Syndrome of the month

Rett syndrome

Angus Clarke

The Rett syndrome (RS) was first described in 1966 by Andreas Rett,^{1,2} who published the first English language account of the condition in 1977 as "Cerebral atrophy with hyperammonaemia".³ Rett syndrome became better known in English language publications when Hagberg *et al*⁴ described 35 affected girls in 1983. The incidence or prevalence among females has been estimated as 1 in 10-15 000 (incidence) in Scotland,⁵ 1 in 15 000 (prevalence) in Sweden,⁶ 1 in 20 000 (prevalence) in Dakota, USA,⁷ and 1 in 22 800 (prevalence) in Texas, USA.⁸ RS therefore accounts for 2-3% of severe mental handicap^{9,10} and perhaps 10% of profound handicap in females. Despite its importance, however, the pathogenesis of RS remains obscure. It is most likely to be an X linked dominant disorder, lethal in hemizygous males, but this is not certain and has been contested.

Key words: Rett syndrome.

Clinical features (fig 1)

Affected girls are often considered to have developed normally in utero and for the first 6 to 18 months, and then their development slows and arrests. A period of regression and social withdrawal ensues that may persist for many months. The onset of the regression may be dramatic or insidious, and the loss of purposeful hand use and of spoken words are important features.¹¹ The presence of non-specific circulating hand-mouth movements and of signs of truncal instability may also suggest the diagnosis of RS.¹² Following the regression, social contact returns and progress can be made in the learning of limited skills; however, girls affected by the classical form of RS remain profoundly mentally handicapped, and many develop progressive physical problems such as scoliosis and spasticity. Many affected girls also have behavioural and emotional problems, including anxiety, low mood, and self-injurious behaviour.¹³ If they had any speech before the period of regression, affected girls will sometimes utter a word or phrase, and occasionally this is in an appropriate context; however, there is virtually no useful speech.

There is a set of diagnostic criteria that is very helpful in assessing patients who may have RS,^{14,15} which is summarised in table 1. The staging system devised by Hagberg and Witt-Engerstrom is also most useful (table 2).¹⁴⁻¹⁶

RS is not associated with specific dysmorphic features, but shortening of the fourth metatarsal bilaterally has been noted in nine of 50 British cases,¹⁷ although it is not known whether this feature is congenital or progressive with age. Growth is characterised by an early deceleration of head growth (leading to frank microcephaly in some cases) and a subsequent deceleration in linear growth leading to short stature by later childhood.¹⁸

The disordered breathing of RS girls is present only during wakefulness, typically with episodes of hyperventilation followed by central apnoea. The hyperventilation is not preceded by hypoxaemia, which only develops as a consequence of the central apnoea, and can result in a marked respiratory alkalosis.^{19,20} Although sleep is not entirely normal in RS, hyperventilation is generally absent, and rapid eye movement (REM) sleep is more disturbed than non-REM sleep.^{20,21} In wakefulness, abnormal EEG records are associated with normal breathing, and hyperventilation is associated with a normalisation of the EEG. If a metabolic abnormality underlies the hyperven-

Figure 1 A girl with Rett syndrome aged 7 years. (Photograph reproduced with parental permission.)

Table 1 Summarised diagnostic criteria for Rett syndrome*

Necessary criteria	
Apparently normal prenatal and perinatal period	
Developmental progress within the normal range for the first 5 to 6 months	
Normal head circumference at birth, with deceleration in head growth thereafter	
Reduction or loss of acquired skills (onset from 3 months to 3 years), in particular:	
Purposeful hand use	
Vocalisation or speech (words)	
Communication	
Appearance of marked delay in development	
Acquisition of hand stereotypies	
Gait and truncal apraxia (by 4 years)	
Supportive criteria	
Breathing dysfunction	
Periodic apnoea during wakefulness	
Intermittent hyperventilation	
Breath holding	
Forced expulsion of air or saliva	
EEG abnormalities	
Slow waking background and intermittent rhythmical slowing (3-5 Hz)	
Epileptiform discharges, with or without clinical seizures	
Spasticity, later with muscle wasting/dystonia	
Peripheral vasomotor disturbance	
Scoliosis	
Growth retardation	
Hypotrophic, small, cold feet	
Exclusion criteria	
Evidence of prenatal onset of growth retardation or microcephaly	
Organomegaly or other evidence of a storage disorder	
Retinopathy or optic atrophy	
Existence of identifiable metabolic or other neurodegenerative disorder	
Acquired neurological disorder resulting from severe infection or head trauma	
Diagnosis remains tentative until 2-5 years.	

