated in the 2010 publication, it is a clinical feature that can alert a clinician to the potential diagnosis. Exclusion criteria were also simplified in the 2010 revision to any other primary cause of neurological dysfunction, either genetic or acquired. While individuals with pathogenic MECP2 mutations can also have a concurrent genetic disorder (e.g. trisomy 21, pathogenic mutations in the NF-1 gene), they do not present the typical evolution of RTT or that of the second entity. Consequently, they should be labeled as having atypical RTT if they meet the respective criteria. A second exclusion criterion for typical RTT remains and that is the presence of major deviations in typical development in the first 6 months of life. This does not exclude minor developmental abnormalities during this period, as retrospective use of videos and other approaches have revealed relatively common early mild deviations in communication or motor development (Einspieler et al. 2005; Marschik et al. 2013). As emphasized in the 2010 guidelines, this distinction is important since one of the atypical forms of RTT, termed congenital variant, is characterized by grossly atypical development from birth.

Sex is not an exclusion criterion for typical RTT, as a few males meet all criteria (Christen and Hanefeld 1995). Similarly, absence of MECP2 mutation or abnormality in another gene are not exclusionary criteria considering that there is still a small percentage of individuals with RTT who do not present with MECP2 mutations (e.g. 2.2% in Neul et al. 2014), and new sequencing techniques reveal other genes associated with typical RTT (Sajan et al. 2017). This issue is discussed in the ‘Genotype–Phenotype’ section below and in Chapter 3 on the Clinical Genetics of RTT.
TABLE 1.1

Current diagnostic criteria of typical and atypical Rett syndrome (RTT)

<table>
<thead>
<tr>
<th>Revised diagnostic criteria for RTT (Neul et al. 2010)</th>
</tr>
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<tbody>
<tr>
<td>Consider diagnosis when postnatal deceleration of head growth observed.</td>
</tr>
</tbody>
</table>

**Required for typical or classic RTT**

1. A period of regression followed by recovery or stabilization
2. All main criteria and all exclusion criteria
3. Supportive criteria are not required, although often present in typical RTT

**Required for atypical or variant RTT**

1. A period of regression followed by recovery or stabilization
2. At least two out of the four main criteria
3. Five out of 11 supportive criteria

**Main criteria**

1. Partial or complete loss of acquired purposeful hand skills.
2. Partial or complete loss of acquired spoken language (best acquired spoken language skill, not strictly the acquisition of distinct words or higher language skills).
3. Gait abnormalities: impaired (dyspraxic) or absence of ability.
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms.

**Exclusion criteria for typical RTT**

1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems with clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction.
2. Grossly abnormal psychomotor development in first 6 months of life to the point that normal milestones (acquiring head control, swallowing, developing social smile) are not met.

**Supportive criteria for atypical RTT** (counted if an individual has or ever had a clinical feature listed)

1. Breathing disturbances when awake
2. Bruxism when awake
3. Impaired sleep pattern
4. Abnormal muscle tone
5. Peripheral vasomotor disturbances
6. Scoliosis/kyphosis
7. Growth retardation
8. Small, cold hands and feet
9. Inappropriate laughing/screaming spells
10. Diminished response to pain
11. Intense eye communication – “eye pointing”

The current diagnostic guidelines eliminated the use of supportive criteria for the diagnosis of typical RTT because, as demonstrated by the large-scale validation study (Percy et al. 2010), they are not necessary. On the other hand, recognition of features commonly present in individuals with RTT is helpful in cases that do not follow the typical trajectory, as reported by the same study (Percy et al. 2010).
Increased awareness about RTT and greater availability of genetic testing for MECP2 mutations have emphasized the need for a clear delineation of the boundaries of the disorder. Diagnosing atypical or variant RTT has always been challenging. The 2010 revised criteria attempted to simplify the process and, at the same time, to add precision (Neul et al. 2010). The current guidelines use the same main criteria applied to typical RTT but with a lower threshold (i.e. developmental regression plus two or three of the four main criteria). This is complemented by supportive criteria that increase the certainty of a RTT profile. Evaluating loss of skills in individuals with limited or protracted early neurological development could be very difficult. This is further complicated by the presence, in some individuals of seizures since the first few months of life that make the differentiation between primary regression and post-epileptic changes very difficult. Despite all these issues, it is important to make the distinction between RTT, which is associated with developmental regression, and other disorders that have a relentless neurodegenerative course, or from other forms of intellectual disability. Nonetheless, these diagnostic challenges, in conjunction with the genetic diversity of atypical RTT, have raised the possibility of removing some subgroups of atypical RTT from the disorder’s spectrum.

