



The relationship between *MECP2* mutation type and health status and service use trajectories over time in a Rett syndrome population

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ABSTRACT

This study aimed to investigate the trajectories over time of health status and health service use in Rett syndrome by mutation type. Data were obtained from questionnaires administered over 6 years to 256 participants from the Australian Rett Syndrome Database. Health status (episodes of illness and medication load) and health service use (general practitioner and specialist visits and hospital stays) were summarized into composite scores with principal component analysis. Linear and mixed regression models examined effects of mutation type and other variables on these scores over time. For some mutations (such as p.R255X and p.R168X) health status was poorer at a younger age and improved over time, while for p.R133C it was better at a younger age and deteriorated with time. For those with p.R133C health service use was lowest at a younger age and highest at 25 years. With other mutations, such as p.R255X, p.R270X, p.R294X, C terminal and p.R306C, health service use was higher at a younger age, but dropped off considerably by 25 years of age. Health service use generally declined in parallel with deterioration in health status, although this pattern differed by mutation type, demonstrating important variability in the course of Rett syndrome.

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1. Background

Rett syndrome is a neurodevelopmental disorder with a cumulative incidence of 1.09 per 10,000 females by the age of 12 years (Laurvick et al., 2006). Children with Rett syndrome generally do not appear to have any problems at birth, but development subsequently regresses, with loss of hand function and communication skills usually evident by 18 months.

The association between Rett syndrome and mutations in the methyl-CpG binding protein 2 (*MECP2*) gene was first identified in 1999 (Amir et al., 1999). Mutations have been reported in 73–96% of classical Rett syndrome cases in various studies with the percentage increasing as techniques improve (Colvin et al., 2003; Renieri et al., 2003). More than 200 different pathogenic *MECP2* mutations have now been identified, with eight accounting for just over two-thirds of mutation positive cases (Bebbington et al., 2008; Colvin et al., 2004). In a study combining Australian and international cases, mutations at the C terminal (CT), early truncating (ET) mutations and large deletions (LD) accounted for another fifth of mutation positive cases (Young et al., 2008). Amongst mutation types there is considerable phenotypic variation. Some mutations, such as p.R270X, p.R255X (Bebbington et al., 2008; Colvin et al., 2004; Huppke, Held, Handefeld, Engel, & Laccone,

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2002) and p.R168X (Neul et al., 2008) have been shown to be associated with a severe clinical presentation and others, such as p.R294X and p.R133C, with a milder phenotype (Bebbington et al., 2008; Colvin et al., 2004; Leonard et al., 2003).

Genotype–phenotype relationships have previously been investigated (Bebbington et al., 2008; Colvin et al., 2004; Schanen et al., 2004) using information about the regression period, current functioning and co-morbidities (e.g., epilepsy and scoliosis), often in the form of severity scales (Amir et al., 2000; Kerr et al., 2001; Monros et al., 2001). Given the known clinical progression in Rett syndrome (Hagberg, Witt-Engerström, Opitz, & Reynolds, 1986), the relationship between phenotype and genotype may be confounded by age. This has been accounted for in at least one study (Bebbington et al., 2008). However, no research has investigated the change in composite health status by mutation type over time. Is it possible that the health status of those affected by mutations with an apparently mild phenotype and better functioning will later deteriorate quite markedly? Conversely, might the health status of those with apparently severe mutations and very limited functioning have a less aggressive trajectory?

The only study, to our knowledge, that has been undertaken on the association between health service use and other factors is our earlier study showing that use was highest in younger cases and lowest in cases with milder phenotypes (Moore et al., 2005). Some relationships with specific genotypes were also identified. The aim of the present study was to examine the health status and health service use of females with Rett syndrome over time and identify any variation by age and by mutation using data from the Australian Rett Syndrome Database (ARSD).

2. Methods

2.1. Data source

The Australian Rett Syndrome Database (ARSD) is an ongoing population-based register of Australian Rett syndrome participants born since 1976 (Laurvick et al., 2006). Cases (~15 per birth year) are identified most commonly either by clinicians through the Australian Paediatric Surveillance Unit (APSU) (Gazarian et al., 1999) or by families via the parent support group (Leonard & Bower, 1998). Since 2000, follow-up questionnaires have been administered every 2 years to Australian study families (Jian et al., 2006). Data collection procedures and this study have been approved and monitored by the Princess Margaret Hospital for Children Human Ethics Committee. There have now been four follow-up questionnaires completed by the parents or carers in the years 2000, 2002, 2004 and 2006, collecting demographic data and information on functional ability, medical conditions and healthcare service use. The data provide a longitudinal profile of the individual's clinical history (over a period up to 6 years) – particularly in relation to episodes of illness, use of health services (doctors' visits and hospitalizations) and use of medication. Data were available for the 256 cases whose parents or carers had completed at least one of the four follow-up questionnaires. The number of questionnaires completed on each participant depended on the year of recruitment and on whether they remained alive. Thus, four questionnaires were completed for 91 (35.5%) participants. Of these, 44 (17.2%) participants (many of whom were more recently recruited) had one questionnaire, 62 (24.2%) had two, and 59 (23.1%) three questionnaires. These cases yielded a total of 713 observations on health status and health service use, which form the basis of this analysis. Age at the time of questionnaire completion was grouped as follows: 0 to less than 5 years; 5 to less than 10 years; 10 to less than 15 years; 15 to less than 20 years; 20 to less than 25 years and 25 years and over.

2.2. Health status

Four specific aspects of health were used to assess health status: epilepsy, gastro-intestinal problems, nutritional problems and episodes of illness. We selected the first three because we found that the range of medication use in case subjects related almost entirely to these three areas. These four aspects of health status, along with scoliosis, are the major co-morbidities in Rett syndrome (Weaving, Ellaway, Gecz, & Christodoulou, 2005). We measured the impact of scoliosis through health service encounters (see below).

A severity code for epilepsy was based on use of antiepileptic drugs (AEDs). AEDs were coded by the number of drugs taken, and by the type of drug. First-line medications (carbamazepine, phenobarbitone, ethosuximide, sodium valproate and phenytoin) were given a score of 1. All other AEDs were categorised as second line drugs and given a higher score (1.5). Cases with any two AEDs were scored 2; any three AEDs were scored 3 and so on. Short-term rescue medications were not included. Based on the information about reflux and/or constipation management requirements, each individual was given a gastro-intestinal (GI) score from 0 to 10 (0 = nil GI problems, 10 = severe). A score from 0 to 4 was given for nutritional difficulty based on questionnaire information related to eating ability and need for nutritional support: 0 = nil difficulty; 4 = percutaneous endoscopic gastrostomy (PEG) in-situ.

A categorical variable was calculated based on quartiles of the distribution of all episodes of illness in the year preceding completion of each questionnaire. Episodes of illness were defined here as cold/flu, tonsillitis, pneumonia, bronchitis, episodes of asthma, ear infection, urinary tract infection (UTI), and other. Each individual was assigned a score of 1–4 with 1 representing no or 1 episode of illness in an average year, 2 representing more than 1 visit and less than 2.5 in an average year, 3 representing more than 2.5 and less than 5 visits in an average year and 4 being the maximum representing 5 or more episodes of illness in an average year.

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