* Adapted from references 14 and 15.

Table 2 Clinical stages of Rett syndrome*

Stage I. Early onset stagnation	
Onset age 5-18 months	
Developmental progress delayed but still not significantly abnormal. Postural delay, hypotonia, and bottom shuffling are common	
Often only diagnosed in retrospect	
Duration: weeks or months	
Stage II. Rapid developmental regression	
Onset age 1-4 years, may be abrupt	
Loss of acquired skills (hand use, voice, communication, active play)	
Gross motor functions may be relatively preserved	
Temperament may change, and sometimes the girl is distressed, seemingly "toxic"	
Autistic features appear, including stereotypies	
Eye contact is often preserved	
Significant developmental delay and dementia become apparent	
Breathing irregularities and seizures may be noted	
Duration: weeks to months, possibly one year	
Stage III. Pseudostationary period	
Onset 2-10 years Some restoration of communication, "wake up" period	
Ambulation preserved, but unapparent, slow neuromotor regression	
Prominent hand apraxia/dyspraxia	
Seizures are common.	
Duration: years to decades	
Stage III/IV	
Describes girls whose regression has ceased but who are not ambulant. If a girl then learns to walk she is reassigned to stage III. If she is still unable to walk at age 10, she is reassigned to stage IV because she is unlikely ever to walk	
Stage IV. Late motor deterioration	
Onset when stage III ambulation ceases, often in teenage years, but may be at any age from 5 years	
Severe physical disability, wasting, spasticity, dystonia and bradykinesia, distal distortions	
Complete wheelchair dependency	
Duration: decades	
Subclassification of stage IV	
Stage IVA: previous walkers (ex-stage III)	
Stage IVB: never ambulant (ex-stage III/IV)	

* Adapted from references 14-16.

tilation in RS, it must be strictly localised within the central nervous system (see below). Alternatively, the origin of the hyperventilation could be cortical.²⁰

Defects of cortical function have been found in electrophysiological studies of motor cortex stimulation²² and of sensory evoked potentials.^{23 24} Other sites within the nervous system, however, are also affected. Nerve conduction studies and electromyography (EMG) suggest

a motor axonopathy, which could be a secondary feature, as well as involvement of the spinal cord and spinothalamic system.²⁵ The characteristic and progressive EEG changes in RS have been well described and reviewed.^{26 27} Girls with RS also have electrocardiographic anomalies that increase with age, longer rate corrected QT intervals and more T wave abnormalities.²⁸

Rett syndrome variants

In the absence of a biological marker for RS, the diagnosis has to be clinical, and investigations serve largely to exclude other possibilities. The accepted diagnostic criteria are provisional, but are important because they are essential for research into the basis of RS. It may be that some patients with similar histories, but who do not fulfil the strict criteria for classical RS, have the same underlying pathology. Equally, other patients with a similar phenotype may have very different underlying pathologies. Hagberg has described five possible variant forms of RS, however, and these need to be considered.

First, there are cases of apparently classical RS whose presentation is dominated by seizures and in whom the onset of illness may be earlier than normal (before 6 months).²⁹⁻³¹ Secondly, there are patients in whom regression is never clearly shown, but whose clinical picture is otherwise classical, so called congenital or precocious RS.^{31 32} Third, there are those cases in whom the regression has been later in childhood and more gradual than in classical RS, but who do develop clinical features typical of classical RS.³¹ Fourthly, there is "forme fruste" RS in which the clinical course is milder, incomplete, and protracted. Regression occurs at 1 to 3 years of age, but is not so severe as in classical RS; hand use may be preserved, and stereotypies may be minimal or atypical.^{31 32} The final possible variant form of RS to be considered is the "preserved speech" variant, but it is important to distinguish speech used purposefully as a form of communication from the infrequent and apparently purposeless uttering, out of context, of a few residual words learnt before regression. Some cases of "forme fruste" RS may have preservation of useful speech, while other, more classical cases may rarely utter a few inappropriate words. This variant, then, is not a distinct RS variant at all.^{31 33}

"Forme fruste RS" is an important entity for the geneticist because several families have been reported in whom one girl has classical RS and there is a sister or maternal aunt with this phenotype.^{34 35} Whether or not any of these RS variants have the same pathogenesis as classical RS is simply not known; all such variant cases should be clearly distinguished from classical RS if unhelpful confusions are not to occur, and if research into the basis of RS is not to be hindered.