Supportive criteria are helpful in the diagnosis of atypical RTT, but only as a group of features since individual symptoms could be present in either other neurodevelopmental disorders (e.g. diminished pain response, seen also in nonsyndromic autism spectrum disorder), or many neurological disorders (e.g. abnormal muscle tone). In sum, the 2010 criteria require that, in addition to a history of regression, individuals with atypical RTT must have at least two of the four main criteria and five of 11 supportive criteria (Table 1.1).

Atypical RTT is a heterogeneous entity. Although some specific clinical presentations or variants have long been recognized (see below), many patients are better defined as simply having a milder or more severe atypical RTT presentation. A recent study used scores on the Clinical Severity Scale, a commonly applied instrument of RTT clinical severity (Cuddapah et al. 2014), to divide individuals with atypical RTT into better function and poorer function categories (Neul et al. 2014). In addition to the developmental and neurological phenotype differences, the better function group had a close association to MECP2 mutations (92% vs 80.5% in the poorer function group), although lower than in those with typical RTT (97.8% in the same study). These genotype–phenotype profiles are in line with the characteristics of the variants described below (see also Fig. 1.1).

Three atypical/variant forms of RTT have been delineated: the preserved speech variant, the early seizure variant, and the congenital variant (Fig. 1.1). The preserved speech (Zappella) variant (Zappella 1992; Renieri et al. 2009) would correspond to the better function category, with milder clinical features as well as MECP2 mutations in the majority of individuals. The other two variants have a more severe clinical profile; therefore, the congenital (Rolando) and early seizure (Hanefeld) variants would be considered poorer function forms of atypical RTT (Hanefeld 1985; Rolando 1985). In both, MECP2 mutations have only rarely been identified. Indeed, the early seizure variant is closely linked to mutations in the CDKL5 gene (Artuso et al. 2010). A relatively larger number of individuals with CDKL5 mutations have been identified in genetic screens for epileptic (early onset)
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Variant forms of RTT

- Meets criteria for atypical RTT
- Assess for presence of clinical features of defined variant forms

<table>
<thead>
<tr>
<th>Preserved Speech Variant (Zappella variant)</th>
<th>Early Seizure Variant (Hanefeld variant)</th>
<th>Congenital Variant (Rolando variant)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td><strong>Clinical features</strong></td>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td>• Regression at 1–3 years, prolonged plateau phase</td>
<td>• Early onset of seizures</td>
<td>• Grossly abnormal initial development</td>
</tr>
<tr>
<td>• Milder reduction of hand skills</td>
<td>• Before 5 months of life</td>
<td>• Severe psychomotor delay</td>
</tr>
<tr>
<td>• Better retained hand use</td>
<td>• Infantile spasms</td>
<td>• Inability to walk</td>
</tr>
<tr>
<td>• Recovery of language after regression</td>
<td>• Refractory myoclonic epilepsy</td>
<td>• Severe postnatal microcephaly before 4 months</td>
</tr>
<tr>
<td>• Mean age of recovery is 5 years</td>
<td>• Seizure onset before regression</td>
<td>• Regression in first 5 months</td>
</tr>
<tr>
<td>• Single words or phrases</td>
<td>• Decreased frequency of typical RTT features</td>
<td>• Lack of typical intense “RTT” eye gaze</td>
</tr>
<tr>
<td>• Milder intellectual disability (IQ up to 50)</td>
<td></td>
<td>• Typical RTT autonomic abnormalities present</td>
</tr>
<tr>
<td>• Autistic behaviors common</td>
<td><strong>Molecular genetics</strong></td>
<td>• Small cold hands and feet</td>
</tr>
<tr>
<td>• Decreased frequency of typical RTT features</td>
<td>Mutations in MECP2 rarely found. Analysis for mutations in CDKL5 should be performed.</td>
<td>• Peripheral vasomotor disturbances</td>
</tr>
<tr>
<td>• Rare epilepsy</td>
<td></td>
<td>• Breathing abnormalities while awake</td>
</tr>
<tr>
<td>• Rare autonomic dysfunction</td>
<td></td>
<td>• Specific movement abnormalities</td>
</tr>
<tr>
<td>• Milder scoliosis and kyphosis</td>
<td></td>
<td>• Tongue stereotypies</td>
</tr>
<tr>
<td>• Normal head circumference</td>
<td></td>
<td>• Jerky movements of the limbs</td>
</tr>
<tr>
<td>• Normal height and weight in most</td>
<td></td>
<td><strong>Molecular genetics</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutations in MECP2 rarely found. Analysis for mutations in FOXG1 should be performed.</td>
</tr>
</tbody>
</table>

Fig. 1.1. Flow diagram of specific atypical (variant) forms of RTT. Reproduced from Neul et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol 68: 944–950 © 2010 with permission from John Wiley and Sons Ltd.

encephalopathy (Gursoy and Ercal 2016; von Deimling et al. 2017). Although the delineation of the phenotype associated with CDKL5 mutations is work in progress, there is substantial evidence for a distinctive neurodevelopmental disorder (Fehr et al. 2013). Characterization of the congenital variant, linked to FOXG1 mutations (Mencarelli et al. 2010), is still incomplete (Ma et al. 2016). However, as for CDKL5 mutations, data suggest that a clinical entity defined by mutations in FOXG1 and not phenotype deserves consideration.