Differential diagnosis

Regression of an apparently normal child with subsequent stabilisation, leaving the child severely damaged, is found in several circum-

stances apart from RS. Children with seizure disorders, such as infantile spasms associated with hypsarrhythmia, may show a similar clinical course.^{29–36} Two children with infantile seizures associated with tuberous sclerosis and with this type of clinical presentation have been described.³⁷ The Lennox-Gastaut syndrome and related seizure disorders may also need to be considered in the differential diagnosis.

Metabolic disorders such as ornithine carbamoyl transferase (OCT) deficiency in heterozygous females with variable hyperammonaemia may also present with an apparently similar clinical course, although in that condition regression will usually result from episodes of hyperammonaemic encephalopathy.³⁸

Girls with RS are often initially misdiagnosed as having autism, although this will be recognised as a misdiagnosis once the loss of motor skills and the severity of the handicap have become clear.^{5–39} Children with autism do lose speech and social skills, but their stereotypies often involve manipulation of objects with preservation of the pincer grasp, and they do not usually exhibit bruxism or respiratory irregularities.⁴⁰

Although these differential diagnoses are important, the most difficult assessment to make is of a young girl with possible RS who is still regressing. At that point, the differential diagnosis is much wider. The only abnormal features may be developmental delay, possible early features of regression, and some autistic behaviours. Other conditions to be considered in such a differential diagnosis may include disorders of amino acid and organic acid metabolism (including glutaric aciduria), the neurovisceral storage disorders, acute or chronic encephalitis, mitochondrial cytopathy, ataxic cerebral palsy, and Angelman syndrome. During this stage of regression, the diagnosis of RS has to remain provisional and is made by exclusion.

One specific condition that may need to be excluded in the differential diagnosis of RS is infantile Batten's disease (infantile neuronal ceroid lipofuscinosis (INFL)). In Sweden and Finland, this is an important cause of regression in the second year of life. The distinguishing features are discussed by Witt-Engerstrom⁴¹ and include transient drop attacks at the onset of symptoms, loss of head control, progressive visual failure, hyperexcitability, and extensor posturing. By the age of 2 to 3 years, there are also clear abnormalities on brain imaging and electrophysiological testing (ERG and EEG).

Finally, a few children have been reported with a history somewhat suggestive of RS but with a specific cytogenetic anomaly.^{42–43} None of these cases has shown convincingly an autosomal cytogenetic anomaly as the likely cause of an RS phenotype. Anomalies of the X chromosome will be considered separately.

Neuropathology and neurochemistry

Neuropathological and neuroimaging studies of the brain in RS females are consistent. Neuropathology shows decreased global size of the

brain to 66% to 88% of expected values,⁴⁴ without a reduction in numbers of neurones but with a marked reduction in the extent and complexity of the dendritic trees from neurones in layers III and V of the cortex, especially in the frontal areas.⁴⁵ There is hypopigmentation of the substantia nigra, accounted for by a reduction in the number of melanin granules per neurone rather than a reduction in the number of neurones.⁴⁴ The spinal cord shows spongy change in the corticospinal tracts with reduced myelin and some gliosis; axonal changes are not prominent; there may be some reduction in anterior horn cell numbers.^{45–46} Cerebellar pathology is particularly interesting in that the cerebellum is reduced in size, proportionately to the brain as a whole, but in addition there is a cerebellar atrophy, especially of the vermis and along the folia, which has onset in childhood and is progressive over many years. The Purkinje cells are particularly affected, while other neuronal types are relatively spared.^{45–47} This agrees with the findings of MRI scans in a series of 13 cases,⁴⁸ although another MRI study found atrophy affecting all areas, especially the caudate nucleus and midbrain, but without evidence of any progression.⁴⁹

Changes in neurotransmitters and related metabolites have been found in the cerebrospinal fluid (CSF) of girls with RS. These studies have been reviewed^{50–51}; no consistent abnormality has been identified, and the unusual findings that have been reported are unlikely to represent the primary pathology in RS. Altered patterns of neurotransmitter metabolites,⁵² beta-endorphin,⁵³ bipterin,⁵⁴ and certain gangliosides^{55–56} in the CSF are all likely to reflect secondary changes. Postmortem neurochemical studies found reduced activity of choline acetyltransferase in many cortical and subcortical areas, but the interpretation of this is also unclear.⁵⁷ A trial of therapy with naltrexone, an opiate antagonist, found that it was unhelpful.⁵⁸ Preliminary studies of blood and urine bipterin levels have been normal,⁵⁹ but further studies of urine during the phase of acute regression are in progress.

Metabolic studies and mitochondria

The initial reports of hyperammonaemia in RS^{1–3} were not confirmed in all cases, but transient and variable hyperammonaemia has been reported from a substantial minority of females with RS, and increased urinary excretion of orotic acid has also been found in some cases, as in female carriers of OCT deficiency,^{4–60–63} especially after provocation with intravenous alanine or oral allopurinol. In one series, one of 12 RS girls had increased urinary excretion of orotic acid, as did the mother and grandmother, and as did three of 17 other mothers of RS girls.^{64–65} It was suggested that the RS gene may be located on the X chromosome and encode a mitochondrial protein related functionally to OCT.⁶⁵ A number of studies of urea cycle metabolism in RS have since been performed, and increased orotic acid excretion has been found in 12 of 24 affected girls, and

another two had raised ammonia levels.⁶⁶⁻⁶⁹ The possible effects of sodium valproate, commonly used in RS, must be considered in the interpretation of such results.

There have also been reports of abnormalities of intermediary carbohydrate metabolism in at least 50% of girls with RS, with modest rises of blood lactate and pyruvate levels.⁶⁰⁻⁷⁰ Two of seven cases with normal blood lactate and pyruvate levels had raised CSF levels but normal levels of all tricarboxylic acid cycle (Krebs' cycle) intermediates.⁷¹ Disturbances of these metabolites in the CSF can be associated with anomalous patterns of ventilation, apnoea, and hyperventilation, and with systemic alkalosis.⁷¹⁻⁷²

These reports of abnormalities in urea cycle function and intermediary metabolism have led to the suggestion that mitochondria may be involved in the pathogenesis of RS. Structural anomalies of mitochondria have been identified in muscle tissue at biopsy and necropsy in females with RS,⁴⁵⁻⁷³⁻⁷⁵ and abnormalities in the mitochondrial respiratory chain have been found.⁷⁵⁻⁷⁶ The suggestion that mitochondria are involved in the pathogenesis of RS is strengthened by the pattern of metabolic abnormality in one particular family, in which two sisters have RS. Both girls have abnormalities of lactic acid metabolism, and one girl and their mother have increased urinary excretion of orotic acid.⁶⁷ Furthermore, two unrelated girls with classical RS are known, who have had sisters with lactic acidosis of undefined cause (report in preparation).⁶⁷ There is a strong case that mitochondria are involved in the pathogenesis of RS, although no consistent or specific abnormality has yet been identified.

Inheritance

Rett syndrome is almost always sporadic in a family, except in the case of monozygotic twins, who are almost invariably concordant for RS. It was proposed that RS could be an X linked dominant, male lethal (XDML) disorder, in which virtually every case would represent a new mutation.⁴⁻⁷⁷ A few families with two affected females, however, have been reported. Affected sibs can be accounted for on the basis of mosaicism in either parent for an X chromosome mutation causing RS. Affected aunt-niece pairs, related through the female line, can be accounted for by skewed X inactivation in the relevant tissues or cells in the mother of the affected niece, together with mosaicism in either maternal grandparent or skewed X inactivation in the maternal grandmother. Given that almost all cases would represent new mutations, no deficit of males or excess of females or of miscarriages would be expected in the families of girls with RS, except perhaps in the very few families with more than one affected person.