**Early diagnosis**

Because MECP2 testing is included in the diagnostic work up of individuals with global developmental delay (Moeschler et al. 2014) or autism spectrum disorder (Schaefer et al. 2013), mutations are now identified in some individuals prior to any clear evidence of regression. Consequently, we recommend the diagnosis of ‘possible’ RTT should be given to individuals under 3 years old who have not lost any skills but present with clinical features suggestive of RTT. These individuals should be reassessed every 6–12 months for evidence of developmental regression. If regression manifests, the diagnosis should then be changed to definite RTT, either typical or atypical. However, if the child does not show any evidence of regression by 5 years, the diagnosis of RTT should be questioned since loss of skills is unusual after this age (Neul et al. 2010, 2014).

**Genotype–phenotype correlations and Rett syndrome diagnosis**

There is a strong but imperfect correlation between MECP2 mutations and phenotype. While most individuals with pathogenic mutations in MECP2 present with RTT, others
do not have the clinical features of the disorder. The phenotypical spectrum of MECP2 mutations includes, at one end, asymptomatic female carriers found in familial RTT, who have extreme skewing of their X chromosome inactivation that allows a typical development (Wan et al. 1999; Lombardi et al. 2015). At the opposite extreme are boys with MECP2 mutations known to cause typical RTT in girls, but presenting with severe early postnatal encephalopathy, early death, and absence of the distinctive clinical features of RTT (Wan et al. 1999; Kankirawatana et al. 2006). There are also multiple reports of rare individuals with MECP2 mutations who present with other neurodevelopmental or neuropsychiatric disorders, including autism spectrum disorder (Carney et al. 2003; Li et al. 2005; Campos et al. 2011), Angelman syndrome-like presentation (Watson et al. 2001), attention-deficit–hyperactivity disorder (Adegbola et al. 2009), nonspecific intellectual disability (Grozeva et al. 2015; Bianciardi et al. 2016), bipolar disorder (Klauck et al. 2002), and schizophrenia (Cohen et al. 2002). Although most of these individuals have developmental abnormalities, they lack features that characterize RTT, including the defining one, a history of regression. These clinical phenotypes emphasize that mutations in MECP2 are not synonymous with RTT and that a mutation in MECP2 is not sufficient to make the diagnosis of RTT. In 2010, we proposed that all individuals with clinical disorders and MECP2 mutations be called MECP2-related disorders, which includes RTT and other neurological conditions associated with MECP2 mutations (Neul et al. 2010).

As mentioned in the preceding section, typical RTT has the strongest association with MECP2 mutations, followed by the milder forms of atypical RTT, with the lowest proportion of MECP2 positive individuals in the severe presentation of atypical RTT. Since the publication of the current diagnostic guidelines (Neul et al. 2010), efforts at applying newer genetic methods such as whole exome sequencing (i.e. coding regions) to identify the bases of mutation negative cases have narrowed the MECP2-RTT gap. These studies have also tested the limits of the RTT’s phenotypical profile by investigating the relationship between RTT-related features, beyond the diagnosis of RTT, and mutations in MECP2 and other genes. They have confirmed the preferential association between typical RTT and MECP2 mutations (Olson et al. 2015; Sajan et al. 2017). However, these studies have also found in individuals with typical RTT mutations in genes involved in chromatin regulation, neuronal homeostasis, and synaptic activity (Lucariello et al. 2016; Sajan et al. 2017). These investigations have also reported the association of atypical RTT with mutations in genes implicated in chromatin regulation, glutamatergic and GABAergic function, or synaptic ion channels (Lucariello et al. 2016; Sajan et al. 2017), some of them previously reported in other neurodevelopmental disorders (e.g. TCF4, linked to Pitt-Hopkins syndrome). As expected, mutations in genes linked to epileptic encephalopathy tend to be found in individuals with early onset seizure variant (Sajan et al. 2017). Interestingly, Olson and colleagues (2015) reported that females showing some RTT features but not meeting all criteria for atypical RTT could have abnormalities in the same genes found to have sequence abnormalities in RTT (i.e. IQSEC2, SCN8A, FOXG1). All these studies have shown that sequencing techniques fail to identify mutations in a small proportion of individuals with typical or atypical RTT. Higher resolution analyses of copy number variations and sequencing of noncoding regions have rarely been applied to RTT.
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Thus, in the future, the proportion of mutation negative RTT cases will be most likely to decrease further.