Reports of possible sisters affected by RS include two sets of maternal half sisters⁴⁻⁷⁸ and several pairs of full sisters²⁹⁻⁶⁷⁻⁷⁹⁻⁸¹; in addition, there are several unreported pairs of full sisters. In at least one of these families,⁶⁷ one girl has classical RS while the second one has a very

similar disorder but does not fulfil all the criteria of classical RS, there being insufficient evidence of regression. One Brazilian family may have three affected girls (report in preparation). There is one Swedish family with a girl with classical RS who has a maternal aunt with apparent "forme fruste" RS,³⁴ and a similar family in Britain (report in preparation). There are several sets of monozygotic (MZ) twins who are concordant for RS, although there are differences in the clinical presentation of the condition between some twins (report in preparation).⁸²⁻⁸⁶ One set of MZ twins is discordant for RS.⁸⁶ An affected girl has been born to an affected woman.⁸⁷ There are no known cases of dizygotic twins both affected by RS.

Studies of X inactivation in lymphocytes from RS females have failed to show consistent evidence of significantly skewed X inactivation,⁸⁸⁻⁸⁹ even in familial cases.⁸⁶⁻⁸⁸ The unusual pattern of replication of the late replicating X reported by two groups⁹⁰⁻⁹¹ has not been confirmed.⁹² X inactivation studies in postmortem brain and liver have also failed to show significant non-randomness.⁸⁸⁻⁹³

A variation of the XDML model of RS inheritance that could account for some of the familial cases would be the suggestion that the RS mutation is an unstable triplet repeat. The existence of such a mutational instability at an X chromosome locus could account for familial cases with unaffected intervening relatives as long as there is no male to male transmission, and this is compatible with the reported familial cases in which the affected relatives are no more distant than second cousins.

The concept of RS as an XDML disorder, similar in inheritance to incontinentia pigmenti (IP) and the Aicardi and Goltz syndromes, can account for the observations made in RS families. Other models of inheritance, however, have been proposed including uniparental disomy and metabolic interference. Uniparental disomy would not really be expected to cause the RS phenotype, given the lack of comparable problems in males with Klinefelter syndrome or females with Turner syndrome, but has anyway been excluded as a frequent event in RS.⁸⁶⁻⁸⁹⁻⁹⁴

Metabolic interference of an X chromosome locus has been proposed as an explanation of the abnormalities found in the mitochondria of skeletal muscle from RS girls.⁷⁴ On this model, a female homozygous for either of two alleles at the RS locus would be healthy, but a heterozygote would be affected because of "metabolic interference" between the protein products of the two different alleles. The existence of such allelic metabolic interference for an X chromosome locus is intrinsically unlikely, unless the relevant protein is extracellular or unless the locus is exempt from X inactivation, and no example of such a system is known. Metabolic interference of both allelic and non-allelic types has been proposed by Buhler *et al.*⁹⁵ involving allelic metabolic interference for an X chromosome locus and an autosomal suppressor locus. This is an even more elaborate model, which could be made to fit the facts but

is not attractive; there is no such model system known, and it would be very difficult to test the hypothesis.

One line of inquiry, however, has produced results that appear to contradict the simple, X linked model of RS inheritance. Genealogical studies in Sweden have shown common ancestry in the male and female antecedents of many affected girls, including male to male transmission and consanguinity in preceding generations, although consanguinity in the parents of affected girls was not found.⁹⁶⁻⁹⁸ This would require an autosomal locus for the RS gene, with perhaps an interaction at one or more X chromosomal loci. Before rejecting the X chromosome as the probable site of "the" RS gene, however, it must be made clear that the genealogical studies are difficult to interpret. Thus, with seventh cousins, the chance of a new mutation causing RS (at 1 in 15 000 girls) is substantially greater than the proportion of their genomes that is identical by descent. More detailed mathematical modelling needs to be performed, incorporating demographic information as well as genetics, to clarify these findings.

The conventional, XDML model of RS inheritance has also been criticised by Migeon *et al*⁸⁶ on the grounds that uniparental disomy has not been found and that there is no evidence of significantly skewed X inactivation in affected girls. Such criticisms, however, ignore the fact that the clinical variability found in RS, within families and particularly between MZ twins, would be more difficult to explain if the RS locus were autosomal, and is precisely what would be expected on the XDML model, in which clinical severity could vary with the tissue specific pattern of X inactivation in each person.