The aforementioned studies highlight the close but not absolute association between \textit{MECP2} mutations with typical RTT and the greater variety of genetic abnormalities in atypical RTT, particularly in the more severe cases, which appear to extend to individuals with borderline features of RTT. Despite this complex picture, genotype–phenotype correlations are relatively consistent for individuals with RTT and \textit{MECP2} mutations. Distinctive profiles of severity can be identified for each common \textit{MECP2} mutation (Bebbington et al. 2008; Neul et al. 2008), which are more evident when examining longitudinal trajectories (Cuddapah et al. 2014). The 2010 publication on diagnostic criteria also includes a section on nomenclature, focused on \textit{MECP2} mutations (Neul et al. 2010).

More detailed information about diagnostic issues and clinical presentation, with emphasis on genetics, can be found in Chapter 3 on the Clinical Genetics of RTT and Chapter 4 on Genetic Sources of Variation in RTT.

Rett syndrome spectrum vs \textit{MECP2} spectrum

The continuous progress in the delineation of the features of RTT, and their relationship with specific genetic abnormalities, has raised the question about the existence of more than one disorder under the RTT umbrella. Typical RTT with \textit{MECP2} mutation would constitute the ‘core’ disorder of this spectrum (i.e. some propose the term RTT disorder for these individuals; Kerr et al. 2001b), which would also include atypical RTT presentations linked to other genes, and even individuals with most but not all diagnostic features of RTT (e.g. one main criterion plus six supportive criteria). An easily identifiable common manifestation of the RTT spectrum would be hand stereotypies. An advantage of this approach would be the interpretation of genetic findings, already reported in RTT and in individuals who do not meet RTT criteria (Olson et al. 2015). On the other hand, the value of a RTT spectrum is already questioned for most individuals with \textit{CDKL5} or \textit{FOXG1} mutations who do not present with RTT-like features. In these instances, a diagnosis based on genotype similar to that of fragile X syndrome (Hagerman et al. 2009) seems more sensible. The development of targeted therapies based on the primary genetic defect, as the case of \textit{MECP2} deficit mutations (Kaufmann et al. 2016), further supports the rationale for separating some groups of atypical RTT from the spectrum.

The identification of \textit{MECP2} duplications, with a relatively distinctive clinical presentation quite different from RTT (Van Esch 2012) and a pathophysiology linked to increased MeCP2 function, has led to the proposal of a \textit{MECP2} spectrum of disorders (Lombardi et al. 2015). As for the RTT spectrum, there are advantages and shortcomings of this classification. While a \textit{MECP2} disorders category would help to understand the effect of gene dosage upon neural function, and the consequent development of MeCP2-focused treatments, other practical diagnostic and management applications are less clear.

In future years, the greater ability to identify \textit{MECP2} pathogenic mutations prior to the development of overt neurodevelopmental abnormalities will test the current diagnostic criteria of RTT. In addition, sensitive sequencing techniques are revealing an increased number of variants of unknown significance and even multiple genetic abnormalities, which
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require careful interpretation in the clinical context. This is particularly difficult in individuals with atypical RTT since many of their manifestations are relatively non-specific. Although in the distant future, newborn screening for MECP2 mutations will be the ultimate challenge for the concept of RTT.

Conclusion

The continuous expansion of our knowledge on RTT, MECP2, and related disorders has already required several revisions of diagnostic criteria. Fifty years after its original description, and 15 years after the association of MECP2 mutations with RTT, the diagnosis of RTT remains clinical and challenges to the delineation and classification of RTT variants have arisen. The 2010 diagnostic criteria are the first with some level of validation in RTT; however, their eventual obsolescence is already anticipated by the emergence of new entities (e.g. CDKL5 disorder) and the increasing complexity of the genetics of RTT. It is important to remember the multiple implications of a diagnosis, including clinical practice, epidemiology, and research. However, the ultimate goals of a diagnosis are management and prognosis. Any future revision of RTT diagnostic criteria needs to take these factors into consideration. A similar mechanism to the one used in the generation of the 2010 criteria, through RettSearch or another authoritative group, followed by an assessment of the guidelines in an appropriate clinical sample will certainly be necessary. The constitution of a permanent entity updating RTT-related criteria and nomenclature may even be needed. Diagnostic confusion cannot only have negative impact upon research endeavors, but also on clinical management decisions and patient identity.

REFERENCES

The Diagnosis of Rett Syndrome


Rett Syndrome


The Diagnosis of Rett Syndrome