X chromosome cytogenetic studies

Two X;autosomal balanced translocation cases of RS have been reported. In one case with t(X;22), the X breakpoint is at Xp11.22, although the girl's history is not entirely typical, with an early onset of seizures, and the mother and sister also have the same translocation but without definite features of classical RS.³⁵ The other translocation case, with t(X;3), is more typical of the RS phenotype⁹⁹: she has a de novo translocation with an X breakpoint at Xp21.3,⁷⁸ not Xp22 as was originally reported, and a more typical clinical course. However, there must be reservations about the relevance of these translocation cases to standard RS because the skewed X inactivation usually associated with such translocations would be expected to leave the female as functionally hemizygous, and should result in lethality as in the male.

There have been other reports of X chromosome cytogenetic anomalies in people with RS. Wahlstrom and Anvret⁴³ suggested an association with expression of the common fragile site at Xp22, particularly expressed in cell cultures exposed to caffeine, but this has not been confirmed by other studies.¹⁰⁰ There has also

been one report of increased chromosome breakage in culture of lymphocytes of girls with RS.¹⁰¹

Molecular genetic studies

The occurrence of occasional familial cases of RS creates an opportunity to determine what portion of the maternal X chromosome is shared between affected sibs. On the assumptions that the familial cases do represent the same disorder as sporadic RS, and that the disease is genetically homogeneous, then combining results from several families should allow the RS locus to be excluded from large parts of the X chromosome, using the approach of Romeo *et al*¹⁰⁰ and Zoghbi.⁷⁷ Affected half sisters have been studied by Archidiacono *et al*¹⁰² and by Ellison *et al*,⁷⁸ who used the same (Swedish) family as Archidiacono *et al*,¹⁰² and another family. Curtis *et al*¹⁰³ reported linkage analysis results in a British sister pair and the Swedish half sisters. Beuten *et al*⁹ studied three sister pairs with RS, including the family described by Hanefeld.²⁹ These studies have concentrated on the X chromosome short arm, where more markers have been available, and appear to have excluded much of the distal X short arm (but not the pseudoautosomal region), the proximal short arm, and across the pericentromeric region to Xq13, and a few scattered markers on the long arm. The region of the translocation breakpoint at Xp21.3 has since also been excluded by Ellison *et al*¹⁰⁴ in two families with affected half sisters. Physical mapping of the Xp21.3 region in the translocation case is in progress but its relevance to classic RS is uncertain.

A Swedish aunt-niece pair has also been studied³⁴; the aunt is thought to have a "forme fruste" of RS. In this family, the affected niece received the maternal grandfather's copy of most X short arm markers used; this led to the suggestion that he may have been mosaic for the RS mutation, and that two separate mutation events may be required for the condition to manifest. The X chromosome long arm was not fully investigated. This family and a similar British aunt-niece pair were also studied by Curtis *et al*,¹⁰³ but the results are difficult to interpret.

Given that RS affects only females, it would seem unlikely that the underlying molecular genetic cause of RS would be located in the mitochondrial genome. It is therefore difficult to interpret the recent demonstration of an unusual T to C transition in the mitochondrial tRNA^{Arg} at position 10463 in a single female with RS.¹⁰⁵ A mitochondrial genome mutation could produce an unusual inheritance pattern and inconsistent metabolic anomalies, rather as in RS, but why would only females be affected? Clearly, further research is required.

Future research

The pathogenesis of this important and intriguing disorder is hardly understood at all. While the classical RS phenotype is now well defined, there is a need for further work to identify early signs indicative of the disorder. Further pathological and neurochemical stud-

ies of RS, and further developmental neurobiological work on the mammalian brain, will be helpful in providing guidance to geneticists interested in identifying potential candidate genes for this disorder. In addition, further exclusion mapping in familial cases may be helpful in selecting from among potential candidate genes those which should be studied in detail in classical, sporadic cases of RS. These exclusion mapping studies should examine the pseudoautosomal region of Xp and the greater part of Xq, which have not yet been adequately investigated.

From what is known so far, candidate genes to be considered would include X chromosome loci whose protein products are involved in the following biological functions: (1) neurotransmitter synthesis and release and the corresponding neurotransmitter receptors; (2) members of the neurotrophin gene family, and neurotrophin receptors; (3) mitochondrial proteins involved in intermediary metabolism or having a structural or a protein import role. Despite these being the most likely candidate genes, however, there is so little known with certainty about the biology of RS that the possibility of autosomal loci or even the mitochondrial genome being involved, or of the RS gene having some unanticipated biological role, should not be dismissed.

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